Real-world evidence regulatory and public health applications using secondary healthcare data sources for post licensure vaccine safety: the use case of the Human papillomavirus vaccine.

Corinne Willame

Real-world evidence regulatory and public health applications using secondary healthcare data sources for post licensure vaccine safety: the use case of the Human papillomavirus vaccine

Corinne Willame

Real-world evidence regulatory and public health applications using secondary healthcare data sources for post licensure vaccine safety: the use case of the Human papillomavirus vaccine

Real-world data en evidence voor monitoring van de veiligheid van vaccins na toelating op de markt: toepassingen voor het humaan papillomavirusvaccin

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 13 februari 2024 des ochtends te 10.15 uur

door

Corinne Willame

geboren op 14 mei 1980
te La Louviere, België

Promotor:

Prof. dr. M.C.J.M. Sturkenboom

Copromotor:

Dr. D.M. Weibel

Beoordelingscommissie:

Prof. dr. M.J.M. Bonten
Prof. dr. O.H. Klungel (voorzitter)
Prof. dr. D.L. Oberski
Prof. P. Rijnbeek
Prof. dr. M. van der Sande

A ma fille, Maia.

Contents

Chapter 1: General Introduction

Vaccination is one of the most effective preventive measures against infectious diseases. Benefits of vaccination have been demonstrated throughout the years with, as example, the eradication of smallpox at worldwide level [1]. The majority of vaccine-preventable diseases are under close monitoring by supranational authorities or at national level [2]. So far, dozens of prophylactic vaccines have been approved for use by health regulatory authorities and they are made available to the public through traditional healthcare settings or mass vaccination campaigns such as for the H1N1 pandemic vaccine or COVID-19 vaccine. Besides proven benefits of any medicinal product, unexpected medical events or adverse events may occur following administration of vaccine(s). Because prophylactic vaccines are generally administered to healthy people including pediatric population, and to a large population, tolerance to risk of developing adverse events is low (Figure 1). The harm associated with vaccines ranges from common and mild symptoms such as fever or pain at injection site [3] to rare and more serious adverse events such as autoimmune diseases [4]. Serious adverse events are rare and therefore may go undetected during clinical development phases. For this reason, the monitoring of benefits and risks of vaccines beyond clinical development is crucial to detect and measure potential rare adverse events and to maintain public confidence in vaccines [5].

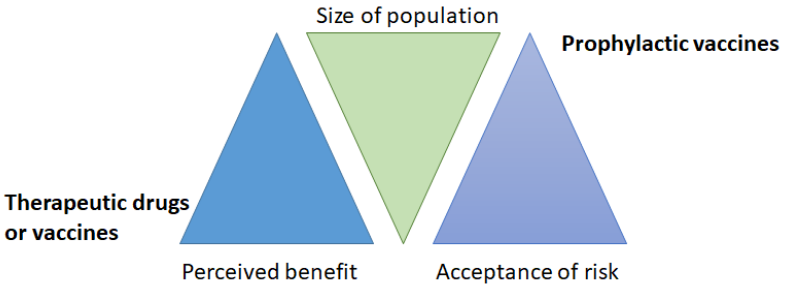


Figure 1: Perceived benefit and risk acceptance for prophylactic vaccines versus therapeutics. Adapted from Pharmacovigilance for Biologics training, European programme in Pharmacovigilance and Pharmacoepidemiology [6]

Background and objectives of the thesis

The background of this thesis is based on the legislation of vaccine safety assessment in Europe guided by the Good Pharmacovigilance Practices (GVP) [7] and methods from detection to validation of safety signals. The thesis further highlights the challenges in using existing healthcare data sources for real-world regulatory and public health applications in the monitoring and assessment of post-licensure vaccine safety.

This thesis deals with methodological approaches for analysis of real-world data in existing healthcare data sources to assess the safety of vaccines. It highlights the diversity of methods from single data source study to multi-data sources study that are implemented for the monitoring of vaccine safety in both passive and active surveillance phases. The safety assessment of the Human papillomavirus (HPV)

vaccine is used as an example to illustrate the diversity of vaccine safety methods that are implemented post-licensure.

Pharmaco-epidemiological concepts: from safety signal detection to safety signal evaluation

Vaccine pharmacovigilance is defined as the science and activities related to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine-related issues, and to the prevention of untoward effects of vaccines [8,9]. Adverse events following immunisation (AEFI) are any untoward medical occurrence which follows immunisation, and which does not necessarily have a causal relationship with the usage of the vaccine [10,11]. An AEFI may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease, it can be non-serious and resolved within a few days with minimal medical intervention, but AEFIs that are life-threatening or require hospitalization or may cause congenital anomaly are considered as serious AEFIs [12]. Adverse events of special interest (AESIs) are those of scientific, medical and public interest that have the potential to be causally associated with a vaccine and for which a careful safety monitoring and further investigation are required to characterize and understand it [13,14]. At European level, vaccine safety assessment follows the process of safety signal management which consists of a set of activities that include collection of data from passive surveillance, enhanced surveillance, and active surveillance (Figure 2) [10,11,15,16].

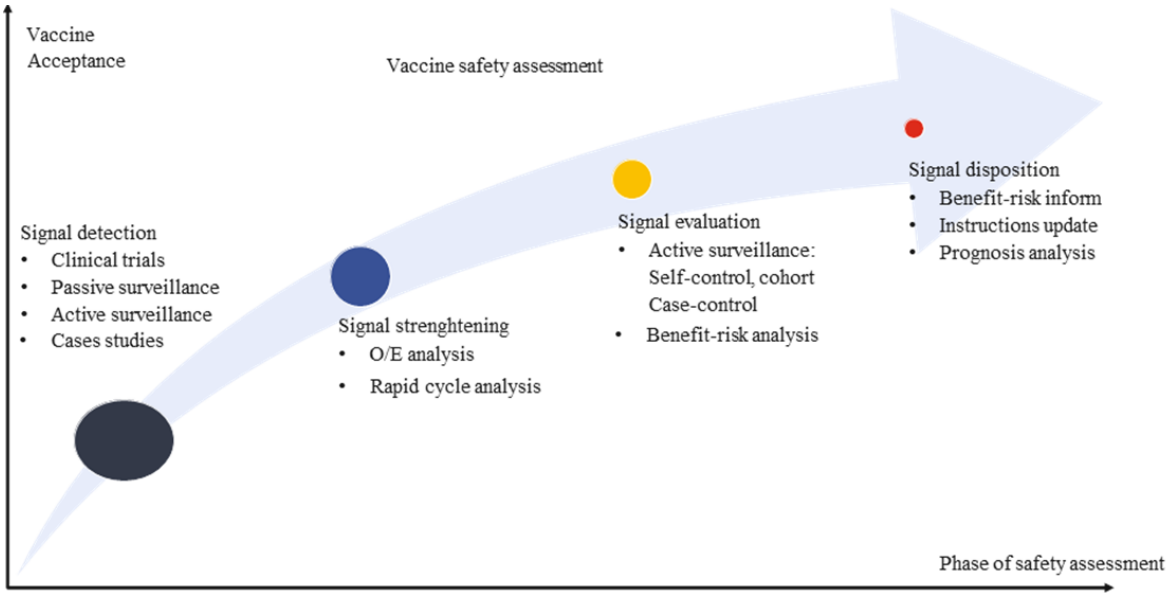


Figure 2: Phase of vaccine safety assessment in post-licensure. Adapted from Lui et al. 2021.

1- Passive surveillance

Passive safety surveillance is a pharmacovigilance surveillance system based on spontaneous reporting which can help detect usual patterns or higher than expected frequencies of vaccine adverse reactions [11]. It relies on spontaneous reporting of adverse events following administration of vaccine by medical professionals or consumers. While passive surveillance is considered as the minimum form of pharmacovigilance system, in many low- and middle-income countries, safety surveillance capacity is limited. The last Global Vaccine Safety Blueprint provides guidance to assist low- and middle-income countries achieve and build upon minimal capacity for vaccine adverse event surveillance. To this end, the World Health Organization (WHO) developed a tool indicator to evaluate performance at country level, and between the years 2010 to 2018, from 80 to 120 countries reached the target level for global monitoring of vaccine adverse events [11]. Globally, WHO and participating member states (more than 170 members and associate members in 2022) contribute to the aggregated database Vigibase, which is the largest drug or vaccine safety data repository in the world with over 30 million reports of suspected adverse events submitted since 1968 [17]. The programme covers about 99% of the world's population. The US Vaccine Adverse Event Reporting System (VAERS) and the European Eudravigilance database are also well-established passive surveillance systems [17,18]. While spontaneous reporting databases have the benefits to detect in near real-time potential safety concerns, analysis of such databases has limitations due to reporting bias. Data are self-reported, and misclassification of outcome and exposure cannot be excluded. In addition, under-reporting of events in spontaneous databases ranged between 6% and 100% [20,21], also the reporting pattern may change overtime due to media attention or for newly authorized vaccines, with a higher number of events reported soon after vaccine launch. Moreover, incomplete data on onset of symptoms, vaccine manufacturers or vaccine batches are observed, also a lack of reliable denominator forcing to use assumptions on the populations that are vaccinated [9,22,23]. Nevertheless, a set of robust techniques and methods has been developed for the detection of safety signals in spontaneous reporting systems. Disproportionality analyses are numerator-based methods and compare the reporting of a specific exposure-outcome pair relative to the rest of the data available in the spontaneous database meaning comparing 'other type of exposure *versus* the same outcome of interest' or 'the exposure of interest *versus* another outcome' [25-27]. A disproportionate reporting method based on time-to-onset has also been developed by van Holle et al. [28] in which distribution of time-to-onset of a pair exposure-outcome is assessed in 'between-vaccines' comparison and in 'within-vaccine' comparison. Time-to-onset distribution provides an overview of temporal association between exposure and outcome and allows the identification of potential temporal cluster of events.

2- Enhanced surveillance

Enhanced safety surveillance is implemented to rapidly detect a potential increase of a specific adverse event that is intrinsic to the vaccine in near real-time or to refine safety signals that are detected in passive surveillance [16,29]. Methods for enhanced surveillance are diverse and include observed-to-expected (O-E) analysis [30,31] or rapid assessment with sequential analyses in existing healthcare data sources. O-E analysis can optimise the utility of passive surveillance data, allowing determination of the strength of a signal for prioritisation and further evaluation [31]. The O-E analysis relies on disease and age-specific background incidence rates and estimates of vaccine exposure. In O-E analysis, observed cases from spontaneous reporting systems are compared with an expected number of cases calculated based on background incidence rates from other sources such as epidemiological studies of national statistics. This method is particularly useful during mass vaccination campaigns where rapid decision-making about a safety concern is required, it has been largely used for the safety monitoring of COVID-19 vaccines. With the COVID-19 pandemic, efforts have been made to conduct rapid vaccine safety assessment in existing healthcare data sources. The United States Food and Drug Administration (US FDA) Biologics Effectiveness Safety (BEST) System initiative [32] conducted rapid safety surveillance via sequential testing to assess the rate of AESI following COVID-19 vaccination compared to a baseline rate using the Maximized Sequential Probability Ratio Test (MaxSPRT) method [33,34]. The method was applied in US administrative claims data sources and was built on previous experiences to monitor the safety of vaccines in Vaccine Safety Datalink and in the FDA Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system [35-39]. In the United Kingdom (UK), the Medicines and Healthcare products Regulatory Agency (MHRA) conducted near real-time safety surveillance using repeated weekly application of the MaxSPRT method in the UK CPRD data source [40]. In Europe, the Early Covid Vaccine Monitoring (ECVM) study was conducted in four healthcare databases to monitor the use of COVID-19 vaccines and estimate incidence rates of pre-selected AESI prior and after COVID-19 vaccination [41].

3- Active surveillance

Active safety surveillance seeks to ascertain more completely the number of adverse events in a given population via a continuous organized process [42]. It is meant to evaluate safety signals that were identified during clinical development or through passive surveillance. Active surveillance can also proactively detect additional safety signals that could not be identified or could not be reported during passive surveillance. Active surveillance mainly covers the scope of formal epidemiological studies which are designed and powered specifically to test a hypothesis in an unbiased way and allow to characterize and quantify a potential safety signal [43]. A number of observational study designs which includes cohort, case-control, or self-controlled study designs are useful in validating safety signals from spontaneous reports, active surveillance programmes or case series [14]. Primary or secondary

data collection approaches can be used to collect prospectively or retrospectively medical data that are needed for the assessment of a potential relationship between adverse event and vaccine.

Over the last decades, existing healthcare data sources have been increasingly used to evaluate safety of vaccines in active surveillance [44]. A variety of data sources may be used in pharmacoepidemiological studies, there are two main types of electronic data sources: those that contain comprehensive medical information including disease diagnosis, drug prescriptions, referral and discharge letters, and those mainly created for administrative purposes, which require record-linkage between pharmacy claims and medical claims [14]. Existing healthcare data sources offer the advantages to cover large and geographically disperse populations allowing to increase sample size of the studied population(s) and potentially identify adverse events that are rarely reported in clinical routine practice. For long, single data source studies including electronic healthcare data sources and general practitioners' data were used to assess the safety of vaccines post-licensure [45]. Advantages of single data source studies is that data are set in a consistent structure and the data collection is homogenous in the sense that data are collected for a similar purpose (eg. routine medical follow-up or reimbursement purpose). However, data from a single data source may be limited in size and in scope because collected data may not fit the need for a specific research question. As example, general practitioner data sources may not properly capture medical conditions that are usually reported in a hospital setting. In addition, in a single country or a single region, exposure to a vaccine may be insufficiently represented due to low vaccine uptake or limited market share for a specific vaccine brand. Over the last years, multi-data sources studies including collaborative approaches have been implemented in the field of evidence generation for safety assessment of vaccines [46,47]. Following the H1N1 pandemic in 2009, the need for robust surveillance systems to monitor benefit and risk of vaccines was highlighted as crucial by governments. In this context, the Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE), a public-private consortium, was launched by the Innovative Medicines Initiatives in 2013 to bring together stakeholders (ie. regulators, academics and vaccine manufacturers) and built a system to generate evidence on background rates, vaccine coverage and assess benefit-risk of vaccines using existing healthcare databases in Europe [48]. The ADVANCE initiative led to the creation of the Vaccine Monitoring Collaboration for Europe (VAC4EU), an ecosystem, in which tools and methods have been developed to standardize ways of working among several European healthcare data source partners. In 2020, with the COVID-19 pandemic, the expertise of the VAC4EU network was leveraged to prepare the safety monitoring of COVID-19 vaccines in Europe with the launch of the EMA funded ACCESS project (vACCine COVID-19 monitoring readiness) in which several European healthcare data sources were used to generate background incidence rates of AESI in a harmonized manner to control for bias due to heterogeneity across data sources [49].

From a global perspective, several initiatives were launched to improve the effectiveness of safety surveillance measures of vaccines [50,51]. The Global Vaccine Data Network (GVDN) is a multinational consortium of vaccine experts and data owners that utilizes existing healthcare data globally to generate evidence on benefits and risks of vaccines. Among its objectives, the GVDN attempts to build and reinforce capabilities from countries with less developed infrastructures in terms of surveillance systems and access to existing health data. The global approach allows to optimize the robustness of epidemiological safety studies with the inclusion of large population increasing the likelihood of detecting very rare adverse events [4,52]. Also, this global approach supports evidence generation at country and/or regional level which strengthens geographical diversity. The COVID-19 pandemic has accelerated the implementation of international collaboration. The Coalition for Epidemic Preparedness Innovations (CEPI) is an innovative global partnership between public, private, philanthropic, and civil society organizations created in 2017 that aims to accelerate the development of vaccines and other biologics in a pandemic situation [53]. The International Network of Special Immunization Services (INSIS), created in 2020 in response to the COVID-19 pandemic, is a platform of international vaccine experts who aim to address knowledge gaps in the understanding of mechanistic modes of action of vaccines and the risk of developing specific rare adverse events and to inform on benefit-risk assessment of vaccine in low-, middle- and high-income countries [54,55]. The primary focus was on COVID-19 vaccines, but INSIS plans to broaden the scope to future vaccines as well.

4- Benefit-Risk (B/R) concept and public acceptance

Vaccines are constantly evaluated for safety and efficacy from the early stages of clinical development through to regulatory assessments for approval of use. The continuous qualitative and quantitative assessments of benefits and risks of vaccines is making the basis for informed judgment as to whether the benefits outweigh the risks under the intended conditions of use [56-58]. It allows to formulate recommendations on vaccine use and ultimately gain public confidence. Continuous post-approval B/R assessment is also necessary given that vaccine uptake is growing and risk for rare and undetected adverse events during clinical development may be observed in real-world setting [59,60]. When new or changing risk is identified in the general population or in subpopulations such as pregnant women or people with comorbidities during the vaccine life cycle, it is recommended to re-evaluate the benefit using all available evidence and estimate the impact of the newly identified or changing risk on the benefit-risk balance [9].

Regulatory framework and significance

Health regulatory authorities assess and approve the use of vaccines, or drugs based on a set of evidence that are generated during the clinical development of the product. Marketing authorization

of products are granted based on an assessment that adequate and sufficient data support the conclusion that the benefits outweigh the risks in the populations for which the indication is made [11]. The clinical development of vaccines is a three-phase process starting from Phase I to Phase III. During the clinical development, vaccine candidates are rigorously tested in clinical studies for both safety and efficacy. At each development phase, clinical studies include a number of people that increases from dozen in Phase I to several thousands in Phase III. However, most of the time, vaccines are tested in healthy people or in people satisfying pre-specified criteria before being enrolled in a clinical study. In addition, the studied population in clinical studies is often limited in size and the observational follow-up is of limited span time. Therefore, there are a couple of information related to the use of the vaccine in certain populations such as pregnant women or people with comorbidities that are missing when a vaccine reaches the late development stage and Phase IV. Moreover, given the limited sample size of people enrolled in clinical studies, only common adverse events can be detected raising questions on potentially rare or delayed safety concerns or long-term effectiveness which must be addressed in post-licensure phase.

Licensure and procurement of efficacious and safe vaccines are codified by national health regulatory authorities or supranational health authorities such as WHO [61]. In Europe (EU), European law requires marketing authorization holder (MAH), national competent authority, and European Medicine Agency (EMA) to conduct appropriate pharmacovigilance activities once a vaccine is launched on a market and throughout the vaccine life cycle [62]. In 2012, the EU Pharmacovigilance legislation enforced new obligations for conducting and reporting post-authorization safety studies (PASS) with the creation of guideline on good pharmacovigilance practices (GVP – Module VIII) [42]. A PASS is defined as any studies aiming to identify, characterize or quantify a safety risk of an authorized vaccine or any medicine. When pertaining to MAH obligations, the EU regulation may impose additional pharmacovigilance activities to address missing information or potential safety concerns related to the authorized vaccine. In line with EU legislation, EMA is accountable to coordinate and operate surveillance activities of medicines including vaccines under development and authorized for use. The EMA pharmacovigilance system is designed to monitor the safety of vaccines through data monitoring, signal detection and signal validation activities and to identify any change in the benefit-risk profile of a vaccine [62-64]. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), a network coordinated by the EMA, was created in 2009 and aims to strengthen the monitoring of benefit-risk profiles of medicines, including vaccines, by providing guidance on methods for post-authorization studies (PAS), by cataloging EU PAS and data sources and strengthening a collaborative network of pharmacoepidemiologist experts [65,66]. The guidance is built as a methodological checklist covering core elements and methodological aspects of pharmacoepidemiologic research. The last revision of the ENCePP guidance (revision 10, June 2022)

expanded on the use of artificial intelligence in pharmacoepidemiology and on real-world evidence in pharmacoepidemiology [67]. More recently, the EMA and the ECDC has jointed effort for strengthening the continuous monitoring of the safety and effectiveness of vaccines in the EU through the Vaccine Monitoring Platform (VPM). This joint initiative will support the decision-making process by generating real-world evidence on vaccine independently from the industry interest [68] aiming to build and maintain public confidence in vaccines.

The use case of Human papillomavirus vaccines

Prophylactic human papillomavirus vaccines have been developed to protect against oncogenic HPV types, by reducing HPV infections and preventing cervical, anal and oropharyngeal precancers and cancers. Currently, four HPV vaccines received pre-qualification by the World Health Organization (WHO): a nonavalent HPV vaccine (9vHPV, *Gardasil9*, *Merck*); a quadrivalent vaccine (4vHPV *Gardasil*, *Merck*) and two bivalent HPV vaccines (2vHPV, *Cervarix*, *GSK* and *Cecolin*, *Innovax*) [69,70]. Three of them are approved for use by health regulatory authorities worldwide: 9vHPV, 4vHPV and 2vHPV *Cervarix*. The four HPV vaccines, highly immunogenic, are virus-like particles (VLPs) based vaccines meaning they induce the production of neutralizing antibodies against HPV L1 capsid protein which can spontaneously self-assembled into virus-like particles (VLPs) and mimic the natural surface of native papilloma virus virions [71,72]. In addition, to enhance the immune response, the four HPV vaccines are complemented by an adjuvant, one of the numerous vaccine platform technologies. Notable differences exist between the four HPV vaccines in terms of target HPV types, expression system and adjuvanted platform. The main characteristics of the approved HPV vaccines are summarized in Table 1. Since their first use in 2006, 2007 and 2014 respectively for *Gardasil*, *Cervarix* and *Gardasil9*, the three vaccines demonstrated favorable benefit-risk profiles. To date, important potential safety risks are still under investigation for *Gardasil* and *Gardasil9* and are related to the use of the vaccine during pregnancy (*Gardasil* and *Gardasil9*) and the risk of developing autoimmune diseases (*Gardasil*). *Cecolin* (*Innovax*) has recently received WHO pre-qualification in 2021 and while the interim analysis of the pivotal Phase 3 clinical study showed a favorable tolerability profile, its long-term benefit-risk profile still needs to be demonstrated [73-75].

Table 1 Characteristics of the four HPV vaccines

Trade Name	Vaccine manufacturer	First approval date	Approved indication	Target antigens	Expression system	Adjuvant platform

Gardasil*	Merck, USA	2006 by the US FDA	Cervical, anal cancers Cervical, vulvar, vaginal and anal precancerous lesions Genital warts	Major capside protein L1 epitope of HPV types: 6,11, 16, 18	Yeast cells	Adsorbed on amorphus aluminium hydroxyphosphate sulfate adjuvant
Gardasil9	Merck, USA	2014 by the US FDA	Oropharyngeal, head and neck cancers** Cervical, vulvar, vaginal, anal cancers and precancerous lesions Genital warts	Major capside protein L1 epitope of HPV types: 6,11, 16, 18, 31, 33, 45, 52, 58	Yeast cells	Adsorbed on amorphus aluminium hydroxyphosphate sulfate adjuvant
Cervarix	GSK, Belgium	2007 by EMA	Cervical, anal cancers Cervical, vulvar, vaginal and anal precancerous lesions	Major capside protein L1 epitope of HPV types: 16, 18	Baculovirus-insect cells	AS04 containing aluminium hydroxide and monophosphoryl lipid A (MPL)
Cecolin	Innovax, China	2019 by NMPA	Cervical, vulvar, vaginal, anal cancers	Major capside protein L1 epitope of HPV types: 16, 18	Escherichia coli	AS04 containing monophosphoryl lipid A (MPL) adsorbed on Aluminium hydroxide

*Gardasil is no longer distributed in the USA [76] and has been replaced by Gardasil9. The approved indication is for Europe.

**The Gardasil9 indication has been expanded to oropharyngeal and other head and neck cancers in the USA [77] (approval in June 2020) and Canada [78,79] (approval in April 2022).

US: United States; FDA: Food and Drug Administration; EMA: European Medicine Agency; NMPA: National Medical Products Administration of China

Outline of this thesis

The work describes in this thesis consists of a set of scientific papers that focus on retrospective observational studies using existing healthcare data sources and on recommendations on good practices for the implementation of vaccine safety evaluation studies. The aim of the thesis is to highlight the diversity of methods from single data source study to multi-data sources study that are implemented in vaccine safety research.

In **Chapter 2:** *Background incidence rates for vaccine safety assessment,* two studies which generated background incidence rates of AESIs for vaccines safety assessment are presented. *Chapter 2.1* consists of a study that was conducted in the context of the ADVANCE project and that generated background incidence rates of autoimmune diseases using several European electronic healthcare data sources. The ADVANCE project developed and tested new methods and data analysis tools to create Europe-wide system that can generate robust evidence once vaccines are launched on the market [80].

Chapter 2.2 presents a second background incidence rates study which was conducted as part of the ACCESS project and which used a distributed data network of 10 data sources across 7 European countries. ACCESS was an EMA funded project that was launched to prepare for the real-world safety monitoring of COVID-19 vaccines using a European infrastructure. The two studies were conducted using existing healthcare data sources from several European countries, they differ in the method for collecting and analyzing data. The ACCESS study was conducted in a distributed manner using a common data model and common analytical methods. The use of distributed data networks is a novel approach in vaccine safety assessment, it ensures harmonization in the process for evidence generation and reduce bias linked to the heterogeneity of the diversity of data sources. Background incidence rates studies inform whether data sources are fit-for-purpose to study effects of vaccines because it generates incidence rates that can be benchmarked against data from published references, and subsequently informs on the level of accuracy of the generated data. In vaccine assessment, background incidence rates are extremely useful to contextualize emerging safety signals that are observed post-vaccine launch.

Chapter 3: *Overview of methods for vaccine safety signal evaluation,* provides a review of study designs and methods that were implemented to assess the risk of rare adverse events that occurred after administration of HPV vaccines. The systematic literature review highlights the diversity of data sources and study designs that can be used in studies on vaccines safety signal evaluation. It also highlights the need for more systematic collaborations to monitor rare safety events.

Chapter 4: *Safety evaluation of the bivalent HPV vaccine,* presents three observational safety evaluation studies that were conducted to assess the risk of adverse events following administration of the bivalent HPV *Cervarix* vaccine (2vHPV *Cervarix*). The three studies were industry-sponsored and addressed requests from regulatory health authorities. In *Chapter 4.1*, the association between autoimmune diseases and 2vHPV *Cervarix* vaccine is assessed by applying two study designs: a cohort and a self-controlled case series. For both studies, the UK CPRD data source was used because it was the largest data source in terms of exposure for the 2vHPV *Cervarix* vaccine at the time health regulatory agencies made the request for the studies. *Chapter 4.2* presents a meta-analysis that was conducted to evaluate the risk of developing three pre-specified autoimmune diseases (Guillain Barré Syndrome, inflammatory bowel disease and autoimmune thyroiditis) that were identified as potential safety signals for the 2vHPV *Cervarix* vaccine. The meta-analysis combined two types of data: data from interventional clinical studies and data from observational epidemiological studies. *Chapter 4.3* focuses on pregnant women exposed to the 2vHPV *Cervarix* vaccine. The risk of spontaneous abortion following administration of the 2vHPV *Cervarix* vaccine is evaluated in a retrospective cohort study design using the UK CPRD.

Finally, **Chapter 5:** *Recommendations for implementation of observational safety studies,* provides a framework to conduct feasibility assessment before to implement a formal association safety study.

Table 2 Summary of thesis chapters

Chapter	Title	Project	Type of study, data processing	Data Source(s)	EUPAS Register number
2.1	Incidence rates of autoimmune diseases in European Healthcare databases: A contribution of the ADVANCE Project	ADVANCE	Multi-data source, distinct data sources	ARS, PEDIANET, Val Padana (Italy); BIFAP (Spain); Danish registries (Denmark); RCGP RSC, THIN (United Kingdom)	N/A
2.2	Background rates of 41 Adverse Events of Special Interest for COVID-19 vaccines in 10 European healthcare databases - An ACCESS cohort study	ACCESS	Multi-data source, distributed data network	ARS, PEDIANET (Italy); FISABIO, SIDIAP, BIFAP (Spain); Danish registries (Denmark); GePaRD (Germany); SNDS (France); PHARMO (The Netherlands); CPRD (United Kingdom)	EUPAS37273
3.1	Systematic review and meta-analysis of post-licensure observational studies on human papillomavirus vaccination and autoimmune and other rare adverse events	N/A	N/A	N/A	N/A
4.1	Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom	GSK Vaccines sponsored study	Single data source	CPRD	EUPAS4584
4.2	Meta-analysis of the risk of autoimmune thyroiditis, Guillain-Barré syndrome, and inflammatory bowel disease following vaccination with AS04-adjuvanted human papillomavirus 16/18 vaccine	GSK Vaccines sponsored study	Multi- data source, distinct data sources	Clinical database, CPRD (United Kingdom), PGRx, SNDS (France)	EUPAS13332
4.3	Risk of spontaneous abortion in 15 to 25 years old women exposed to human papillomavrus-16/18 ASO4-adjuvanted vaccine in the United Kingdom.	GSK Vaccines sponsored study	Single data source	CPRD	EUPAS3310
5.1	Importance of feasibility assessments before implementing non-interventional pharmacoepidemiologic studies of vaccines: lessons learned and recommendations for future studies	N/A	N/A	N/A	N/A

ACCESS: vACcine *Covid-19* monitoring readinESS*;* ADVANCE: Accelerated Development of VAccine beNefit-risk Collaboration in Europe; ARS: Agenzia regionale di sanità; AUH: Aarhus University Hospital; BIFAP: Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CPRD: Clinical Practice Research Datalink; FISABIO: Foundation for the Promotion of Health and Biomedical Research of Valencia Region; EUPAS: European Post-Authorisation Studies; GePARD: German Pharmacoepidemiological Research Database; GSK: GlaxoSmithKline; PHARMO: PHARMO Institute for Drug

Outcomes Research or PHARMO Data Network; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; SIDIAP: Information System for Research in Primary Care [Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària] Catalonia; SNDS: Système National des Données de Santé*;* THIN: The Health Improvement Network; PGRx: Pharmacoepidemiologic General Research eXtension*;* N/A: Not Applicable.

References

1. Hinman A. Eradication of vaccine-preventable diseases. *Annu Rev Public Health* 1999; **20**(20): 211-29.
2. European Centre for Disease Prevention. Vaccine-preventable diseases. 2023. https://www.ecdc.europa.eu/en/vaccine-preventable-diseases (accessed 18 April 2023).
3. Willame C, Henry O, Lin L, Vetter V, Baril L, Praet N. Pain caused by measles, mumps, and rubella vaccines: A systematic literature review. *Vaccine* 2017; **35**(42): 5551-8.
4. Weibel D, Sturkenboom M, Black S, de Ridder M, Dodd C, Bonhoeffer J, Vanrolleghem A, van der Maas N, Lammers GJ, Overeem S, Gentile A, Giglio N, Castellano V, Kwong JC, Murray BJ, Cauch-Dudek K, Juhasz D, Campitelli M, Datta AN, Kallweit U, Huang WT, Huang YS, Hsu CY, Chen HC, Giner-Soriano M, Morros R, Gaig C, Tio E, Perez-Vilar S, Diez-Domingo J, Puertas FJ, Svenson LW, Mahmud SM, Carleton B, Naus M, Arnheim-Dahlstrom L, Pedersen L, DeStefano F, Shimabukuro TT. Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines - Multi-country assessment. *Vaccine* 2018; **36**(41): 6202-11.
5. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, Wassilak SG. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994; **12**(6): 542-50.
6. European programme in Pharmacovigilance and Pharmacoepidemiology. 2023. https://www.eu2p.org/ (accessed 18 April 2023).
7. European Medicines Agency. Good pharmacovigilance practices 2023. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices (accessed 18 April 2023).
8. Council for International Organizations of Medical Scienes (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance); 2012.
9. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases, 2013.
10. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Annex I - Definitions (Rev 4), 2017.
11. WHO. Global vaccine safety blueprint 2.0 (GVSB2.0) 2021-2023, 2021.
12. WHO. Monitoring and responding to AESI: training slides COVID-19_VS_AESI. https://cdn.who.int/media/docs/default-source/covid-19-vaccines-safety-surveillance-manual/training-slides_covid-19_vs_aesi02927042-43ab-4449-b633-e203b1a1bf31_12ab4d79-31b5-4aff-b301-260d5e5dbe78.pdf (accessed 18 April 2023).

13. Council for International Organizations of Medical Scienes (CIOMS). Management of Safety Information from Clinical Trials, 2005.
14. WHO. COVID-19 VACCINES: SAFETY SURVEILLANCE MANUAL. MONITORING AND RESPONDING TO ADVERSE EVENTS OF SPECIAL INTEREST (AESIS), 2020.
15. Hahné S, Bollaerts, K., & Farrington, P. Vaccination Programmes: Epidemiology, Monitoring, Evaluation (1st ed.); 2021.
16. Klungel OH, Pottegard A. Strengthening international surveillance of vaccine safety. *BMJ* 2021; **374**: n1994.
17. Uppsala Monitoring Centre. About VigiBase. 2023. https://who-umc.org/vigibase/ (accessed 18 April 2023).
18. Centers for Disease Control and Prevention. Vaccine Adverse Event Reporting System (VAERS). https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html (accessed 18 APril 2023.
19. European Medicines Agency. EudraVigilance system overview. https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-system-overview (accessed 03 April 2023).
20. Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. *Drug Saf* 2006; **29**(5): 385-96.
21. Prevots DR, Sutter RW, Strebel PM, Weibel RE, Cochi SL. Completeness of reporting for paralytic poliomyelitis, United States, 1980 through 1991. Implications for estimating the risk of vaccine-associated disease. *Arch Pediatr Adolesc Med* 1994; **148**(5): 479-85.
22. Dodd C, Pacurariu A, Osokogu OU, Weibel D, Ferrajolo C, Vo DH, Becker B, Kors JA, Sturkenboom M. Masking by vaccines in pediatric drug safety signal detection in the EudraVigilance database. *Pharmacoepidemiol Drug Saf* 2018; **27**(11): 1249-56.
23. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf* 2002; **11**(1): 3-10.
24. 49. Elas M, Villatoro N, Pezzoli L. Disproportionality analysis of reported drug adverse events to assess a potential safety signal for pentavalent vaccine in 2019 in El Salvador. *Vaccine* 2021; **39**(34): 4849-55.
25. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf* 2009; **18**(6): 427-36.

26. Clothier HJ, Lawrie J, Russell MA, Kelly H, Buttery JP. Early signal detection of adverse events following influenza vaccination using proportional reporting ratio, Victoria, Australia. *PLoS One* 2019; **14**(11): e0224702.
27. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions, 2017.
28. Van Holle L, Tavares Da Silva F, Bauchau V. Signal detection based on time-to-onset: extending a new method from spontaneous reports to observational studies. *Pharmacoepidemiol Drug Saf.* 2014 Aug;23(8):849-58.
29. European Medicines Agency. Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU. 2014.
30. Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. *Pharmacoepidemiol Drug Saf* 2016; **25**(2): 215-22.
31. European Medicines Agency. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 10). 2010.
32. Center for Biologics Evaluation and Research. COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol. 2021. https://bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-Protocol-2021.pdf (accessed 03 April 2023).
33. Kulldorff M, Davis RL, Kolczak† M, Lewis E, Lieu T, Platt R. A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance. *Sequential Analysis* 2011; **30**(1): 58-78.
34. Lieu TA, Kulldorff M, Davis RL, Lewis EM, Weintraub E, Yih K, Yin R, Brown JS, Platt R, Vaccine Safety Datalink Rapid Cycle Analysis T. Real-time vaccine safety surveillance for the early detection of adverse events. *Med Care* 2007; **45**(10 Supl 2): S89-95.
35. Brown JS, Kulldorff M, Chan KA, Davis RL, Graham D, Pettus PT, Andrade SE, Raebel MA, Herrinton L, Roblin D, Boudreau D, Smith D, Gurwitz JH, Gunter MJ, Platt R. Early detection of adverse drug events within population-based health networks: application of sequential testing methods. *Pharmacoepidemiol Drug Saf* 2007; **16**(12): 1275-84.
36. Lee GM, Greene SK, Weintraub ES, Baggs J, Kulldorff M, Fireman BH, Baxter R, Jacobsen SJ, Irving S, Daley MF, Yin R, Naleway A, Nordin JD, Li L, McCarthy N, Vellozzi C, Destefano F, Lieu TA, Vaccine Safety Datalink P. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. *Am J Prev Med* 2011; **41**(2): 121-8.
37. Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, Kulldorff M, Lewis E, Fireman B, Daley MF, Klein NP, Weintraub ES. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine* 2011; **29**(46): 8279-84.

38. Yih WK, Kulldorff M, Sandhu SK, Zichittella L, Maro JC, Cole DV, Jin R, Kawai AT, Baker MA, Liu C, McMahill-Walraven CN, Selvan MS, Platt R, Nguyen MD, Lee GM. Prospective influenza vaccine safety surveillance using fresh data in the Sentinel System. *Pharmacoepidemiol Drug Saf* 2016; **25**(5): 481-92.
39. Yih WK, Kulldorff M, Fireman BH, Shui IM, Lewis EM, Klein NP, Baggs J, Weintraub ES, Belongia EA, Naleway A, Gee J, Platt R, Lieu TA. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink project. *Pediatrics* 2011; **127 Suppl 1**: S54-64.
40. Medicines and Healthcare products Regulatory Agency. Report of the Commission on Human Medicines Expert Working Group on COVID-19 vaccine safety surveillance. 2021. https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance (accessed 03 April 2023).
41. Sturkenboom M, Messina D, Paoletti O, de Burgos-Gonzalez A, García-Poza P, Huerta C, Llorente- García A, Martin-Perez M, Martinez M, Martin I, Overbeek J, Padros-Goossens M, Souverein S, Swart K, Klungel O, Gini R. Cohort monitoring of 29 Adverse Events of Special Interest prior to and after COVID-19 vaccination in four large European electronic healthcare data sources. Available on https://www.medrxiv.org/content/10.1101/2022.08.17.22278894v1.full.pdf. Accessed on June 2023.
42. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3). 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf (accessed 03 April 2023).
43. Medicines and Healthcare products Regulatory Agency. Report of the Commission on Human Medicines Expert Working Group on COVID-19 vaccine safety surveillance. 2021. Available on https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance. Accessed on June 2023.
44. Arlett P, Kjaer J, Broich K, Cooke E. Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. *Clin Pharmacol Ther* 2022; 111(1): 21-3.

45. Osokogu OU, Dukanovic J, Ferrajolo C, Dodd C, Pacurariu AC, Bramer WM, 'tJong G, Weibel D, Sturkenboom MC, Kaguelidou F. Pharmacoepidemiological safety studies in children: a systematic review. Pharmacoepidemiol Drug Saf. 2016 Aug;25(8):861-70.
46. Black S, Sturkenboom M, Bonhoeffer J, Destefano F, Shimabukuro T, Dodd C, De Ridder M, Weibel D, Gentile A, Giglio N, Mahmud S, Svenson L, Carleton B, Naus M, Kwong JC, Murray B, Dahlstrom LA, Pedersen L, Huang W-T, Goner-Soriano M, Perez-Vilar S, Lammers GJ, Overeem S, Datta A, Kallweit U. The Risk of Narcolepsy Following Receipt of Adjuvanted Pandemic 2009 The Subtype of Influenza A Virus (H1N1) Vaccines: Results of the SOMNIA Global Collaborative Study. *Open Forum Infectious Diseases* 2016; **3**(suppl_1).
47. Andrews N, Stowe J, Miller E, Svanstrom H, Johansen K, Bonhoeffer J, Hviid A, consortium V. A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark. *Vaccine* 2012; **30**(19): 3042-6.
48. Sturkenboom M, Braeye T, van der Aa L, Danieli G, Dodd C, Duarte-Salles T, Emborg HD, Gheorghe M, Kahlert J, Gini R, Huerta-Alvarez C, Martin-Merino E, McGee C, de Lusignan S, Picelli G, Roberto G, Tramontan L, Villa M, Weibel D, Titievsky L. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations. *Vaccine* 2020; **38 Suppl 2**: B8-B21.
49. ACCESS. Vaccine COVID-19 monitoring readiness. Available on: https://vac4eu.org/covid-19-vaccine-monitoring/. Accessed on June 2023.
50. Global Vaccine DataNetwork. https://www.globalvaccinedatanetwork.org/ (accessed 03 April 2023).
51. ADVANCE consortium. Blueprint of a framework to rapidly provide scientific evidence on post-marketing vaccination benefits and risks for informed decisions. WP7 – Implementability analysis. 2013. Available on https://vac4eu.org/wp-content/uploads/2019/02/D77Blueprint.pdf. Accessed on June 2023.
52. Dodd C, Andrews N, Petousis-Harris H, Sturkenboom M, Omer SB, Black S. Methodological frontiers in vaccine safety: qualifying available evidence for rare events, use of distributed data networks to monitor vaccine safety issues, and monitoring the safety of pregnancy interventions. *BMJ Glob Health* 2021; **6**(Suppl 2).
53. Coalition for Epidemic Preparedness Innovations (CEPI). Preparing for future pandemics. https://cepi.net/about/whyweexist/ (accessed 18 April 2023).
54. International Network of Special Immunization Services (INSIS). https://insisvaccine.org/ (accessed 18 April 2023).
55. Top KA, Chen RT, Levy O, Ozonoff A, Carleton B, Crawford NW, Creech CB, Kochhar S, Poland GA, Gutu K, Cutland CL. Advancing the Science of Vaccine Safety During the Coronavirus

Disease 2019 (COVID-19) Pandemic and Beyond: Launching an International Network of Special Immunization Services. *Clin Infect Dis* 2022; **75**(Suppl 1): S11-S7.

56. Arlegui H, Bollaerts K, Bauchau V, Nachbaur G, Begaud B, Praet N. Benefit-Risk Assessment of Vaccines. Part II: Proposal Towards Consolidated Standards of Reporting Quantitative Benefit-Risk Models Applied to Vaccines (BRIVAC). *Drug Saf* 2020; **43**(11): 1105-20.
57. Arlegui H, Bollaerts K, Salvo F, Bauchau V, Nachbaur G, Begaud B, Praet N. Benefit-Risk Assessment of Vaccines. Part I: A Systematic Review to Identify and Describe Studies About Quantitative Benefit-Risk Models Applied to Vaccines. *Drug Saf* 2020; **43**(11): 1089-104.
58. Center for biologics Evaluation and Research. Benefit-risk assessment for new drug and biological products. Guidance for Industry. 2021. Available on https://www.fda.gov/media/152544/download. Accessed on June 2023.
59. Funk PR, Yogurtcu ON, Forshee RA, Anderson SA, Marks PW, Yang H. Benefit-risk assessment of COVID-19 vaccine, mRNA (Comirnaty) for age 16-29 years. *Vaccine* 2022; **40**(19): 2781-9.
60. Bollaerts K, De Smedt T, Donegan K, Titievsky L, Bauchau V. Benefit-Risk Monitoring of Vaccines Using an Interactive Dashboard: A Methodological Proposal from the ADVANCE Project. *Drug Saf* 2018; **41**(8): 775-86.
61. Chen RT, Shimabukuro TT, Martin DB, Zuber PL, Weibel DM, Sturkenboom M. Enhancing vaccine safety capacity globally: A lifecycle perspective. *Vaccine* 2015; **33 Suppl 4**(0 4): D46-54.
62. European Medicines Agency. EMA pharmacovigilance system manual. Version 1.3. 2021. Available on: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-pharmacovigilance-system-manual_en.pdf (accessed 03 April 2023).
63. European Medicines Agency. EudraVigilance system overview https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-system-overview (accessed 18 April 2023).
64. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). 2017. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf (accessed 03 April 2023).
65. European Medicines Agency. ENCePP Work Plan 2009 (European Network for Centres of Pharmacoepidemiology and Pharmacovigilance) 2009.

66. European Medicines Agency. ENCePP Activity Report January – December 2021. 2021. https://www.encepp.eu/publications/documents/ENCePPActivityReport_2021.pdf (accessed 03 April 2023.
67. European Medicines Agency. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 10), 2010.
68. European Medicines Agency. ECDC and EMA collaborate on vaccine safety and effectiveness monitoring studies. 2022. https://www.ema.europa.eu/en/news/ecdc-ema-collaborate-vaccine-safety-effectiveness-monitoring-studies (accessed 03 April 2023).
69. European Medicines Agency. Gardasil9: Product Information. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/gardasil-9-epar-product-information_en.pdf (accessed 03 April 2023).
70. European Medicines Agency. Cervarix: EPAR. 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/cervarix (accessed 03 April 2023).
71. Buck CB, Day PM, Trus BL. The papillomavirus major capsid protein L1. *Virology* 2013; **445**(1-2): 169-74.
72. Nooraei S, Bahrulolum H, Hoseini ZS, Katalani C, Hajizade A, Easton AJ, Ahmadian G. Virus-like particles: preparation, immunogenicity and their roles as nanovaccines and drug nanocarriers. *J Nanobiotechnology* 2021; **19**(1): 59.
73. European Medicines Agency. Gardasil9: Risk management Plan Summary. https://www.ema.europa.eu/en/documents/rmp-summary/gardasil-9-epar-risk-management-plan-summary_en.pdf (accessed 03 April 2023).
74. European Medicines Agency. EMA commissions independent research to prepare for real-world monitoring of COVID-19 vaccines. 2020. https://www.ema.europa.eu/en/news/ema-commissions-independent-research-prepare-real-world-monitoring-covid-19-vaccines (accessed 18 April 2023).
75. Qiao YL, Wu T, Li RC, Hu YM, Wei LH, Li CG, Chen W, Huang SJ, Zhao FH, Li MQ, Pan QJ, Zhang X, Li Q, Hong Y, Zhao C, Zhang WH, Li YP, Chu K, Li M, Jiang YF, Li J, Zhao H, Lin ZJ, Cui XL, Liu WY, Li CH, Guo DP, Ke LD, Wu X, Tang J, Gao GQ, Li BY, Zhao B, Zheng FX, Dai CH, Guo M, Zhao J, Su YY, Wang JZ, Zhu FC, Li SW, Pan HR, Li YM, Zhang J, Xia NS. Efficacy, Safety, and Immunogenicity of an Escherichia coli-Produced Bivalent Human Papillomavirus Vaccine: An Interim Analysis of a Randomized Clinical Trial. *J Natl Cancer Inst* 2020; **112**(2): 145-53.
76. Food and Drug Administration. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. 2018. https://www.fda.gov/news-events/press-announcements/fda-

approves-expanded-use-gardasil-9-include-individuals-27-through-45-years-old (accessed 03 April 2023).

77. Food and Drug Administration. Gardasil9. 2020. https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9 (accessed 03 April 2023).
78. News release. Health Canada Approves GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant) for the Prevention of Oropharyngeal and Other Head and Neck Cancers. 2022. Available on: https://www.newswire.ca/news-releases/health-canada-approves-gardasil-r-9-human-papillomavirus-9-valent-vaccine-recombinant-for-the-prevention-of-oropharyngeal-and-other-head-and-neck-cancers-812857465.html. Accessed on June 2023.
79. Gardasil9. Product monograph. Available on: https://www.merck.ca/en/wp-content/uploads/sites/20/2021/04/GARDASIL_9-PM_E.pdf. Accessed on June 2023.
80. Innovative Medicines Initiative. ADVANCE - Europe's partnership for health. Available on: https://www.imi.europa.eu/projects-results/project-factsheets/advance. Accessed on June 2023.

Chapter 2: Background incidence rates for vaccine safety assessment

2.1 Incidence rates of autoimmune diseases in European healthcare databases: a contribution of the ADVANCE project

Corinne Willame, Caitlin Dodd, Lieke van der Aa, Gino Picelli, Hanne- Dorthe Emborg, Johnny Kahlert, Rosa Gini, Consuelo Huerta, Elisa Martín-Merino, Chris McGee, Simon de Lusignan, Giuseppe Roberto, Marco Villa, Daniel Weibel, Lina Titievsky, Miriam CJM Sturkenboom

Drug Safety, 2021; 44: 383-395.

Abstract

Introduction: The public-private ADVANCE collaboration developed and tested a system to generate evidence on vaccine benefits and risks using European (EU) electronic healthcare databases. In the safety of vaccines, background incidence rates are key to allow proper monitoring and assessment. The goals of this study were to compute age, sex and calendar year stratified incidence rates of 9 autoimmune diseases in 7 EU healthcare databases from 4 countries and to assess validity by comparing with published data.

Methods: Event rates were calculated for the following outcomes: Acute disseminated encephalomyelitis, Bell's palsy, Guillain-Barré syndrome, immune thrombocytopenia purpura, Kawasaki disease, optic neuritis, narcolepsy, systemic lupus erythematosus and transverse myelitis. Cases were identified by diagnosis codes. Participating organizations/databases originated from Denmark, Italy, Spain and United Kingdom. The source population comprised all persons registered, with at least one year of data prior to the study start, or follow-up from birth. Stratified incidence rates were computed per database over the period 2003 to 2014.

Results: Between 2003 and 2014, 148,947 incident cases of 9 autoimmune diseases were identified. Crude incidence rates were highest for Bell's palsy (23.8/100,000 PY, 95%CI: 23.6-24.1) and lowest for Kawasaki disease (0.7/100,000 PY, 95%CI: 0.6-0.7). Specific patterns were observed by sex, age, calendar time and data sources. Rates were comparable to published estimates.

Conclusion: A range of autoimmune events could be identified in the ADVANCE system. Estimation of rates indicated consistency across selected EU healthcare databases as well as consistency with US published data.

1. Introduction

The Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE) was a public-private consortium was launched by the Innovative Medicines Initiatives in 2013 to bring together stakeholders (ie. regulators, academics, and vaccine manufacturers) actively involved in the post-marketing monitoring of benefits and risks (B/R) of vaccines [1]. The aim of the ADVANCE project was to build an efficient system to generate robust evidence on background rates, vaccine coverage and ultimately, to assess rapidly B/R of vaccines using existing healthcare databases in Europe. ADVANCE has transitioned to the Vaccine Monitoring Collaboration for Europe that will implement the ecosystem [2]. In that context, several tools and methods have been developed to standardize ways of working among selected European (EU) healthcare databases. A description of the system and the methods/workflows can be found in the article by Sturkenboom et al [3].

With the entry of new vaccines to the market and their use at a large scale, rare adverse events not detected during clinical development phases may occur. Large sample sizes are required to rapidly evaluate suspected causal associations between rare adverse events such as autoimmune diseases and vaccines in a real-world setting. Preparedness to investigate safety signals and safety concerns is a necessary requirement of vaccination programs stipulated in the Vaccine Safety Blueprint [4]. Based on a stakeholder analysis in Europe, background rates are important from a regulatory, manufacturer and public health perspective [1]. Because of the mode of action of vaccines and the fact that adjuvants, which stimulate immune response, may be used, autoimmune diseases are often event of interest to monitor and investigate. This is especially relevant considering that they have age related patterns of onset that may coincide with age at vaccination. Moreover, autoimmune diseases are rare and because of possible impact of environmental factors on their occurrence [5-6], there is a constant need to generate up-to-date background incidence rates (IR). As part of being prepared to respond to signals, background rates are a crucial source of information in the assessment of suspected cases, especially during mass vaccination campaigns [7] or for continuous safety monitoring of vaccines in a growing recipient population [8].

As part of the database characterization efforts of the ADVANCE project, we estimated background IRs of 9 autoimmune diseases. We described and tried to explain heterogeneity among sources of data (e.g., hospital-based outcomes and/or primary care based), and compared them with external published data [9].

2. Methods

Setting

The ADVANCE project had access to 20 different data sources, seven of which could be used in this assessment, representing four countries: Denmark, Spain, Italy and the United Kingdom (**Table 1**). Detailed descriptions of these databases can be found in the **Supplementary File**.

All participating data sources extracted study data into a common data model (CDM). As described in Sturkenboom et al. [10], the CDM comprises three data files: population, events and vaccinations.

Table 1 Database characteristics

Country	**Denmark**	**Spain**	**Italy**			**UK**	
Name	AUH/SSI	BIFAP	PEDIANET	Val Padana	ARS	THIN	RCGP RSC
Type of organisation providing access	Different public data holders	Spanish Agency of Medicines and Medical Devices	Private organisation; vaccines from public health	Local public health agency	Regional public health agency	Academic License holder (Erasmus MC)	Charity
Origin of data	Hospital discharge diagnoses linked to population and vaccination registries. National health care	Family paediatricians and GP medical records	Family paediatricians medical records linked to Veneto vaccine register	Hospitalisation discharge diagnoses linked to population and vaccination registries	Hospitalisation discharge diagnoses linked to population and vaccination registries	GP medical records	GP medical records
Geographic spread	National	Multiregional 9 out of 17	Sample from Veneto Region	Regional, province	Tuscany Region	National sample	National sample
Data governance	Approval Danish Data Protection Agency posterior check	Protocol-based approval	Generic consent from parents collected once	Generic approval	Generic approval (monthly meeting, posterior check)	Protocol-based approval	Protocol-based approval

Age range covered	All	All	0-14 years	All	All	All	All
Disease diagnosis coding	ICD-10 Danish version	ICD-9, ICPC & text	ICD-9 and text	ICD-9	ICD-9	READv2	READCTV 3 & READv2
Type of outcomes covered	Emergency visits, hospitalisation, death	Primary care, incomplete specialist & hospitalisations only if GP enters	Primary care, incomplete specialist & hospitalisations only if FP enters	Only hospitalisations	Hospitalisations, emergency visits, death	Primary care, specialist & hospitalisations	Primary care, incomplete specialist & hospitalisations only if GP enters

FP= fingerprint (feasibility assessment), ICD= International Classification of Diseases, ICPC= International Classification of Primary Care, GP= General practitioners, MC= Medical Center

Population

The source population comprised all persons registered with at least one year of data prior to the start of the study period or follow-up from birth. Data for all individuals recorded in each database from the start of follow-up (defined as birth or first data availability, whichever was latest) until the end of follow-up (defined as the date at last data retrieval, leaving the database, the date of first event or death whichever date was earliest), were used to define the follow-up for database characterisation. The only eligibility criteria were that the date of birth, start and end of follow-up dates, and sex needed to be present. The study start date varied between databases, depending on when the database collection started, and ended in 2017 for all databases. Data access providers (DAPs) created a population file in the format of the CDM including patient identifier, date start follow-up, date end follow-up, birthdate and sex.

Events

The autoimmune diseases of interest were Acute Disseminated Encephalomyelitis (ADEM), Bell's palsy, Guillain-Barré syndrome (GBS), Immune Thrombocytopenia Purpura (ITP), Kawasaki disease, optic neuritis, narcolepsy, Systemic Lupus Erythematosus (SLE) and transverse myelitis. The outcomes were defined using definitions from the Brighton Collaboration and learned societies, the World Health Organisation or the European Centre for Disease prevention and Control. The case definitions were mapped to an initial list of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9), and tenth revision (ICD-10), Read, and the International Classification of Primary

Care (ICPC) codes using the ADVANCE Code mapper tool [11]. DAPs for each database were asked to modify and verify the proposed codes based on local coding habits and prior experience. Each DAP extracted the final list of codes for the specific events in their local terminology and transformed the data into the event file of the CDM containing the following fields: patient identifier, event type, date, original code (ICD-9/10, Read, ICPC or text). The event file was linked to the population file to calculate event IRs and to assess whether these rates were as expected by benchmarking rates within data source, between data sources and against published data. This assessment allowed us to demonstrate the appropriateness of the data processing steps used. The code list for each outcome of interest is available in the **Supplementary file (*Table S 1*)**. The ITP condition was defined according to narrow and broad concepts. Details on the harmonization process for data extraction are described elsewhere [10].

Data management and analyses

The DAPs extracted data from their database using the local data format and software, which were transformed into the ADVANCE CDM (CSV format). We used Jerboa data processing software, which is JAVA-based, for event code counting and incidence calculations. The Jerboa software has been used for multiple studies and is freely available. The script and instructions were sent to the DAPs, who ran the script against their input files and the outputs were sent through a secure file transfer protocol (File Zilla or HighTail) to a private remote research environment (PRRE) [10].

The event characterization included code counts by type of event and database and event IRs in the population by calendar year, sex and age. Age was categorized per year until 17 years old, from 18-24 years, and then in 5- year categories. We subsequently categorized age in 0-1, 2-4, 5-14, 15-24, 25-64, 65 and older for description, as this coincides with age of routine vaccination in general and because this categorization was compatible with the Post-licensure Rapid Immunization Safety Monitoring Programme (PRISM) [9] US database age categories, allowing for age-specific comparisons of incidence rates between the US and EU networks. For the incidence estimates calculated with Jerboa, there was a one-year run-in period for individuals aged 6 months onward, individuals with an entry date within 6 months of birth started their follow-up at birth. Events recorded in the one-year run-in prior to start

of follow-up were not considered and only first events recorded after the run-in period were considered to be incident. To have a comparable period of calendar time across databases, incidence rates were limited to calendar years 2003-2014. Healthcare databases were classified according to the type of data sources: general practitioners databases including Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP), The Health Improvement Network (THIN), Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) and Pedianet and hospitalization record linkage databases including Aarhus University Hospital (AUH)/ Staten Serum Institute (SSI), Agenzia regionale di sanità (ARS) and Val Padana. We calculated crude IRs as the number of incident events within the follow-up period divided by the total person-time at risk and 95% confidence intervals (CIs) using the Exact method for each event. IRs were expressed per 100,000 person-years (PY). We also computed yearly pooled IRs for each autoimmune disease to compare the type of data sources (general practitioners *versus* hospitalization record linkage) by using random effects model (Der Simonian-Laird method). Higgins I^2 statistics were measured to determine heterogeneity between type of data sources. Upon higher rates of narcolepsy observed in AUH/SSI, we conducted a post-hoc analysis to estimate age-stratified IRs of narcolepsy in Denmark over the study period. Data handling and computation of rates were performed in SAS 9.4, meta-analyses were conducted in Stata v14.0.

3. Results

Over the period 2003 to 2014, the total person-time of follow-up was more than 233 million person-years for the 7 EU healthcare databases. The largest contributions in follow-up was from AUH/SSI databases (30.9%), THIN (27.0%) and ARS (20.0%) (***Table 2***). The population aged between 15 to 64 years has most of the person-time represented in each database, except for Pedianet which only captures the pediatric population.

Table 2 Follow-up duration and number of autoimmune events for each database over the period 2003 to 2014

	Denmark	Italy			Spain	UK	
	AUH/SSI	ARS	Val Padana	Pedianet	BIFAP	RCGP RSC	THIN
Person-time (in years) per age groups and databases							

Overall	71,963,997	46,690,197	4,429,415	414,725	29,654,858	16,845,082	63,107,306
0-1 years	1,630,983	784,016	78,040	82,862	696,022	438,305	1,572,725
2-4 years	2,495,269	1,152,313	116,835	110,105	888,063	571,917	2,127,038
5-14 years	9,224,436	3,910,548	404,509	221,758	2,721,747	1,916,302	7,140,915
15-24 years	10,413,928	3,951,513	382,907	-	4,936,428	1,945,611	6,908,561
25-44 years	19,350,418	13,002,241	1,177,745	-	9,343,807	4,601,269	17,333,183
45-64 years	17,953,083	12,977,224	1,247,063	-	6,829,082	4,454,574	17,064,552
65+ years	10,895,877	10,912,341	1,022,316	-	4,239,709	2,917,103	10,960,332
Total number of incident events databases for each autoimmune disease							
Autoimmune diseases							
ADEM	3,866	5,521	527	6	619	353	601
Bell's Palsy	14,087	2,758	130	24	12,542	4,194	18,398
GBS	1,711	1,085	109	<5	321	257	1,021
ITP (broad definition)	10,020	8,970	474	11	14,796	3,447	9,923
ITP (narrow definition)	3,775	872	63	7	484	639	2,536
Kawasaki disease	412	420	12	30	47	123	407
Narcolepsy	1,333	144	7	<5	201	132	549
Optic neuritis	2,982	1,048	72	<5	694	533	2,163
SLE	3,526	1,438	151	<5	1,985	1,078	3,477
Transverse myelitis	678	144	12	<5	<5	213	783

ADEM: Acute disseminated encephalomyelitis, GBS: Guillain Barré syndrome, ITP: Immune Thrombocytopenia Purpura, SLE: Systemic Lupus Erythematosus

Between 2003 and 2014, there were 148,947 incident cases of 9 predefined autoimmune diseases. Of the 9 individual autoimmune diseases, the crude IR of Bell's palsy was the highest (23.8/100,000 PY, 95%CI: 23.6-24.1), followed by ITP broad definition (21.7/100,000 PY, 95%CI: 21.6-22.0), SLE (5.3/100,000 PY, 95%CI: 5.2-5.4), ADEM (5.3/100,000 PY, 95%CI: 5.2-5.3), ITP narrow definition (3.8/100,000 PY, 95%CI: 3.7-3.9), optic neuritis (3.4/100,000 PY, 95%CI: 3.3-3.5), GBS (2.1/100,000 PY, 95%CI: 2.0-2.1), narcolepsy (1.1/100,000 PY, 95%CI: 1.0-1.1), transverse myelitis (1.0/100,000 PY, 95%CI: 0.9-1.0) and Kawasaki disease (0.7/100,000 PY, 95%CI: 0.6-0.7). The sex specific crude IRs of several autoimmune diseases were higher in females than in males (***Table 3***), the most pronounced was SLE with an IR of 8.5/100,000 PY in females and 2.1/100,000 in males. Age- and sex specific crude IRs are presented for each database in **Supplementary file, *Table S 2***.

Table 3 Crude incidence rates (/100,000 PY) per sex for each autoimmune disease

Autoimmune diseases	IR (95%CI) per 100,000 PY	
	Female	Male
ADEM	6.14 (6.00-6.29)	4.31 (4.19-4.44)
Bell's Palsy	23.82 (23.54-24.11)	23.86 (23.57-24.15)
GBS	1.74 (1.66-1.82)	2.39 (2.30-2.48)
ITP (broad definition)	20.47 (20.20-20.73)	23.11 (22.83-23.40)

ITP (narrow definition)	3.95 (3.84-4.07)	3.69 (3.57-3.80)
Kawasaki disease	0.52 (0.47-0.56)	0.81 (0.76-0.87)
Narcolepsy	1.12 (1.06-1.19)	1.04 (0.98-1.10)
Optic neuritis	4.42 (4.29-4.54)	2.39 (2.29-2.48)
SLE	8.47 (8.30-8.65)	2.05 (1.97-2.14)
Transverse myelitis	1.10 (1.03-1.17)	0.83 (0.77-0.89)

ADEM: Acute disseminated encephalomyelitis, GBS: Guillain Barré syndrome, ITP: Immune Thrombocytopenia Purpura, SLE: Systemic Lupus Erythematosus

Age-stratified incidence rates per database

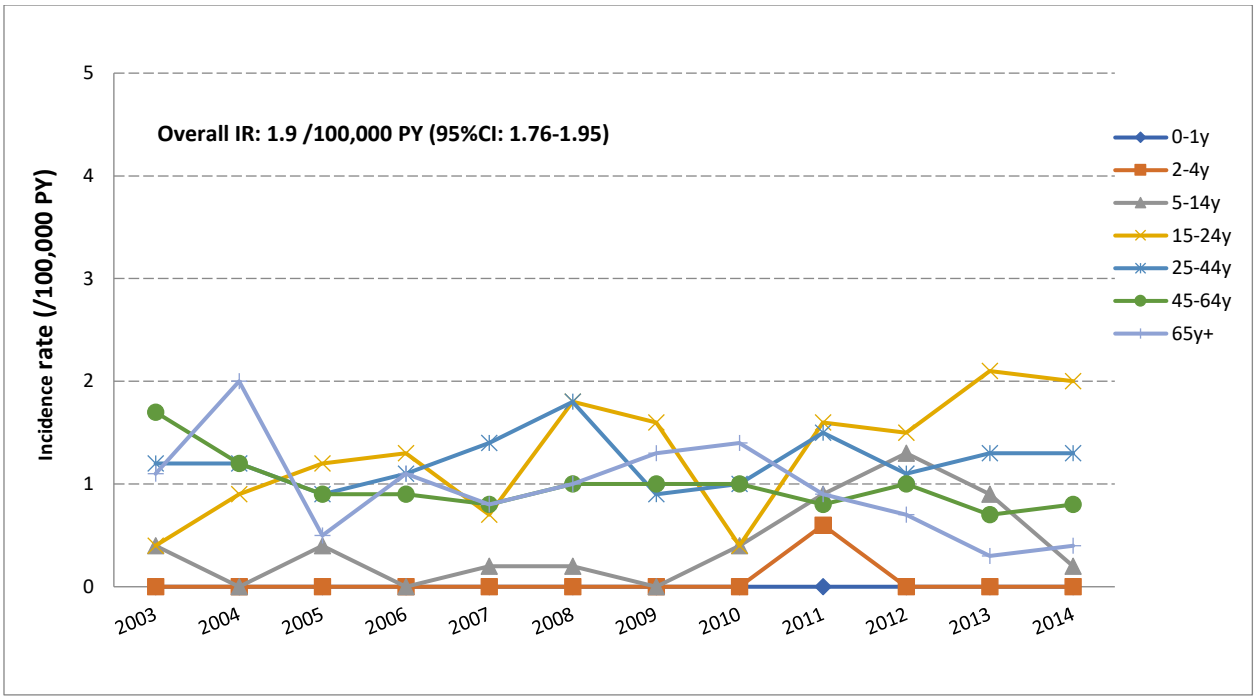
Overall and age-stratified IRs are presented in ***Table 4***. We observed that the age patterns differ across different autoimmune diseases: IRs increased with increasing age for Bell's palsy, GBS and SLE. The narrow definition of ITP shows the highest rates in the age group 0-4 years. This rate decreased in children aged between 5 to 24 years and increased by age from the age of 25 years. A similar pattern with a higher magnitude of rates was observed using the ITP broad definition. In the elderly (65+) IRs ranged between 22 to 64/100,000 PY, except in BIFAP where IRs peaked at 130/100,000 PY. IRs for narcolepsy were low (≤ 1/100,000 PY), but slightly higher rates were observed in the Danish database. In Denmark, the IR for narcolepsy was as high as 3.1/100,000 PY in the 15-24 age group. A specific analysis of this age group per calendar year in AUH/SSI database showed that IRs increased at the beginning of the study period and tended to level out during the period 2008-2012, potentially followed by a slight increase towards the end of the study period (***Figure 1***). The pattern of IRs for optic neuritis was similar across databases, increasing by age and peaking in the 25-44 age group, except in the BIFAP database where a constant increase by age was observed. Although no clear pattern was observed for ADEM, IRs peaked in the 25-44 age group in both record linkage Italian databases (ARS and ASCLR). The pattern of IRs for Kawasaki disease was similar across databases with most of the events occurring before the age of 14 years. IRs for transverse myelitis varied from 0.0 to 2.2/100,000 PY; no events were reported in the BIFAP and Pedianet databases.

Table 4 Crude incidence rates (/100,000 PY) for each autoimmune disease per age groups and databases over the period 2003-2014

		Italy			Denmark	Spain	UK		EU	US
		ARS	Val Padana	Pedianet	AUH/SSI	BIFAP	RCGP	THIN	ADVANCE	PRISM
Health Outcome	Age Groups	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR
Acute disseminated encephalomyelitis	0-1y	6.8 (5.14-	1.4 (0.20-	1.2 (0.17-	4.5 (3.6-5.6)	1.3 (0.67-	0.8 (0.25-	0.6 (0.28-	2.86 (2.43-	1
	2-4y	5.8 (4.54-	4.8 (2.01-	1.0 (0.14-	3.8 (3.1-4.6)	0.2 (0.06-	1.2 (0.55-	1.2 (0.79-	2.71 (2.35-	1
	5-14y	4.2 (3.58-	2.8 (1.50-	1.9 (0.73-	2.0 (1.8-2.4)	0.7 (0.47-	1.3 (0.83-	0.7 (0.52-	1.79 (1.63-	1
	15-24y	12.1	10.1 (7.23-	.	2.5 (2.3-2.8)	0.8 (0.56-	1.6 (1.06-	1.0 (0.76-	3.10 (2.90-	1
	25-44y	20.2	22.9	.	6.7 (6.3-7.0)	1.2 (1.01-	3.1 (2.57-	1.1 (0.96-	6.99 (6.79-	2
	45-64y	15.0	14.4	.	7.1 (6.7-7.5)	2.2 (1.87-	2.9 (2.42-	1.2 (1.08-	6.31 (6.11-	3
	65y+	8.6 (8.02-	8.6 (6.86-	.	6.4 (5.9-6.8)	6.8 (6.02-	2.5 (1.97-	0.9 (0.77-	5.34 (5.11-	6
	Overall	13.5	13.4	2.1 (1.93-	5.4 (5.2-5.5)	2.1 (1.93-	2.4 (2.19-	1.0 (0.96-	5.25 (5.15-	-
Bell's palsy	0-1y	4.7 (3.34-	5.7 (2.15-	3.7 (1.19-	8.1 (6.82-	14.8 (12.20-	3.2 (1.79-	3.5 (2.69-	6.76 (6.08-	22
	2-4y	5.5 (4.20-	3.9 (1.45-	3.9 (1.45-	8.1 (7.09-	8.9 (7.14-	7.6 (5.47-	5.8 (4.86-	7.05 (6.45-	17
	5-14y	6.5 (5.66-	6.4 (4.26-	8.2 (5.11-	10.4 (9.81-	19.3 (17.68-	12.3	13.8 (12.94-	11.83	24
	15-24y	3.2 (2.67-	1.5 (0.62-	.	12.2 (11.56-	35.2 (33.53-	22.9	26.5 (25.25-	19.06	40
	25-44y	4.9 (4.48-	2.1 (1.37-	.	21.6 (20.96-	42.3 (40.97-	29.7	33.7 (32.84-	24.90	90
	45-64y	6.9 (6.41-	2.8 (1.99-	.	24.3 (23.60-	51.3 (49.66-	36.7	40.1 (39.16-	28.83	121
	65y+	10.5 (9.82-	4.6 (3.36-	.	27.5 (26.49-	62.9 (60.52-	39.0	41.8 (40.59-	31.13	174
	Overall	6.7 (6.47-	3.3 (2.79-	6.1 (4.11-	19.6 (19.28-	42.4 (41.62-	28.9	32.1 (31.65-	23.84	-
Guillain-Barré Syndrome	0-1y	1.0 (0.47-	0.0	0.0	0.4 (0.17-	0.4 (0.14-	0.8 (0.25-	0.4 (0.19-	0.50 (0.34-	2
	2-4y	1.7 (1.03-	0.0	1.9 (0.48-	1.0 (0.68-	0.5 (0.17-	1.2 (0.55-	1.0 (0.67-	1.05 (0.84-	2
	5-14y	0.9 (0.64-	1.1 (0.42-	0.0	0.7 (0.51-	0.5 (0.28-	0.5 (0.24-	0.6 (0.48-	0.66 (0.57-	2
	15-24y	1.5 (1.14-	1.2 (0.45-	.	1.2 (0.99-	0.5 (0.33-	1.0 (0.59-	1.0 (0.76-	1.03 (0.92-	3
	25-44y	1.7 (1.47-	1.8 (1.14-	.	2.0 (1.83-	1.0 (0.77-	1.4 (1.08-	1.3 (1.15-	1.57 (1.47-	6
	45-64y	3.1 (2.79-	2.8 (1.99-	.	3.4 (3.12-	1.6 (1.36-	2.2 (1.74-	2.3 (2.12-	2.73 (2.60-	12
	65y+	4.5 (4.14-	5.7 (4.32-	.	4.6 (4.19-	1.8 (1.43-	3.4 (2.75-	3.2 (2.86-	3.84 (3.65-	23
	Overall	2.6 (2.49-	2.8 (2.30-	0.5 (0.13-	2.4 (2.27-	1.1 (0.97-	1.8 (1.57-	1.8 (1.67-	2.06 (2.00-	-
ITP (broad)	0-1y	26.5	22.9	2.5 (0.62-	22.3 (20.08-	29.3 (25.56-	15.5	14.5 (12.63-	20.77	9
	2-4y	26.1	28.0	1.9 (0.48-	14.9 (13.47-	20.6 (17.84-	14.9	11.1 (9.69-	16.22	9
	5-14y	10.6 (9.56-	6.7 (4.49-	3.4 (1.61-	5.3 (4.85-	15.8 (14.38-	4.6 (3.68-	5.1 (4.59-	7.15 (6.82-	5
	15-24y	8.7 (7.73-	3.3 (1.81-	.	4.9 (4.58-	22.9 (21.63-	9.8 (8.42-	6.3 (5.72-	9.31 (8.95-	6
	25-44y	9.5 (8.95-	6.5 (5.15-	.	7.9 (7.49-	30.2 (29.11-	13.9	9.5 (9.07-	12.39	9
	45-64y	19.9	11.7 (9.81-	.	15.9 (15.37-	66.4 (64.50-	24.2	17.7 (17.01-	23.76	12
	65y+	47.5	22.0	.	35.7 (34.63-	130.3	64.0	45.5 (44.17-	53.30	31
	Overall	21.9	12.1	2.8 (1.56-	13.9 (13.66-	50.0 (49.17-	23.8	17.3 (16.92-	21.76	-
ITP (narrow)	0-1y	5.8 (4.29-	4.3 (1.39-	1.2 (0.17-	13.6 (11.93-	4.6 (3.25-	7.9 (5.52-	8.4 (7.04-	9.00 (8.21-	9
	2-4y	8.1 (6.52-	7.7 (3.85-	1.0 (0.14-	11.6 (10.32-	3.8 (2.74-	10.4 (7.92-	9.6 (8.34-	9.26 (8.58-	9
	5-14y	3.2 (2.64-	1.7 (0.75-	2.4 (1.01-	3.6 (3.24-	1.4 (1.05-	3.0 (2.25-	3.7 (3.29-	3.25 (3.03-	5
	15-24y	1.3 (0.99-	0.6 (0.15-	.	2.6 (2.28-	1.0 (0.77-	2.8 (2.06-	2.3 (1.96-	2.05 (1.89-	6
	25-44y	1.0 (0.82-	0.5 (0.20-	.	3.3 (3.05-	1.1 (0.95-	3.0 (2.54-	2.6 (2.33-	2.28 (2.16-	9
	45-64y	1.6 (1.35-	1.1 (0.62-	.	4.7 (4.43-	1.4 (1.11-	3.7 (3.11-	3.7 (3.39-	3.26 (3.12-	12
	65y+	3.2 (2.84-	3.0 (2.06-	.	10.8 (10.18-	3.0 (2.56-	8.1 (7.02-	8.6 (8.08-	7.09 (6.83-	31
	Overall	2.1 (1.99-	1.6 (1.25-	1.8 (0.85-	5.3 (5.08-	1.6 (1.49-	4.4 (4.07-	4.4 (4.24-	3.82 (3.74-	-
Kawasaki	0-1y	28.3	8.6 (3.86-	22.2	7.3 (6.10-	2.2 (1.30-	10.8 (7.95-	8.1 (6.72-	10.28 (9.43-	32
	2-4y	13.8	2.9 (0.93-	9.7 (5.20-	5.9 (5.05-	2.0 (1.28-	7.6 (5.47-	9.6 (8.34-	7.72 (7.09-	35
	5-14y	2.0 (1.59-	0.8 (0.27-	1.0 (0.24-	1.2 (0.78-	0.4 (0.22-	2.2 (1.58-	1.3 (1.06-	1.31 (1.17-	15
	15-24y	0.1 (0.06-	0.0	.	0.1 (0.04-	0.0 (0.00-	0.5 (0.24-	0.1 (0.06-	0.11 (0.08-	-
	25-44y	0.0 (0.01-	0.0	.	0.1 (0.02-	0.0 (0.00-	0.0 (0.00-	0.0 (0.01-	0.03 (0.02-	-
	45-64y	0.0 (0.00-	0.0	.	0.1 (0.05-	0.0 (0.00-	0.0	0.0 (0.01-	0.03 (0.02-	-
	65y+	0.0 (0.01-	0.0	.	0.1 (0.02-	0.0	0.0	0.0 (0.02-	0.03 (0.02-	-
	Overall	1.0 (0.93-	0.3 (0.17-	7.7 (5.36-	0.6 (0.52-	0.2 (0.12-	0.8 (0.71-	0.7 (0.64-	0.66 (0.63-	-
Narcolepsy	0-1y	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1
	2-4y	0.2 (0.05-	0.0	1.0 (0.14-	0.5 (0.27-	0.0	0.0	0.1 (0.01-	0.23 (0.14-	1
	5-14y	0.4 (0.22-	0.8 (0.27-	0.5 (0.07-	0.8 (0.63-	0.2 (0.10-	0.4 (0.16-	0.4 (0.27-	0.53 (0.45-	4
	15-24y	0.4 (0.26-	0.3 (0.04-	.	3.1 (2.78-	0.7 (0.49-	1.4 (0.96-	1.3 (1.05-	1.77 (1.61-	24
	25-44y	0.3 (0.19-	0.0	.	2.5 (2.29-	1.0 (0.82-	1.3 (1.02-	1.2 (1.05-	1.40 (1.31-	38
	45-64y	0.3 (0.24-	0.2 (0.05-	.	1.6 (1.38-	0.7 (0.53-	0.8 (0.59-	1.0 (0.83-	0.97 (0.89-	31
	65y+	0.5 (0.35-	0.1 (0.02-	.	1.5 (1.27-	0.4 (0.29-	0.7 (0.42-	1.0 (0.78-	0.89 (0.80-	27
	Overall	0.4 (0.30-	0.2 (0.09-	0.5 (0.13-	1.9 (1.76-	0.7 (0.59-	0.9 (0.77-	1.0 (0.88-	1.08 (1.04-	-
Optic neuritis	0-1y	0.01 (0.02-	0.0	0.0	0.0	0.1 (0.02-	0.0	0.0	0.04 (0.01-	2

		Italy			Denmark	Spain	UK		EU	US
		ARS	Val Padana	Pedianet	AUH/SSI	BIFAP	RCGP	THIN	ADVANCE	PRISM
Health Outcome	Age Groups	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR
	2-4y	0.2 (0.05-	0.0	0.0	0.2 (0.08-	0.0	0.2 (0.03-	0.2 (0.08-	0.17 (0.10-	3
	5-14y	1.6 (1.26-	0.6 (0.14-	0.0	0.8 (0.63-	0.6 (0.39-	0.9 (0.55-	0.8 (0.57-	0.88 (0.77-	8
	15-24y	3.2 (2.62-	1.5 (0.62-	.	3.8 (3.47-	2.1 (1.74-	2.4 (1.75-	3.4 (2.95-	3.21 (3.00-	16
	25-44y	3.6 (3.32-	3.6 (2.61-	.	7.6 (7.19-	2.3 (2.04-	6.3 (5.52-	7.2 (6.77-	5.77 (5.58-	37
	45-64y	2.5 (2.25-	1.1 (0.62-	.	4.6 (4.30-	3.0 (2.62-	4.6 (3.95-	3.7 (3.44-	3.67 (3.53-	43
	65y+	1.8 (1.52-	1.7 (1.01-	.	1.9 (1.71-	3.5 (2.99-	2.1 (1.59-	1.8 (1.54-	2.04 (1.90-	52
	Overall	2.6 (2.40-	1.8 (1.46-	0.0	4.1 (4.00-	2.3 (2.17-	3.7 (3.37-	3.8 (3.60-	3.42 (3.34-	-
Systemic lupus erythematosus	0-1y	1.0 (0.47-	0.0	1.2 (0.17-	0.9 (0.55-	0.4 (0.14-	0.8 (0.25-	0.6 (0.33-	0.76 (0.55-	1
	2-4y	0.4 (0.15-	1.0 (0.14-	0.0	0.1 (0.02-	0.2 (0.06-	0.0	0.2 (0.08-	0.19 (0.11-	0.3
	5-14y	0.9 (0.61-	1.1 (0.42-	0.5 (0.07-	0.8 (0.64-	1.1 (0.77-	0.2 (0.06-	0.6 (0.44-	0.75 (0.65-	2
	15-24y	2.5 (2.02-	1.2 (0.45-	.	2.5 (2.24-	4.3 (3.77-	2.8 (2.11-	3.1 (2.71-	2.99 (2.79-	16
	25-44y	4.2 (3.87-	4.9 (3.74-	.	5.8 (5.43-	9.2 (8.62-	8.7 (7.87-	7.1 (6.70-	6.53 (6.33-	45
	45-64y	4.2 (3.84-	4.6 (3.45-	.	7.3 (6.91-	9.1 (8.43-	11.5	8.8 (8.36-	7.55 (7.33-	53
	65y+	3.6 (3.25-	4.5 (3.27-	.	6.9 (6.39-	6.0 (5.27-	9.3 (8.22-	7.3 (6.82-	6.18 (5.94-	40
	Overall	3.5 (3.32-	3.9 (3.28-	0.5 (0.13-	4.9 (4.74-	6.7 (6.40-	7.4 (7.00-	6.0 (5.85-	5.32 (5.23-	-
Transverse myelitis	0-1y	0.0	0.0	0.0	0.1 (0.01-	.	0.3 (0.04-	0.6 (0.28-	0.23 (0.13-	0.2
	2-4y	0.0	1.9 (0.48-	0.0	0.2 (0.11-	.	0.8 (0.31-	0.9 (0.55-	0.47 (0.33-	0.2
	5-14y	0.1 (0.01-	0.0	0.0	0.2 (0.15-	.	0.7 (0.37-	0.6 (0.44-	0.34 (0.27-	0.2
	15-24y	0.3 (0.13-	0.3 (0.04-	.	0.6 (0.43-	.	1.1 (0.68-	0.9 (0.70-	0.64 (0.55-	0.3
	25-44y	0.4 (0.27-	0.0	.	1.3 (1.14-	.	2.2 (1.82-	2.0 (1.83-	1.36 (1.26-	1
	45-64y	0.5 (0.36-	0.5 (0.19-	.	1.4 (1.20-	.	1.6 (1.21-	1.6 (1.44-	1.23 (1.14-	1
	65y+	0.4 (0.29-	0.4 (0.17-	.	0.9 (0.74-	.	1.2 (0.84-	0.9 (0.69-	0.76 (0.67-	1
	Overall	0.4 (0.30-	0.3 (0.17-	0.0	0.9 (0.74-	.	1.5 (1.28-	1.4 (1.27-	0.97 (0.92-	-

Figure 1 Incidence rates for narcolepsy in AUH/SSI database per age group and calendar year



Incidence rates over calendar years according to the type of data sources

Yearly pooled IRs of autoimmune diseases were stable over time but differed by type of data source for some diseases (***Figure S1 in Supplementary file***). IRs of ADEM and GBS were higher in hospital based record linkage databases than in primary care databases. On the contrary, IRs of Bell's palsy, ITP narrow, Kawasaki, SLE and transverse myelitis were higher in primary care databases.

4. Discussion

In this study, we estimated age, sex and calendar time specific background rates of 9 autoimmune diseases of interest for vaccine safety assessment from 7 EU electronic healthcare databases. We demonstrated that the ADVANCE system could detect age specific patterns and differences in IRs by the origin of information (e.g. hospital or GPs) as well as sex. IRs were fairly stable over time for each disease, showing that identification or recording was not modified during the study period. The age-dependent patterns are important to know for calculation of observed versus expected cases, as some of the age categories in which rates increase coincide with the age of vaccination. The ADVANCE tools allowed for rapid estimation of the rates by age, calendar time and sex. Overall, IRs from the ADVANCE system were of a lower magnitude than rates generated through the US PRISM system, which covers claims based diagnoses from outpatients, emergency units and hospitalization. Age specific patterns were similar for most of the autoimmune diseases: ADEM, Bell's palsy, GBS, narcolepsy, optic neuritis, SLE and transverse myelitis. IRs for ITP narrow definition matched rates from the US PRISM system more closely than those for the ITP broad definition. For both systems, PRISM and ADVANCE, we observed the highest rates for Kawasaki disease in children less than 4 years of age. The female predominance in SLE is also consistent with recent published literature [12], with female-male ratio for SLE ranging from 4:1 to 9:1 which is aligned with our observation (4:1). In all databases, IRs for optic neuritis peaked between the age 25 and 44 years decreasing thereafter, except in BIFAP where we observed a constant increase by age. Estimates of the incidence of optic neuritis have been published from Barcelona [13], another region in Spain for which data are not captured in BIFAP. The data from Barcelona also confirmed the peak of IRs for optic neuritis in the age group 20 to 40 years over the period from 2008 to 2012. The reason for this variation in rates for optic neuritis between BIFAP and

the other databases in ADVANCE is unknown. The ICPC code that was used is specific for optic neuritis but this code may be used in clinical practice to code suspected conditions as a reason for referral to specialist allowing for testing, diagnosis and confirmation. IRs for narcolepsy were low and stable over time ≤ 1/100,000 PY, except in Denmark where the rate of narcolepsy diagnosis were slightly elevated and showed periods with increase in persons between 15 and 24 years. However, an increase of incidence of narcolepsy in Denmark was already observed before, and happened prior to the administration of influenza A(H1N1)pdm09 pandemic vaccine which has been associated with increases in the IR of narcolepsy in Finland, Norway, Ireland and Sweden [14, 15], but not in countries with low vaccine coverage [16].

Comparisons of our data to the US PRISM system showed similar age patterns in IRs [10]. Rates from PRISM, which is based on US claims data were generally higher than the rates we observed in Europe. This may have several causes: coverage of outpatient specialist diagnoses, inclusion of prevalent cases, general higher disease rates or care seeking behavior. With regards to EU published data, high similarities in rate patterns have been observed for most of the diseases such as Bell's palsy or GBS [7], Kawasaki disease [17, 18] or narcolepsy [16]. Nevertheless, no direct comparison could be made for several reasons: no overlapping in age strata, ascertainment methods used, diverse sources of data and their geographical location. Overall, this benchmark provides reassurance about external validity. We demonstrated that all the participating databases provide crude rates consistent with expectations. However, our pooled crude rates should be interpreted with caution because these rates were not adjusted for any relevant covariates, nor weighted by the data sources with largest person-time contribution and should only be used in the context of each individual DAP's results. Misclassification of incidence as prevalence may occur due to differences in health care provision as some diagnoses are made in primary care, whereas others may lead to hospitalization, and most of the databases do not capture all health care sites. Our analysis by type of data sources highlights the specific process of diagnosis of autoimmune diseases. The quantification of these differences is important to realize when designing a specific study and may profit from the component strategy

introduced in the ADVANCE project for this purpose [19]. Background rates of adverse events of special interest following immunization are always needed to conduct observed/expected analyses [7, 20], to understand burden of disease of adverse events [21] or in cost-evaluation of vaccine implementation [22].

5. Conclusion

The study demonstrated that the EU ADVANCE system can identify specific autoimmune events, that age, sex and time specific rates can be generated based on available tools and that the incidence rates are mostly consistent across selected EU healthcare databases. Some variations were observed according to the type of care that is captured in the data sources.

REFERENCES

1. Sturkenboom M, Bahri P, Chiucchiuini A, Grove Krause T, Hahne S, Khromava A, et al. Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines. *Vaccine.* 2019; https://doi.org/10.1016/j.vaccine.2019.07.081.
2. Vaccine monitoring Collaboration for Europe. VAC4EU 2019. https://vac4eu.org/.
3. Sturkenboom M, van der Aa L, Bollaerts K, Emborg HD, Ferreira G, Gino R, et al. The ADVANCE distributed network system for evidence generation on vaccines coverage, benefits and risks based on electronic health care data. *Vaccine* (Supplement). 2019.
4. Giesecke J, Kramarz P, Kokki M for the ADVANCE project team. Blueprint of a framework to rapidly provide scientific evidence on post-marketing vaccination benefits and risks for informed decisions. WP7- Implementability analysis. V2.0. ADVANCE Consortium. 2018. https://vac4eu.org/wp-content/uploads/2019/02/D77Blueprint.pdf.
5. Shukla S, Singh G, Ahmad S, Pant P. Infections, genetic and environmental factors in pathogenesis of autoimmune thyroid diseases. *Microbial Pathogenesis.* 2018; (116): 279-288.
6. Jorg S, Grohme D, Erzler M, Binsfeld M, Haghikia A, Muller D, et al. Environmental factors in autoimmue diseases and their role in multiple sclerosis. *Cell Mol Life Sci.* 2016; (73): 4611-4622.
7. Black S, Eskola J, Siegrist CA, Halsey N, MacDonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandemic H1N1 influenza vaccines. *Lancet.* 2009; (374):2115-22.
8. Kurz X, Domergue F, Slattery J, Segec A, Szmigiel A, Hidalgo-Simon A. Safety monitoring of influenza A/H1N1 pandemic vaccines in EudraVigilance. *Vaccine.* 2011; (29): 4378-4387.
9. Baker M, Nguyen M, Cole D, Lee G, Lieu T. Post-licensure rapid immunization safety monitoring program (PRSIM) data characterization. *Vaccine.* 2013; (31S): K98-K112.
10. Sturkenboom M, Braeye T, van der Aa L, Becker B, Berensci K, Danieli G, et al. ADVANCE database characterization and fit for purpose assessment for multi-country studies on the coverage, benefits and risks for pertussis vaccinations. *Vaccine* (Supplement). 2019.
11. Becker B, Avillach P, Romio S, van Mulligen E, Weibel D, Sturkenboom M, Kors J for the ADVANCE consortium. CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project. *Pharmacoepidemiol Drug Saf.* 2017; (26): 998-1005.
12. Ji J, Sundquist J, Sundquist K. Gender-specific incidence of autoimmune diseases from national registers. *Journal of Autoimmunity.* 2016; (69): 102-106.

13. Martinez-Lapiscina E, Fraga-Pumar E, Pastor X, Gomez M, Conesa A, Lozano-Rubi R, et al. Is the incidence of optic neuritis rising? Evidence from an epidemiological study in Barcelona (Spain), 2008-2012. *J Neurol.* 2014;(261): 759-767.
14. Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. *Vaccine.* 2013; (31): 1246-1254.
15. O'Flanagran D, Barret AS, Foley M, Cotter S, Bonner C, Crowe C et al. Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010. *Euro Surveill.* 2014; (19):17.
16. Dodd C, de Ridder M, Huang WT, Weibel D, Giner-Soriano M, Perez-Vilar S et al. Incidence rates of narcolepsy diagnoses in Taiwan, Canada, and Europe: The use of statistical simulation to evaluate methods for the rapid assessment of potential safety issues on a population level in the SOMNIA study. *Plos One.* 2018; (13):10: e0204799.
17. Hall G, Tulloh L, Tilloh R. Kawasaki disease incidence in children and adolescents: an observational study in primary care. *Br J Gen Pract*. 2018; e271.
18. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: surveillance from national hospitalization records. *Eur J Pediatr*. 2017; (176): 1061-1065.
19. Gini R, Dodd CN, Bollaerts K, Bartolini C, Roberto G, Huerta-Alvarez C, et al. Quantifying outcome misclassification in multi-database studies: The case study of pertussis in the ADVANCE project. *Vaccine*. 2019. doi:10.1016/j.vaccine.2019.07.045
20. Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. *Pharmacoepidemiol Drug Saf. 2016;* (25:2), 215-222.
21. Mac Donald S, Nijsten D, Bollaerts K, Bauwens J, Praet N, van der Sande M, et al. Methodology for computing the burden of disease of adverse events following immunization. *Pharmacoepidemiol Drug Saf.* 2018; 1-7.
22. Van Hoek A, Choi YH, Trotter C, Miller E, Jit M. The cost-effectiveness of a 13-valent pneumococcal conjugate vaccination for infants in England. *Vaccine* 2012: 30: 7205-7213.

Supplementary materials

Detailed descriptions of the characterisation of the seven European electronic healthcare databases analysed

Denmark

Aarhus University Hospital (AUH) holds a record linkage database that links clinical and prescription data for the 1.8 million inhabitants of the Central Denmark and North Denmark Regions (formerly North-Jutland, Aarhus, Ringkjoebing and Viborg counties). These data are linked to the national registry of information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures, as well as national vaccination, hospital treatments, prescription and reimbursement registries. This data source has been used for numerous pharmaco-epidemiological studies, but not many vaccine-related studies. AUH has vaccination data available from 2003.

The Staten Serum Institute (SSI) has a direct access to the Danish Civil and Health Registration System database via an *ad hoc* linkage between the Danish Civil Registration system, the Danish Vaccination registry, the Danish National Patient registry plus other relevant databases (e.g., disease surveillance, medications, microbiology). The national data have been used for many vaccine studies, including recently safety studies for measles, mumps, rubella (MMR), human papillomavirus (HPV) and childhood vaccination [1-3]. Various studies on the Danish national patient registry reported that the positive predictive values i.e., the proportion of patients registered with a disease who truly had the disease, varied between specialities from 66% to 83% [4]. A study on tetanus, diphtheria, pertussis and polio (Tdap-IPV) booster vaccination in the 2000 to 2003 birth cohort identified substantial underreporting of the Tdap-IPV booster in the childhood vaccination database, mainly due to GPs failing to register vaccinations given [5]. This led to several interventions to improve registration of vaccinations, including the compulsory registration of vaccinations since 2015.

The AUH population is included in the population accessible to SSI and uses the same national patient registry. Danish registries are listed and described in the ENCePP data catalogue: http://www.encepp.eu/encepp/viewResource.htm?id=25067.

Spain

The *BIFAP* (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria) database is a computerised database of primary care medical records operated by the Spanish Medicines Agency (AEMPS) covering data from nine regions in Spain, which are sent annually [6]. Vaccines administered by the paediatrician or GP are recorded using local codes. The database has been recently been used for HPV vaccine-related studies [7,8].

Italy

The *ATS (Local Health Agency in Val Padana*) is responsible for the health of the citizens living in the Cremona and Mantova provinces and for the governance and control of all health-related services (prevention, treatment, residential care, etc.). *ATSVP* is a record linkage database that contains data for mortality (with cause of death), hospitalisations (with diagnosis), drug prescriptions and legally notifiable infectious diseases for this population. It also contains vaccination data, including information on brand and dose for routine childhood vaccines, notified to the *ATS*. The database was used for 2009 H1N1 pandemic safety studies [9].

PEDIANET is a paediatric primary care medical record database based on transmission of specific data (determined by individual studies) from the patient computerised clinical files of the paediatricians in the network [10]. PEDIANET can link to other databases such as the Veneto Regional vaccine register using unique patient identifiers. In this vaccine register information on routine childhood vaccination are captured including brand and dose. Informed consent has to be obtained from the parents before data can be used in studies. For ADVANCE PEDIANET contributed data on children born in 2006 and 2007 that had been linked to the Veneto vaccine register for a previous vaccine-related study [11].

The *Agenzia regionale di sanità (ARS)* database is a record linkage database that contains a copy of the healthcare administrative databases of the Tuscany Regional Healthcare System, linked to other

healthcare registries [12]. It contains mortality and hospitalisation data for the Tuscany region population since 2003 and on emergency healthcare use since 2009. Information on vaccines administered by the personnel of the Regional Healthcare System, including brand, batch number and dose, are available since 2013 and information on vaccinations administered by family paediatricians are available since 2018. Although several pharmaco-epidemiological studies have been conducted with the ARS database, prior to ADVANCE there had been no vaccine-related studies [13,14]. ARS did not participate in the earlier activities of ADVANCE as they joined as a full partner in June 2017. There is no overlap between the populations in the ATSVP, ARS and PEDIANET databases.

United Kingdom

The Health Improvement Network (*THIN*) database is a collaboration between In Practice Systems, who developed Vision software used by GPs to manage patient data in the UK and IMS Health, who provide access to these data for use in medical research [15]. The GPs data are collected during routine practice and regularly transferred to the THIN database. The ADVANCE project had access to the THIN database via a license held by a partner, Erasmus Medical Centre. Many pharmaco-epidemiological studies, including vaccine-related studies, have been conducted using the THIN database [16,17].

The Royal College of General Practitioners Research and Surveillance Centre (*RCGP RSC*) is a primary care sentinel network, was set up to monitor influenza and respiratory disease surveillance in 1967 [18]. Computer recording of diagnostic data in the 1990's facilitated expansion of the database's analytical possibilities to include trend analysis of secular change in the incidence of common diseases and chronic conditions. In 2015 the database was extended to collect all Read-coded data on an individual patient basis ion from 107 GP practices throughout the UK. The RCGP RSC database has been used for several vaccine effectiveness studies [19-22].

Table S1 Code lists for the 9 autoimmune diseases

Autoimmune diseases	Concept Unique Identifier	Concept name	ICD-9	ICD-10	ICPC	READ
ADEM				G35-G37.9		Fyu4.
	C0011302	Demyelinating disease of central nervous system	341.9	G37.9	-	X005b
	C0014038	Encephalitis	-	-	-	XE15D F03z.
	C0014058	Encephalitis, myelitis and encephalomyelitis	323	G04 G04.9	-	XE15B F03..
	C0014070	Encephalomyelitis	-	-	-	X001X Xa3f9 XaEI5 F03.. F03y.
	C0270626	Acute ascending myelitis	-	G04	-	-
	C0477368	Acute disseminated demyelination, unspecified	-	G36.9	-	Fyu42
	C1719353	Encephalitis and encephalomyelitis following immunization procedures	323.51	-	-	-
	C1719359	Acute necrotizing hemorrhagic encephalopathy	-	G04.3	-	-
	C1719360	Other postinfectious encephalitis and encephalomyelitis	323.62	-	-	-
	C1719364	Toxic encephalitis, myelitis, and encephalomyelitis	323.7	-	-	-
	C1719365	Other causes of encephalitis and encephalomyelitis	323.81	-	-	-
	C1719367	Other causes of myelitis	323.82	-	-	-
	C1719369	Unspecified cause of encephalitis, myelitis, and encephalomyelitis	323.9	-	-	-
	C1719722	Infectious acute disseminated encephalomyelitis (ADEM)	323.61	-	-	-
	C2316057	Inflammation of spinal cord due to toxin	323.72	-	-	-
Bell's palsy					N91	
	C0376175	Bell Palsy	351.0	G51.0	N91001	F310.
GBS						F3701 F370z F3700
	C0018378	Guillain-Barre Syndrome	357.0	G61.0	N94005	F370.
ITP narrow	C0272282	Thrombocytopenia, cyclic	-	D69.3	-	-
	C0398650	Immune thrombocytopenic purpura	287.31	D69.3	B83006	D3130
ITP broad						42P2.
	C0040034	Thrombocytopenia	287.5	D69.6	B83012	D315.
	C0154301	Acquired thrombocytopenia	287.4	D69.5	-	D314z D314.
	C0272282	Thrombocytopenia, cyclic	-	D69.3	-	-

Autoimmune diseases	Concept Unique Identifier	Concept name	ICD-9	ICD-10	ICPC	READ
	C0398648	Posttransfusion purpura	287.41	D69.51	-	-
	C0398650	Immune thrombocytopenic purpura	287.31	D69.3	B83006	D3130
	C0477317	Other primary thrombocytopenia	287.39	D69.4	-	Dyu32
	C0701157	Primary thrombocytopenia	287.3	D69.49	-	D313. D313z
	C2873806	Hemorrhagic (thrombocytopenic) purpura	-	D69.3	-	-
	C2921024	Posttransfusion purpura from whole blood (fresh) or blood products	-	D69.51	-	-
	C2921026	Other secondary thrombocytopenia	287.49	D69.59	-	-
Kawasaki disease	C0026691	Mucocutaneous Lymph Node Syndrome	446.1	M30.3	B99022	G7510 G751z
Narcolepsy	C0007384	Cataplexy	-	-	-	F270.
	C0027404	Narcolepsy	347.0	G47.41 G47.419	N99013	F271.
	C0751362	Narcolepsy-Cataplexy Syndrome	347 347.01	G47.4 G47.411	-	F27z. F27..
Optic neuritis	C0029134	Optic Neuritis	377.3 377.30	H46 H46.9	F99011	F4H3z F4H3. F4H30
SLE	C0024138	Lupus Erythematosus, Discoid	-	L93.0	L99034 S99034	M1541
	C0024141	Lupus Erythematosus, Systemic	710.0	M32 M32.9	L99065	N000. N000z
	C0155180	Discoid lupus erythematosus of eyelid	373.34	H01.12	-	F4D33
	C0409974	Lupus Erythematosus	695.4	L93 L93.0	L99056	M154. M154z
Transverse myelitis	C1719356	Myelitis following immunization procedures	323.52	-	-	-
	C0270627	Myelitis, Acute Transverse	341.2 341.20	G37.3	-	-
	C0494470	Acute transverse myelitis in demyelinating disease of central nervous system	-	G37.3	-	-
	C0026975	Myelitis	-	-	N99012	F03..
	C0026976	Myelitis, Transverse	-	-	-	F037.

ADEM: Acute disseminated encephalomyelitis, GBS: Guillain Barré syndrome, ITP: Immune Thrombocytopenia Purpura, SLE: Systemic Lupus Erythematosus

Table S2 Age and sex specific incidence rates (/100,000 PY) for each autoimmune disease per databases over the period 2003-2014

		Italy						Denmark	
		ARS		Val Padana		Pedianet		AUH	
		IR (95%CI)		IR (95%CI)		IR (95%CI)		IR (95%CI)	
Health Outcome	Age	Female	Male	Female	Male	Female	Male	Female	Male
Acute disseminated encephalomyelitis	Overall	16.3 (15.77-16.86)	10.4 (9.91-10.81)	16.0 (14.35-17.85)	10.7 (9.35-12.31)	1.6 (0.51-4.95)	1.5 (0.48-4.57)	5.8 (5.55-6.04)	5.0 (4.73-5.19)
	0-1y	6.7 (4.48-10.14)	6.9 (4.67-10.23)	3.0 (0.42-21.36)	0.0	2.6 (0.36-18.19)	0.0	4.3 (3.06-5.99)	4.7 (3.41-6.38)
	2-4y	6.2 (4.38-8.85)	5.5 (3.82-7.91)	2.0 (0.28-14.27)	7.4 (2.78-19.72)	0.0	1.9 (0.26-13.18)	3.0 (2.20-4.20)	4.5 (3.44-5.78)
	5-14y	3.7 (2.91-4.79)	4.7 (3.75-5.78)	0.6 (0.08-4.07)	4.9 (2.54-9.39)	2.0 (0.50-8.05)	1.9 (0.47-7.44)	1.9 (1.55-2.36)	2.2 (1.78-2.63)
	15-24y	16.3 (14.46-18.30)	8.1 (6.91-9.56)	12.3 (7.92-19.04)	8.1 (4.79-13.67)	-	-	3.0 (2.54-3.48)	2.1 (1.72-2.50)
	25-44y	26.3 (24.99-27.62)	14.0 (13.10-15.04)	29.4 (25.10-34.46)	16.6 (13.47-20.41)	-	-	8.1 (7.59-8.75)	5.2 (4.81-5.71)
	45-64y	18.6 (17.53-19.74)	11.1 (10.24-12.00)	18.0 (14.74-21.90)	10.9 (8.46-14.03)	-	-	7.7 (7.10-8.25)	6.5 (5.98-7.03)
	65y+	8.7 (7.96-9.52)	8.4 (7.58-9.40)	9.2 (6.96-12.19)	7.7 (5.29-11.09)	-	-	5.4 (4.86-6.03)	7.5 (6.79-8.35)
	Overall	16.3 (15.77-16.86)	10.4 (9.91-10.81)	16.0 (14.35-17.85)	10.7 (9.35-12.31)	1.6 (0.51-4.95)	1.5 (0.48-4.57)	5.8 (5.55-6.04)	5.0 (4.73-5.19)
Bells palsy	0-1y	5.6 (3.55-8.72)	3.9 (2.29-6.53)	6.0 (1.51-24.06)	5.5 (1.37-21.88)	2.6 (0.36-18.19)	4.8 (1.19-19.03)	7.9 (6.19-10.15)	8.3 (6.52-10.45)
	2-4y	5.4 (3.72-7.90)	5.5 (3.82-7.91)	8.0 (3.02-21.43)	0.0	2.0 (0.28-14.29)	5.6 (1.80-17.28)	7.3 (5.94-9.00)	8.9 (7.42-10.72)
	5-14y	6.7 (5.61-8.12)	6.2 (5.13-7.47)	7.5 (4.33-12.85)	5.4 (2.92-10.09)	9.1 (4.71-17.41)	7.4 (3.72-14.88)	11.1 (10.15-12.09)	9.8 (8.97-10.77)
	15-24y	3.4 (2.59-4.35)	3.1 (2.37-4.02)	1.2 (0.31-4.91)	1.7 (0.56-5.38)	-	-	11.8 (10.89-12.77)	12.6 (11.70-13.62)
	25-44y	4.2 (3.74-4.79)	5.5 (4.93-6.15)	2.0 (1.11-3.63)	3.6 (2.34-5.62)	-	-	21.6 (20.65-22.53)	21.6 (20.74-22.58)
	45-64y	5.7 (5.07-6.30)	8.2 (7.45-8.96)	2.0 (1.11-3.63)	3.6 (2.34-5.62)	-	-	22.3 (21.39-23.35)	26.2 (25.21-27.32)
	65y+	9.6 (8.79-10.42)	11.7 (10.68-12.83)	3.8 (2.43-5.83)	5.7 (3.74-8.81)	-	-	25.8 (24.55-27.11)	29.6 (28.05-31.13)
	Overall	6.2 (5.85-6.52)	7.3 (6.93-7.69)	3.0 (2.35-3.88)	3.6 (2.87-4.59)	5.8 (3.24-10.56)	6.4 (3.71-11.01)	19.0 (18.53-19.43)	20.2 (19.77-20.70)
Guillain-Barré syndrome	0-1y	0.9 (0.28-2.72)	1.1 (0.41-2.95)	0.0	0.0	0.0	0.0	0.3 (0.06-1.01)	0.5 (0.18-1.27)
	2-4y	1.8 (0.94-3.47)	1.5 (0.76-3.03)	0.0	0.0	4.0 (1.01-16.10)	0.0	0.7 (0.38-1.42)	1.3 (0.77-2.04)
	5-14y	0.8 (0.50-1.42)	1.0 (0.60-1.55)	2.3 (0.86-6.11)	0.0	0.0	0.0	0.6 (0.41-0.87)	0.7 (0.52-1.02)
	15-24y	1.6 (1.09-2.32)	1.4 (0.95-2.07)	0.0	2.3 (0.87-6.16)	-	-	1.1 (0.82-1.39)	1.3 (1.02-1.64)
	25-44y	1.4 (1.13-1.74)	2.0 (1.64-2.36)	1.0 (0.40-2.31)	2.6 (1.54-4.40)	-	-	1.8 (1.55-2.09)	2.2 (1.96-2.55)
	45-64y	2.3 (1.91-2.68)	4.0 (3.48-4.54)	2.4 (1.38-4.10)	3.3 (2.06-5.18)	-	-	2.8 (2.47-3.16)	4.0 (3.57-4.39)
	65y+	3.7 (3.22-4.23)	5.8 (5.06-6.56)	2.8 (1.70-4.68)	9.8 (7.10-13.65)	-	-	3.5 (3.06-4.01)	5.9 (5.26-6.64)
	Overall	2.2 (2.01-2.41)	3.1 (2.88-3.37)	1.8 (1.33-2.53)	3.8 (3.00-4.77)	1.1 (0.27-4.25)	0.0	2.0 (1.86-2.16)	2.8 (2.59-2.93)
ITP (broad)	0-1y	25.8 (20.92-31.77)	27.1 (22.23-33.03)	15.0 (6.26-36.15)	30.1 (16.67-54.37)	2.6 (0.36-18.19)	2.4 (0.34-16.89)	17.1 (14.47-20.25)	27.2 (23.84-30.92)
	2-4y	25.9 (21.80-30.79)	26.4 (22.32-31.12)	34.2 (21.26-55.01)	22.2 (12.62-39.13)	2.0 (0.28-14.29)	1.9 (0.26-13.18)	13.6 (11.64-15.80)	16.2 (14.14-18.57)
	5-14y	10.4 (8.99-12.11)	10.7 (9.31-12.39)	6.9 (3.91-12.13)	6.5 (3.70-11.47)	4.0 (1.51-10.72)	2.8 (0.90-8.65)	5.0 (4.40-5.71)	5.6 (4.95-6.31)
	15-24y	9.2 (7.86-10.76)	8.1 (6.91-9.57)	3.7 (1.65-8.20)	2.9 (1.20-6.95)	-	-	6.0 (5.33-6.67)	4.0 (3.54-4.63)
	25-44y	11.2 (10.34-12.06)	7.8 (7.12-8.56)	8.6 (6.45-11.57)	4.5 (2.99-6.66)	-	-	10.4 (9.77-11.07)	5.5 (5.02-5.94)
	45-64y	16.6 (15.61-17.71)	23.4 (22.14-24.69)	12.6 (9.97-15.99)	10.7 (8.29-13.82)	-	-	14.6 (13.84-15.43)	17.3 (16.42-18.13)
	65y+	38.0 (36.41-39.66)	61.0 (58.56-63.45)	18.4 (15.12-22.46)	27.1 (22.24-32.98)	-	-	28.6 (27.29-29.98)	44.7 (42.87-46.65)
	Overall	20.0 (19.38-20.58)	23.9 (23.24-24.60)	12.5 (11.03-14.12)	11.7 (10.24-13.32)	3.2 (1.43-7.10)	2.5 (1.02-5.91)	13.4 (13.07-13.83)	14.4 (14.03-14.82)

		Italy						Denmark	
		ARS		Val Padana		Pedianet		AUH	
		IR (95%CI)		IR (95%CI)		IR (95%CI)		IR (95%CI)	
Health Outcome	Age	Female	Male	Female	Male	Female	Male	Female	Male
ITP (narrow)	0-1y	6.2 (4.01-9.43)	5.5 (3.57-8.57)	3.0 (0.42-21.36)	5.5 (1.37-21.89)	0.0	2.4 (0.34-16.89)	10.1 (8.09-12.53)	17.0 (14.41-20.02)
	2-4y	9.6 (7.26-12.79)	6.6 (4.76-9.24)	12.1 (5.42-26.85)	3.7 (0.93-14.80)	0.0	1.9 (0.26-13.18)	11.1 (9.37-13.13)	12.1 (10.29-14.11)
	5-14y	3.3 (2.54-4.32)	3.1 (2.35-4.00)	0.6 (0.08-4.07)	2.7 (1.13-6.52)	3.0 (0.97-9.36)	1.9 (0.47-7.44)	3.7 (3.15-4.27)	3.6 (3.05-4.14)
	15-24y	1.3 (0.85-1.97)	1.3 (0.90-2.01)	0.0	1.2 (0.29-4.62)	-	-	3.4 (2.89-3.90)	1.8 (1.48-2.21)
	25-44y	1.1 (0.87-1.42)	0.9 (0.65-1.14)	0.6 (0.19-1.78)	0.4 (0.09-1.49)	-	-	4.4 (3.98-4.83)	2.3 (1.98-2.57)
	45-64y	1.7 (1.41-2.08)	1.4 (1.12-1.75)	0.9 (0.38-2.20)	1.3 (0.61-2.66)	-	-	4.9 (4.46-5.39)	4.6 (4.16-5.04)
	65y+	2.8 (2.38-3.27)	3.7 (3.16-4.37)	3.2 (1.99-5.14)	2.7 (1.47-5.08)	-	-	9.4 (8.62-10.17)	12.6 (11.59-13.60)
	Overall	2.2 (1.99-2.38)	2.1 (1.87-2.28)	1.6 (1.16-2.30)	1.6 (1.10-2.26)	1.6 (0.51-4.95)	2.0 (0.74-5.24)	5.5 (5.23-5.71)	5.0 (4.80-5.26)
Kawasaki	0-1y	23.4 (18.82-29.17)	32.9 (27.49-39.38)	0.0	16.4 (7.38-36.55)	15.4 (6.91-34.21)	28.6 (16.22-50.29)	4.9 (3.59-6.72)	9.6 (7.68-11.91)
	2-4y	12.5 (9.71-15.97)	15.0 (12.01-18.67)	4.0 (1.01-16.08)	1.9 (0.26-13.14)	14. (6.72-29.58)	5.6 (1.80-17.28)	5.1 (3.97-6.53)	6.7 (5.45-8.31)
	5-14y	1.4 (0.92-2.09)	2.6 (1.96-3.49)	0.0	1.6 (0.52-5.05)	1.0 (0.14-7.15)	0.9 (0.13-6.60)	0.9 (0.68-1.25)	1.4 (1.13-1.82)
	15-24y	0.1 (0.01-0.42)	0.2 (0.08-0.60)	0.0	0.0	-	-	0.1 (0.03-0.21)	0.1 (0.03-0.20)
	25-44y	0.0	0.1 (0.02-0.16)	0.0	0.0	-	-	0.0 (0.00-0.07)	0.1 (0.04+0.16)
	45-64y	0.0	0.0	0.0	0.0	-	-	0.1 (0.04-0.16)	0.1 (0.04-0.16)
	65y+	0.0	0.0	0.0	0.0	-	-	0.0 (0.01-0.13)	0.1 (0.02-0.19)
	Overall	0.8 (0.67-0.91)	1.3 (1.13-1.45)	0.1 (0.02-0.40)	0.5 (0.28-0.98)	7.4 (4.41-12.57)	7.9 (4.82-12.84)	0.4 (0.37-0.51)	0.7 (0.63-0.80)
Narcolepsy	0-1y	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	2-4y	0.2 (0.03-1.42)	0.2 (0.03-1.34)	0.0	0.0	0.0	1.9 (0.26-13.18)	0.2 (0.08-0.76)	0.7 (0.37-1.35)
	5-14y	0.4 (0.20-0.88)	0.3 (0.15-0.76)	0.6 (0.08-4.07)	1.1 (0.27-4.34)	0.0	0.9 (0.13-6.60)	0.7 (0.53-1.05)	0.8 (0.61-1.14)
	15-24y	0.4 (0.16-0.79)	0.5 (0.26-0.97)	0.6 (0.09-4.36)	0.0	-	-	3.7 (3.18-4.23)	2.5 (2.15-3.01)
	25-44y	0.2 (0.13-0.38)	0.3 (0.21-0.51)	0.0	0.0	-	-	2.9 (2.60-3.29)	2.1 (1.83-2.40)
	45-64y	0.3 (0.21-0.51)	0.3 (0.21-0.52)	0.2 (0.03-1.30)	0.2 (0.03-1.29)	-	-	1.5 (1.25-1.76)	1.6 (1.38-1.91)
	65y+	0.3 (0.18-0.47)	0.7 (0.51-1.06)	0.0	0.3 (0.04-1.94)	-	-	1.7 (1.40-2.05)	1.2 (0.95-1.58)
	Overall	0.3 (0.23-0.37)	0.4 (0.34-0.52)	0.1 (0.05-0.46)	0.2 (0.08-0.56)	0.0	1.0 (0.25-3.93)	2.0 (1.90-2.19)	1.7 (1.53-1.80)
Optic neuritis	0-1y	0.3 (0.04-2.08)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	2-4y	0.2 (0.03-1.42)	0.2 (0.03-1.34)	0.0	0.0	0.0	0.0	0.2 (0.04-0.66)	0.2 (0.08-0.73)
	5-14y	1.8 (1.26-2.58)	1.5 (1.00-2.17)	1.1 (0.29-4.59)	0.0	0.0	0.0	0.9 (0.70-1.27)	0.6 (0.45-0.92)
	15-24y	4.8 (3.84-5.93)	1.6 (1.13-2.34)	3.1 (1.28-7.37)	0.0	-	-	5.6 (4.96-6.26)	2.1 (1.77-2.56)
	25-44y	4.6 (4.08-5.18)	2.7 (2.30-3.15)	5.0 (3.40-7.33)	2.2 (1.27-3.93)	-	-	10.7 (10.02-11.34)	4.6 (4.22-5.06)
	45-64y	2.7 (2.28-3.31)	2.4 (2.00-2.82)	1.1 (0.49-2.44)	1.1 (0.49-2.42)	-	-	5.7 (5.18-6.17)	3.6 (3.20-3.98)
	65y+	1.8 (1.45-2.15)	1.8 (1.41-2.26)	1.7 (5.19-5.67)	1.6 (0.74-3.65)	-	-	1.9 (1.62-2.32)	2.0 (1.61-2.41)
	Overall	3.0 (2.74-3.20)	2.1 (1.91-2.31)	2.4 (1.79-3.15)	1.3 (0.85-1.88)	0.0	0.0	5.4 (5.19-5.67)	2.8 (2.68-3.03)
Systemic lupus erythematosus	0-1y	0.9 (0.28-2.72)	1.1 (0.41-2.95)	0.0	0.0	0.0	2.4 (0.34-16.89)	0.8 (0.34-1.68)	1.1 (0.56-2.07)
	2-4y	0.4 (0.10-1.60)	0.4 (0.09-1.51)	2.0 (0.28-14.27)	0.0	0.0	0.0	0.0	0.2 (0.04-0.63)
	5-14y	1.3 (0.82-1.94)	0.5 (0.27-0.98)	1.7 (0.55-5.34)	0.5 (0.08-3.85)	0.0	0.9 (0.13-6.60)	1.1 (0.83-1.45)	0.5 (0.34-0.77)

		Italy						Denmark	
		ARS		Val Padana		Pedianet		AUH	
		IR (95%CI)		IR (95%CI)		IR (95%CI)		IR (95%CI)	
Health Outcome	Age	Female	Male	Female	Male	Female	Male	Female	Male
	15-24y	4.4 (3.52-5.54)	0.7 (0.38-1.18)	2.5 (0.92-6.54)	0.0	-	-	4.6 (4.03-5.21)	0.5 (0.35-0.75)
	25-44y	7.0 (6.37-7.73)	1.4 (1.14-1.76)	8.8 (6.62-11.79)	1.1 (0.50-2.49)	-	-	10.1 (9.52-10.80)	1.6 (1.35-1.84)
	45-64y	6.1 (5.53-6.81)	2.2 (1.80-2.58)	7.5 (5.52-10.19)	1.6 (0.85-3.14)	-	-	11.6 (10.95-12.37)	3.0 (2.68-3.40)
	65y+	4.6 (4.05-5.17)	2.2 (1.82-2.76)	6.4 (4.57-8.95)	1.6 (0.74-3.65)	-	-	9.4 (8.66-10.21)	3.7 (3.17-4.25)
	Overall	5.2 (4.94-5.56)	1.6 (1.44-1.79)	6.4 (5.38-7.59)	1.2 (0.76-1.76)	0.0	1.0 (0.25-3.93)	7.9 (7.62-8.20)	1.9 (1.73-2.01)
Transverse myelitis	0-1y	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1 (0.02-0.85)
	2-4y	0.0	0.0	2.0 (0.28-14.27)	1.9 (0.26-13.14)	0.0	0.0	0.0	0.5 (0.21-1.04)
	5-14y	0.1 (0.01-0.43)	0.1 (0.01-0.40)	0.0	0.0	0.0	0.0	0.2 (0.07-0.32)	0.3 (0.18-0.51)
	15-24y	0.4 (0.20-0.86)	0.1 (0.03-0.45)	0.6 (0.09-4.36)	0.0	-	-	0.8 (0.62-1.13)	0.3 (0.17-0.47)
	25-44y	0.4 (0.26-0.59)	0.3 (0.21-0.51)	0.0	0.0	-	-	1.5 (1.30-1.80)	1.1 (0.88-1.29)
	45-64y	0.5 (0.39-0.77)	0.4 (0.25-0.58)	0.5 (0.18-1.70)	0.4 (0.09-1.45)	-	-	1.4 (1.19-1.68)	1.3 (1.09-1.56)
	65y+	0.3 (0.19-0.49)	0.5 (0.35-0.82)	0.4 (0.09-1.50)	0.5 (0.14-2.19)	-	-	0.8 (0.62-1.08)	1.0 (0.75-1.32)
	Overall	0.4 (0.30-0.46)	0.3 (0.25-0.42)	0.3 (0.17-0.73)	0.3 (0.11-0.63)	0.0	0.0	1.0 (0.93-1.14)	0.9 (0.77-0.96)

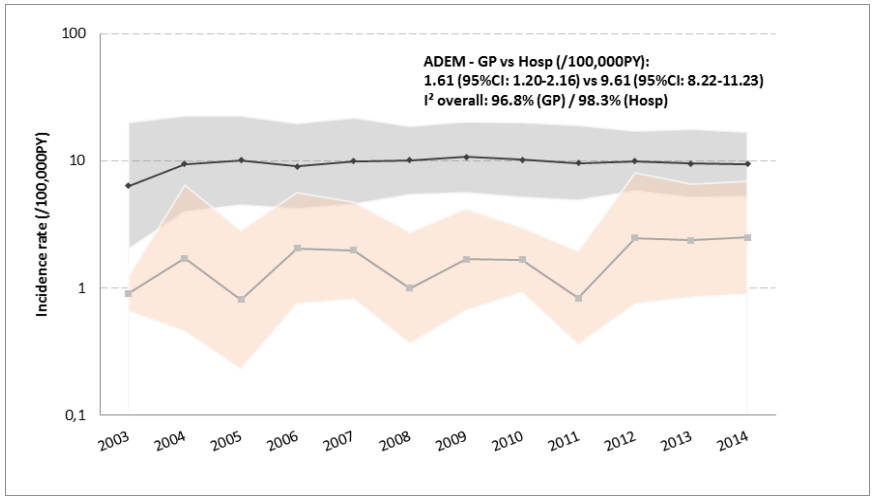
(Continued)

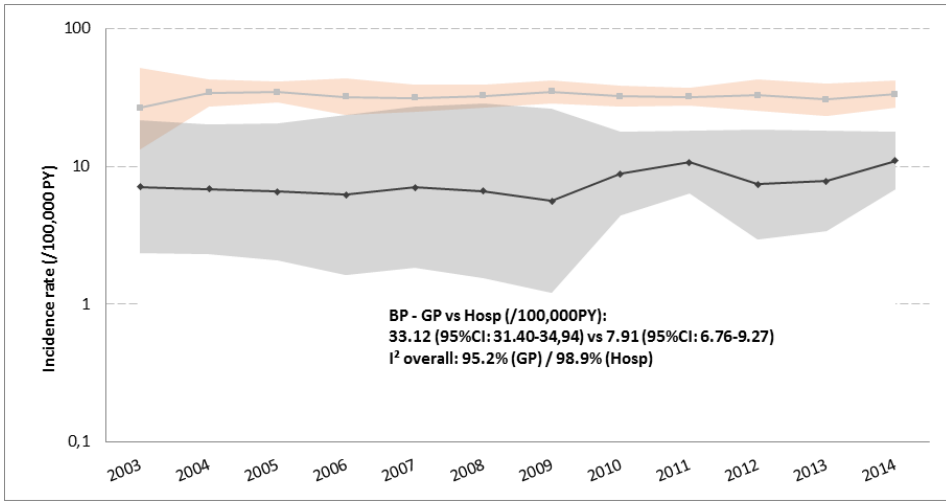
		Spain		UK			
		BIFAP		RCGP RSC		THIN	
		IR (95%CI)		IR (95%CI)		IR (95%CI)	
Health Outcome	Age	Female	Male	Female	Male	Female	Male
Acute disseminated encephalomyelitis	Overall	2.3 (2.10-2.58)	1.8 (1.61-2.06)	3.0 (2.63-3,42)	1.9 (1.56-2.20)	1.3 (1.14-1.40)	0.8 (0.72-0.93)
	0-1y	1.2 (0.44-3.16)	1.4 (0.58-3.35)	0.5 (0.08-3.84)	1.0 (0.26-4.11)	0.4 (0.14-1.33)	0.7 (0.28-1.63)
	2-4y	0.5 (0.12-1.85)	0.0	1.3 (0.40-3.89)	1.2 (0.39-3.71)	1.1 (0.57-1.97)	1.3 (0.76-2.26)
	5-14y	0.6 (0.30-1.21)	0.9 (0.49-1.52)	1.0 (0.50-2.01)	1.5 (0.89-2.63)	0.8 (0.57-1.22)	0.6 (0.36-0.88)
	15-24y	0.9 (0.61-1.38)	0.6 (0.37-1.02)	2.4 (1.51-3.70)	0.8 (0.38-1.69)	1.4 (1.02-1.88)	0.6 (0.39-0.93)
	25-44y	1.6 (1.25-1.96)	0.8 (0.60-1.14)	4.3 (3.45-5.27)	1.9 (1.35-2.57)	1.5 (1.29-1.84)	0.7 (0.53-0.90)
	45-64y	2.3 (1.86-2.87)	2.1 (1.63-2.62)	3.7 (2.97-4.72)	2.1 (1.52-2.83)	1.5 (1.29-1.84)	0.9 (0.75-1.19)
	65y+	6.6 (5.64-7.64)	7.1 (5.91-8.45)	2.3 (1.62-3.24)	2.8 (1.98-4.01)	0.8 (0.62-1.10)	1.1 (0.82-1.45)
	Overall	2.3 (2.10-2.58)	1.8 (1.61-2.06)	3.0 (2.63-3,42)	1.9 (1.56-2.20)	1.3 (1.14-1.40)	0.8 (0.72-0.93)
Bells palsy	0-1y	14.8 (11.22-19.53)	14.8 (11.30-19.37)	3.8 (1.80-7.93)	2.6 (1.07-6.17)	3.7 (2.52-5.44)	3.4 (2.29-5.02)
	2-4y	9.5 (6.99-12.89)	8.3 (6.06-11.45)	7.9 (5.07-12.45)	7.2 (4.53-11.41)	6.1 (4.75-7.94)	5.6 (4.27-7.25)
	5-14y	22.0 (19.63-24.69)	16.6 (14.63-18.93)	13.4 (11.12-16.25)	11.3 (9.23-13.76)	16.7 (15.28-18.15)	11.2 (10.11-12.38)
	15-24y	36.3 (34.05-38.78)	33.9 (31.69-36.33)	24.8 (21.54-28.45)	21.1 (18.27-24.41)	29.0 (27.15-31.04)	24.2 (22.61-25.97)
	25-44y	40.3 (38.52-42.09)	44.4 (42.52-46.42)	30.0 (27.71-32.53)	29.3 (27.01-31.78)	34.5 (33.22-35.82)	33.0 (31.75-34.27)

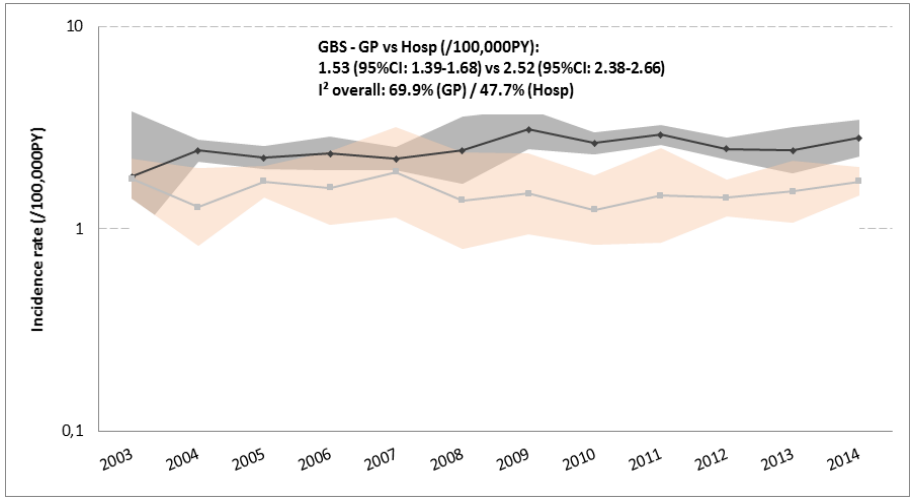
		Spain		UK			
		BIFAP		RCGP RSC		THIN	
		IR (95%CI)		IR (95%CI)		IR (95%CI)	
Health Outcome	Age	Female	Male	Female	Male	Female	Male
	45-64y	50.8 (48.50-53.17)	52.0 (49.53-54.40)	36.6 (34.02-39.44)	36.9 (34.25-39.69)	39.1 (37.77-40.57)	41.1 (39.73-42.58)
	65y+	65.1 (62.04-68.32)	59.5 (55.95-63.30)	39.4 (36.19-42.79)	38.5 (34.96-42.31)	40.3 (38.69-42.04)	43.8 (41.85-45.79)
	Overall	43.1 (42.12-44.19)	41.5 (40.43-42.56)	29.8 (28.54-31.04)	28.1 (26.90-29.35)	32.7 (32.02-33.34)	31.5 (30.90-32.20)
Guillain-Barré syndrome	0-1y	0.3 (0.04-2.10)	0.6 (0.14-2.23)	1.1 (0.27-4.32)	0.5 (0.07-3.65)	0.6 (0.21-1.52)	0.3 (0.07-1.09)
	2-4y	0.2 (0.03-1.64)	0.7 (0.21-2.04)	0.4 (0.06-2.97)	2.0 (0.83-4.80)	1.1 (0.57-1.97)	1.0 (0.54-1.88)
	5-14y	0.5 (0.20-1.01)	0.5 (0.24-1.05)	0.6 (0.26-1.51)	0.4 (0.11-1.09)	0.7 (0.49-1.11)	0.6 (0.36-0.88)
	15-24y	0.3 (0.16-0.64)	0.7 (0.40-1.07)	1.5 (0.85-2.63)	0.5 (0.17-1.23)	1.0 (0.68-1.41)	1.0 (0.68-1.36)
	25-44y	0.8 (0.55-1.05)	1.2 (0.88-1.52)	1.2 (0.77-1.73)	1.7 (1.18-2.34)	1.5 (1.22-1.76)	1.2 (0.95-1.43)
	45-64y	0.9 (0.68-1.33)	2.4 (1.93-3.00)	1.8 (1.26-2.47)	2.5 (1.92-3.37)	2.0 (1.67-2.29)	2.7 (2.39-3.12)
	65y+	1.3 (0.92-1.82)	2.5 (1.88-3.41)	3.2 (2.41-4.32-)	3.6 (2.67-4.96)	2.3 (1.95-2.75)	4.3 (3.74-4.97)
	Overall	0.8 (0.64-0.92)	1.4 (1.24-1.64)	1.7 (1.39-1.98)	1.9 (1.59-2.23)	1.6 (1.46-1.75)	2.0 (1.80-2.12)
ITP (broad)	0-1y	27.8 (22.74-34.07)	30.7 (25.48-37.02)	15.7 (10.89-22.55)	15.4 (10.78-22.06)	11.7 (9.41-14.51)	17.1 (14.37-20.38)
	2-4y	20.8 (16.96-25.63)	20.4 (16.65-25.00)	13.4 (9.46-18.92)	16.4 (12.06-22.25)	8.8 (7.09-10.90)	13.3 (11.17-15.73)
	5-14y	16.8 (14.75-19.17)	14.9 (12.96-17.02)	5.4 (4.01-7.28)	3.9 (2.75-5.45)	4.8 (4.09-5.64)	5.4 (4.67-6.25)
	15-24y	26.4 (24.46-28.49)	19.4 (17.69-21.19)	11.6 (9.43-14.16)	8.2 (6.49-10.33)	8.9 (7.85-10.00)	4.0 (3.41-4.78)
	25-44y	33.4 (31.79-35.04)	26.8 (25.31-28.34)	17.1 (15.34-18.97)	10.8 (9.42-12.32)	11.8 (11.07-12.59)	7.3 (6.77-7.95)
	45-64y	56.1 (53.72-58.63)	77.8 (74.82-80.90)	19.5 (17.64-21.60)	28.8 (26.52-31.33)	15.1 (14.24-15.98)	20.2 (19.22-21.21)
	65y+	104.5 (100.64-108.60)	169.0 (162.88-175.28)	46.7 (43.22-50.40)	86.0 (80.66-91.65)	33.3 (31.82-34.86)	61.0 (581.69-63.33)
	Overall	47.2 (46.14-48.30)	53.0 (51.84-54.25)	21.3 (20.27-22.39)	26.3 (25.14-27.51)	15.7 (15.21-16.13)	18.9 (18.37-19.37)
ITP (narrow)	0-1y	3.6 (2.02-6.26)	5.6 (3.60-8.65)	9.2 (5.71-14.77)	6.7 (3.88-11.51)	6.3 (4.67-8.42)	10.5 (8.36-13.07)
	2-4y	4.2 (2.63-6.61)	3.5 (2.15-5.73)	10.0 (6.72-14.97)	10.8 (7.39-15.72)	7.5 (5.96-9.49)	11.6 (9.69-13.97)
	5-14y	1.7 (1.09-2.52)	1.2 (0.76-1.96)	3.4 (2.33-4.95)	2.6 (1.70-3.92)	3.4 (2.78-4.07)	4.1 (3.44-4.81)
	15-24y	1.0 (0.67-1.48)	1.0 (0.69-1.52)	3.0 (2.00-4.45)	2.5 (1.67-3.85)	3.2 (2.66-3.96)	1.5 (1.11-1.95)
	25-44y	1.5 (1.18-1.87)	0.8 (0.56-1.08)	4.2 (3.36-5.16)	1.9 (1.39-2.63)	3.3 (2.92-3.73)	1.9 (1.59-2.18)
	45-64y	1.3 (0.98-1.74)	1.4 (1.06-1.89)	4.1 (3.25-5.06)	3.3 (2.56-4.19)	3.9 (3.53-4.42)	3.4 (3.03-3.85)
	65y+	3.1 (2.52-3.91)	2.9 (2.18-3.82)	6.7 (5.50-8.25)	9.7 (8.05-11.76)	7.7 (7.04-8.51)	9.8 (8.90-10.76)
	Overall	1.8 (1.57-1.99)	1.5 (1.29-1.69)	4.7 (4.26-5.25)	4.1 (3.63-4.56)	4.5 (4.30-4.79)	4.3 (4.04-4.51)
Kawasaki	0-1y	1.8 (0.80-3.95)	2.5 (1.31-4.83)	9.7 (6.13-15.44)	11.8 (7.85-17.79)	7.3 (5.52-9.56)	8.8 (6.92-11.25)
	2-4y	0.9 (0.35-2.47)	3.1 (1.82-5.18)	6.7 (4.10-10.92)	8.4 (5.47-12.86)	7.7 (6.15-9.72)	11.4 (9.51-13.75)
	5-14y	0.2 (0.07-0.70)	0.6 (0.29-1.15)	2.1 (1.33-3.43)	2.2 (1.42-3.50)	1.2 (0.83-1.60)	1.5 (1.10-1.92)
	15-24y	0.0	0.0 (0.01-0.29)	0.4 (0.12-1.16)	0.6 (0.24-1.38)	0.0 (0.00-0.24)	0.2 (0.10-0.44)
	25-44y	0.0	0.0 (0.00-0.16)	0.0	0.1 (0.01-0.36)	0.0 (0.01-0.10)	0.0 (0.01-0.12)
	45-64y	0.0	0.0 (0.00-0.22)	0.0	0.0	0.0 (0.01-0.10)	0.0 (0.00-0.09)
	65y+	0.0	0.0	0.0	0.0	0.0 (0.01-0.14)	0.0 (0.01-0.18)
	Overall	0.1 (0.05-0.14)	0.2 (0.17-0.34)	0.7 (0.56-0.96)	1.0 (0.76-1.22)	0.6 (0.50-0.67)	0.8 (0.74-0.95)

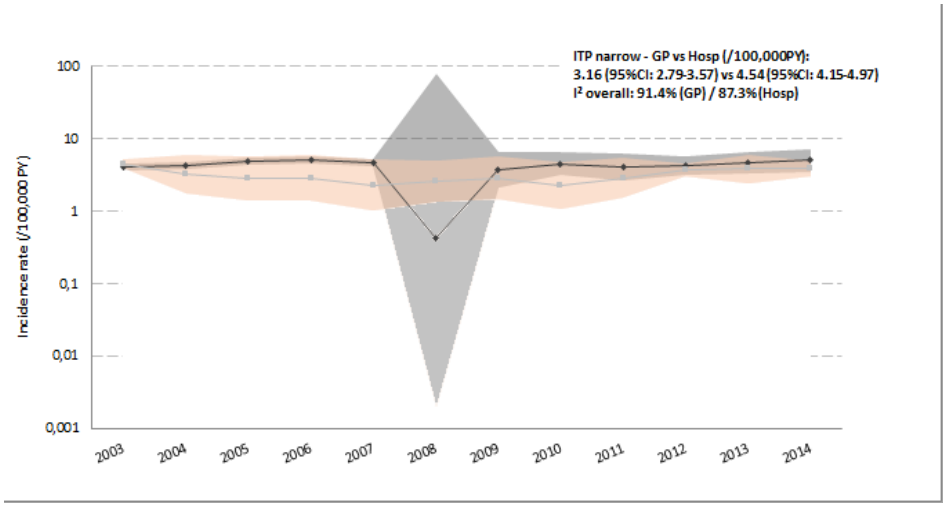
		Spain		UK			
		BIFAP		RCGP RSC		THIN	
		IR (95%CI)		IR (95%CI)		IR (95%CI)	
Health Outcome	Age	Female	Male	Female	Male	Female	Male
Narcolepsy	0-1y	0.0	0.0	0.0	0.0	0.0	0.0
	2-4y	0.0	0.0	0.0	0.0	0.0	0.1 (0.01-0.72)
	5-14y	0.4 (0.16-0.90)	0.1 (0.01-0.51)	0.4 (0.12-1.17)	0.4 (0.11-1.09)	0.3 (0.17-0.59)	0.5 (0.29-0.77)
	15-24y	1.0 (0.71-1.53)	0.3 (0.16-0.66)	1.6 (0.94-2.78)	1.3 (0.70-2.29)	1.6 (1.16-2.07)	1.1 (0.78-1.50)
	25-44y	1.0 (0.73-1.29)	1.0 (0.79-1.39)	1.6 (1.09-2.21)	1.1 (0.73-1.68)	1.2 (1.00-1.49)	1.2 (0.99-1.47)
	45-64y	0.5 (0.34-0.83)	0.9 (0.62-1.29)	0.8 (0.47-1.29)	0.9 (0.55-1.42)	1.0 (0.77-1.22)	1.0 (0.79-1.23)
	65y+	0.4 (0.21-0.73)	0.5 (0.28-1.02)	0.6 (0.29-1.15)	0.8 (0.43-1.57)	0.8 (0.62-1.10)	1.1 (0.84-1.48)
	Overall	0.7 (0.57-0.83)	0.7 (0.55-0.82)	1.0 (0.75-1.21)	0.9 (0.67-1.11)	0.9 (0.84-1.06)	1.0 (0.85-1.08)
Optic neuritis	0-1y	0.0	0.3 (0.04-1.98)	0.0	0.0	0.0	0.0
	2-4y	0.0	0.0	0.4 (0.06-2.97)	0.0	0.2 (0.05-0.85)	0.2 (0.05-0.81)
	5-14y	0.8 (0.46-1.50)	0.4 (0.19-0.96)	1.5 (0.86-2.65)	0.4 (0.11-1.09)	1.0 (0.70-1.41)	0.5 (0.34-0.85)
	15-24y	3.1 (2.46-3.85)	1.1 (0.76-1.62)	3.5 (2.40-5.04)	1.4 (0.79-2.44)	5.1 (4.32-5.95)	1.9 (1.45-2.39)
	25-44y	2.8 (2.39-3.34)	1.8 (1.45-2.24)	9.1 (7.89-10.56)	3.4 (2.65-4.28)	10.8 (10.10-11.56)	3.6 (3.24-4.08)
	45-64y	2.9 (2.42-3.54)	3.1 (2.53-3.75)	6.3 (5.27-7.52)	2.9 (2.19-3.72)	4.8 (4.33-5.31)	2.7 (2.35-3.08)
	65y+	3.5 (2.81-4.26)	3.6 (2.79-4.62)	1.8 (1.21-2.65)	2.5 (1.68-3.58)	1.7 (1.40-2.09)	1.9 (1.51-2.32)
	Overall	2.7 (2.44-2.95)	2.0 (1.74-2.21)	5.0 (4.54-5.57)	2.3 (1.96-2.66)	5.2 (4.93-5.45)	2.3 (2.16-2.51)
Systemic lupus erythematosus	0-1y	0.3 (0.04-2.10)	0.6 (0.14-2.23)	1.1 (0.27-4.32)	0.5 (0.07-3.65)	0.7 (0.30-1.71)	0.5 (0.20-1.45)
	2-4y	0.2 (0.03-1.64)	0.2 (0.03-1.56)	0.0	0.0	0.3 (0.10-0.98)	0.1 (0.01-0.72)
	5-14y	1.9 (1.27-2.79)	0.4 (0.15-0.86)	0.3 (0.06-1.00)	0.1 (0.02-0.83)	0.9 (0.64-1.34)	0.3 (0.16-0.55)
	15-24y	7.4 (6.44-8.58)	1.1 (0.76-1.62)	5.3 (3.96-7.20)	0.5 (0.17-1.23)	5.5 (4.75-6.446)	1.0 (0.68-1.36)
	25-44y	14.4 (13.34-15.48)	3.7 (3.13-4.25)	15.3 (13.68-17.12)	2.2 (1.61-2.92)	12.5 (11.77-13.34)	1.8 (1.56-2.16)
	45-64y	13.3 (12.15-14.54)	4.5 (3.83-5.30)	19.6 (17.75-21.72)	3.5 (2.74-4.42)	14.1 (13.31-14.99)	3.6 (3.19-4.03)
	65y+	7.7 (6.70-8.86)	3.4 (2.59-4.35)	13.4 (11.62-15.48)	4.2 (3.13-5.58)	10.2 (9.43-11.12)	3.7 (3.13-4.26)
	Overall	10.2 (9.67-10.67)	2.9 (2.59-3.15)	12.5 (11.71-13.33)	2.3 (1.94-2.63)	9.9 (9.50-10.22)	2.2 (2.05-2.39)
Transverse myelitis	0-1y	-	-	0.0	0.5 (0.07-3.65)	0.7 (0.30-1.71)	0.4 (0.13-1.26)
	2-4y	-	-	0.4 (0.06-2.97)	1.2 (0.39-3.71)	0.7 (0.35-1.55)	1.0 (0.54-1.88)
	5-14y	-	-	0.4 (0.12-1.17)	0.9 (0.47-1.88)	0.6 (0.41-0.99)	0.6 (0.36-0.88)
	15-24y	-	-	1.6 (0.94-2.78)	0.6 (0.24-1.38)	1.2 (0.85-1.65)	0.7 (0.44-1.00)
	25-44y	-	-	3.3 (2.56-4.16)	1.2 (0.81-1.80)	2.6 (2.29-3.01)	1.5 (1.22-1.75)
	45-64y	-	-	2.0 (1.44-2.72)	1.1 (0.75-1.74)	1.9 (1.57-2.18)	1.4 (1.16-1.69)
	65y+	-	-	1.1 (0.70-1.87)	1.3 (0.75-2.15)	0.8 (0.60-1.08)	0.9 (0.67-1.24)
	Overall	-	-	1.9 (1.57-2.19)	1.1 (0.86-1.34)	1.6 (1.46-1.75)	1.1 (1.01-1.25)

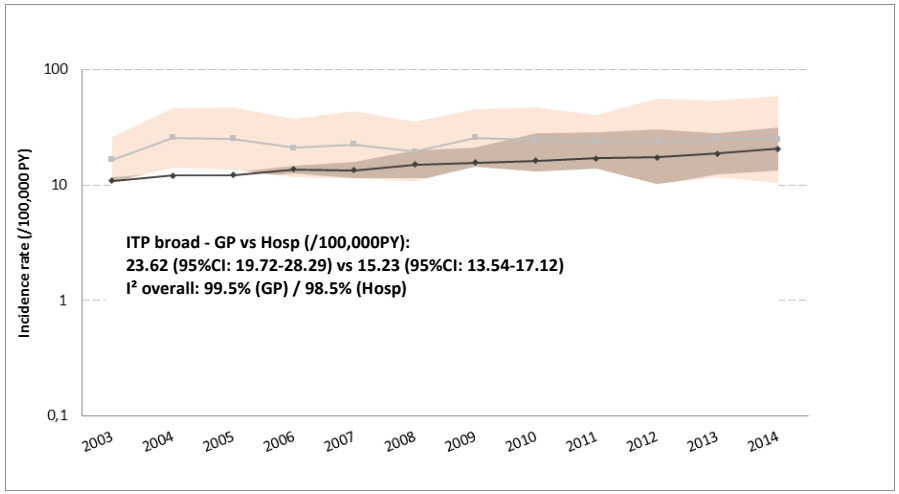
Figure S1 Yearly Incidence rates according to the type of data source (General practitioners versus hospitalization record linkage)

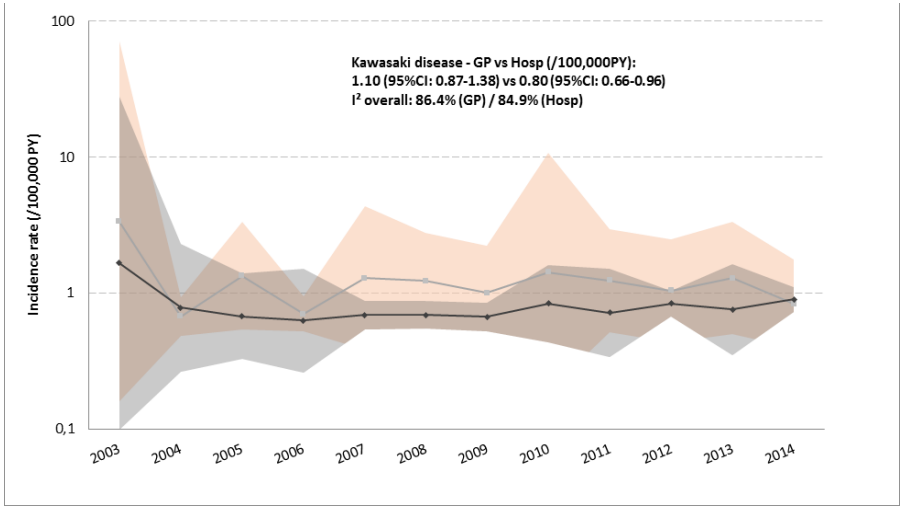


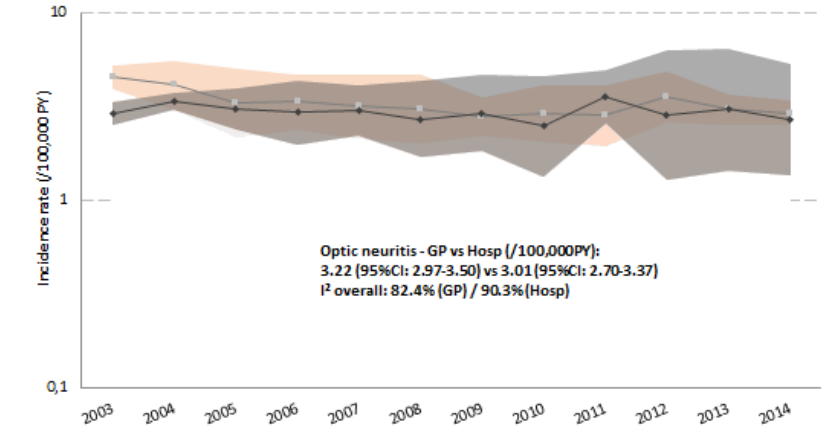


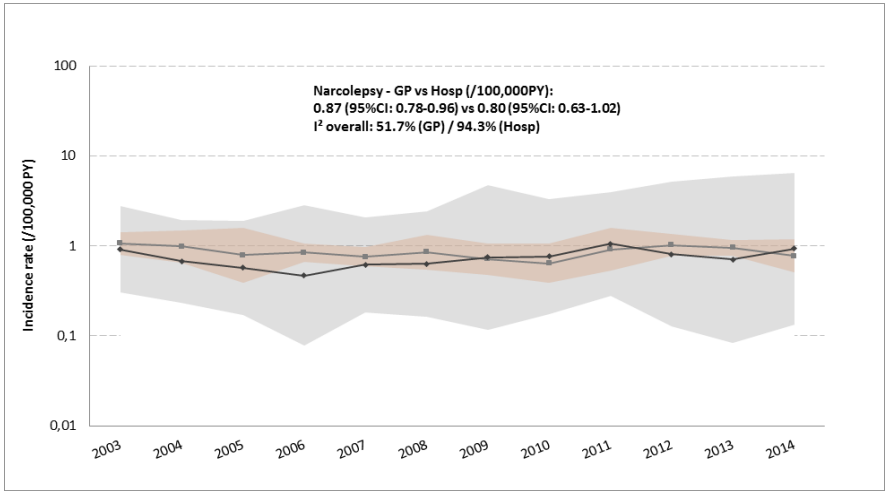


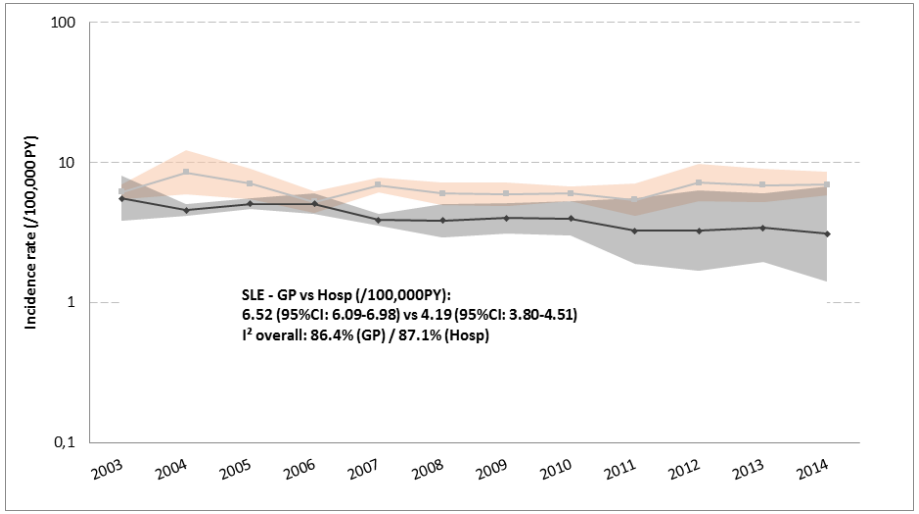


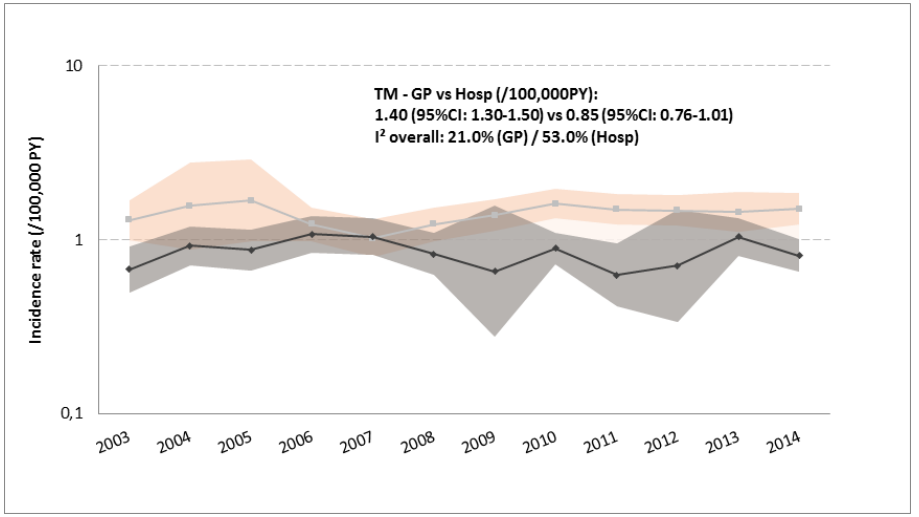

Incidence rate (/100,000 PY)
100
10
1
0,1
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
ITP broad - GP vs Hosp (/100,000PY):
23.62 (95%CI: 19.72-28.29) vs 15.23 (95%CI: 13.54-17.12)
I² overall: 99.5% (GP) / 98.5% (Hosp)


Incidence rate (/100,000 PY)
100
10
1
0,1
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Kawasaki disease - GP vs Hosp (/100,000PY):
1.10 (95%CI: 0.87-1.38) vs 0.80 (95%CI: 0.66-0.96)
I² overall: 86.4% (GP) / 84.9% (Hosp)


Incidence rate (/100,000 PY)
10
1
0,1
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Optic neuritis - GP vs Hosp (/100,000PY):
3.22 (95%CI: 2.97-3.50) vs 3.01 (95%CI: 2.70-3.37)
I² overall: 82.4% (GP) / 90.3% (Hosp)


Incidence rate (/100,000 PY)
100
10
1
0,1
0,01
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Narcolepsy - GP vs Hosp (/100,000PY):
0.87 (95%CI: 0.78-0.96) vs 0.80 (95%CI: 0.63-1.02)
I² overall: 51.7% (GP) / 94.3% (Hosp)





Black line corresponds to hospital record linkage databases, Grey line corresponds to General practitioners' databases. Log scale was used on the Y-axis. ADEM: Acute disseminated encephalomyelitis, BP: Bell's palsy, GBS: Guillain Barré syndrome, GP: General practitioners, Hosp: Hospitalization record linkage, ITP: Immune Thrombocytopenia Purpura, SLE: Systemic Lupus Erythematosus, TM: Transverse Myelitis

References

[1] Hviid A, Hansen JV, Frisch M, Melbye M. Measles, mumps, rubella vaccination and autism: a nationwide cohort study. Ann Intern Med. 2019.

[2] Hviid A, Svanstrom H, Scheller NM, Gronlund O, Pasternak B, Arnheim-Dahlstrom L. Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases. J Intern Med. 2018;283:154-65.

[3] Soegaard SH, Rostgaard K, Schmiegelow K, Kamper-Jorgensen M, Hargreave M, Hjalgrim H, et al. Childhood vaccinations and risk of acute lymphoblastic leukaemia in children. Int J Epidemiol. 2017;46:905-13.

[4] Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clinical epidemiology. 2015;7:449-90.

[5] Wojcik OP, Simonsen J, Molbak K, Valentiner-Branth P. Validation of the 5-year tetanus, diphtheria, pertussis and polio booster vaccination in the Danish childhood vaccination database. Vaccine. 2013;31:955-9.

[6] ENCePP. BIFAP database 2019 [Last accessed 27 March 2019]. Available from: http://www.encepp.eu/encepp/viewResource.htm?id=21501.

[7] Martín-Merino E, Llorente-García A, Montero Corominas D, Huerta C. The longitudinal incidence of human papillomavirus vaccination in Spanish primary care in the first 6 years after approval2019.

[8] Martin-Merino E, Llorente-Garcia A, Montero-Corominas D, Huerta C. The recording of human papillomavirus (HPV) vaccination in BIFAP primary care database: A validation study. Pharmacoepidemiol Drug Saf. 2019;28:201-8.

[9] Villa M, Black S, Groth N, Rothman KJ, Apolone G, Weiss NS, et al. Safety of MF59-adjuvanted influenza vaccination in the elderly: results of a comparative study of MF59-adjuvanted vaccine versus nonadjuvanted influenza vaccine in northern Italy. Am J Epidemiol. 2013;178:1139-45.

[10] ENCePP. 2019 [Last accessed 27 March 2019]. Available from: http://www.encepp.eu/encepp/viewResource.htm?id=20131.

[11] Giaquinto C, Gabutti G, Baldo V, Villa M, Tramontan L, Raccanello N, et al. Impact of a vaccination programme in children vaccinated with ProQuad, and ProQuad-specific effectiveness against varicella in the Veneto region of Italy. BMC Infect Dis. 2018;18:103.

[12] ENCePP. ARS database 2019 [Last accessed 27 March 2019]. Available from: http://www.encepp.eu/encepp/viewResource.htm?id=24417.

[13] Charlton RA, Klungsøyr K, Neville AJ, Jordan S, Pierini A, de Jong-van den Berg LTW, et al. Prescribing of Antidiabetic Medicines before, during and after Pregnancy: A Study in Seven European Regions. PloS One. 2016;11:e0155737.

[14] Roberto G, Bartolini C, Rea F, Onder G, Vitale C, Trifirò G, et al. NSAIDs utilization for musculoskeletal indications in elderly patients with cerebro/cardiovascular disease. Eur J Clin Pharmacol. 2018;74:637-43.

[15] ENCePP. THIN database 2019 [Last accessed 27 March 2019]. Available from: http://www.encepp.eu/encepp/viewResource.htm?id=10237.

[16] Hall GC, Davies PTG, Karim MY, Haag MDM, O'Leary C. Observational safety study of specific outcomes after trivalent cell culture seasonal influenza vaccination (Optaflu((R))) among adults in THIN database of electronic UK primary healthcare records. Pharmacoepidemiol Drug Saf. 2018;27:52-8.

[17] Wijnans L, Dodd CN, Weibel D, Sturkenboom M. Bell's palsy and influenza(H1N1)pdm09 containing vaccines: A self-controlled case series. PloS One. 2017;12:e0175539.

[18] RCGP Research and Surveillance Centre. 2019 [Last accessed 27 March 2019]. Available from: https://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre.aspx.

[19] Correa A, Hinton W, McGovern A, van Vlymen J, Yonova I, Jones S, et al. Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) sentinel network: a cohort profile. BMJ Open. 2016;6:e011092.

[20] Amirthalingam G, Andrews N, Keel P, Mullett D, Correa A, de Lusignan S, et al. Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study. The Lancet Public health. 2018;3:e82-e90.

[21] Pathirannehelage S, Kumarapeli P, Byford R, Yonova I, Ferreira F, de Lusignan S. Uptake of a dashboard designed to give realtime feedback to a sentinel network about key data required for influenza vaccine effectiveness studies. Stud Health Technol Inform. 2018;247:161-5.

[22] Pebody RG, Sinnathamby MA, Warburton F, Andrews N, Boddington NL, Zhao H, et al. Uptake and impact of vaccinating primary school-age children against influenza: experiences of a live attenuated influenza vaccine programme, England, 2015/16. Euro Surveillance: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin. 2018;23

2.2 Background rates of 41 Adverse Events of Special Interest for COVID-19 vaccines in 10 European healthcare databases - An ACCESS cohort study

Corinne Willame, Caitlin Dodd, Carlos Duran, Roel Elbers, Rosa Gini, Claudia Bartolini, Olga Paoletti, Lei Wang, Vera Ehrenstein, Johnny Kahlert, Ulrike Haug, Tania Schink, Javier Diez-Dominigo, Ainara Mira-Iglesias, Juan Jose Carreras, Carlos Vergara-Hernández, Carlo Giaquinto, Elisa Barbieri, Luca Stona, Consuelo Huerta, Maria Martin-Perez, Patricia Garcia-Poza, Airam de Burgos, Mar Martinez-Gonzalez, Felipe Villalobos, Meritxell Pallejà-Millán, Maria Aragón, Patrick Souverein, Nicolas Thurin, Daniel Weibel, Olaf Klungel, Miriam CJM Sturkenboom

Vaccine. 2023 Jan 4;41(1):251-262. doi:10.1016/j.vaccine.2022.11.031. Epub 2022 Nov 22.

Abstract

Background: In May 2020, the ACCESS (The vACCine covid-19 monitoring readinESS) project was launched to prepare real-world monitoring of COVID-19 vaccines. Within this project, this study aimed to generate background incidence rates of 41 adverse events of special interest (AESI) to contextualize potential safety signals detected following administration of COVID-19 vaccines.

Methods: A dynamic cohort study was conducted using a distributed data network of 10 healthcare databases from 7 European countries (Italy, Spain, Denmark, The Netherlands, Germany, France and United Kingdom) over the period 2017 to 2020. A common protocol (EUPAS37273), common data model, and common analytics programs were applied for syntactic, semantic and analytical harmonization. Incidence rates (IR) for each AESI and each database were calculated by age and sex by dividing the number of incident cases by the total person-time at risk. Age-standardized rates were pooled using random effect models according to the provenance of the events.

Findings: A total number of 63,456,074 individuals were included in the study, contributing to 211.7 million person-years. A clear age pattern was observed for most AESIs, rates also varied by provenance of disease diagnosis (primary care, specialist care). Thrombosis with thrombocytopenia rates were extremely low ranging from 0.06 to 4.53/100,000 person-years for cerebral venous sinus thrombosis (CVST) with thrombocytopenia (TP) and mixed venous and arterial thrombosis with TP, respectively.

Interpretation: Given the nature of the AESIs and the setting (general practitioners or hospital-based databases or both), background rates from databases that show the highest level of completeness (primary care and specialist care) should be preferred, others can be used for sensitivity. The study was designed to ensure representativeness to the European population and generalizability of the background incidence rates.

Funding: The project has received support from the European Medicines Agency under the Framework service contract nr EMA/2018/28/PE.

1. Background

On 11 January 2020, the release of the genetic sequence of SARS-CoV-2 triggered the rapid development of COVID-19 vaccines on a global level[1]. More than two hundred vaccine candidates were in the development pipeline. One year later, 26 vaccines were in use across the world[2], and as of January 10th, 2022, 9.46 billion COVID-19 vaccine doses have been administrated worldwide, and about half of the world population has been vaccinated[3]. Due to the rapid development of new COVID-19 vaccines, questions arose about the benefits and risks of the vaccines at individual and population levels. Several emerging safety signals have been detected soon after COVID-19 vaccines launches. Researchers have reported case series with unusual thrombotic events after immunization with ChAdOx1nCov-19 (Oxford/AstraZeneca)[4][5][6] and Ad26.COV2.S (Janssen/Johnson & Johnson)[7])vaccines, which led to several regulatory measures, mainly in Europe and in the United States[8] [9]. These thrombotic events were shown to occur, in most instances, in co-occurrence with thrombocytopenia. This new phenomenon, named thrombosis with thrombocytopenia syndrome (TTS), was further characterized with the initiation of the development of a case definition by the Brighton Collaboration Working Group[10]. Furthermore, the spectrum of adverse events has been expanded to conditions such as myocarditis and pericarditis[11] with series of cases initially reported after vaccination with Comirnaty (Pfizer) in Israel[12]. Other very rare events of capillary leak syndrome were reported after vaccination with adenovector viral vaccines[13] and more recently, Guillain Barré Syndrome (GBS) has been detected as a potential safety concern following administration with Ad26.COV2.S vaccine[14]. The experience with COVID-19 vaccines highlights once more the importance and the need for robust surveillance systems and collaboration to carefully monitor adverse effects even after regulatory approvals for timely adoption of public health measures. The same conclusion, made after the 2009 H1N1 pandemic, had led to the Innovative Medicines Initiative funded project that designed and tested a system in Europe, which was implemented by the Vaccine Monitoring Collaboration for Europe (VAC4EU) in January 2020[15]. In May 2020, ACCESS (The vACCine covid-19 monitoring readinESS), a project funded by the European Medicines Agency (EMA) leveraging

expertise in the European Pharmacoepidemiology & Pharmacovigilance research network and the VAC4EU, was launched to prepare real-world monitoring of COVID-19 vaccines[16]. This ACCESS study aimed to generate background incidence rates of adverse events of special interest (AESI) that would allow contextualization of potential safety signals detected following administration of COVID-19 vaccines.

2. Methods

Study design and setting

A multi-database dynamic cohort study was conducted in 10 healthcare databases from 7 European countries: Italy, Spain, Denmark, Netherlands, Germany, France and United Kingdom (UK). The study protocol (EUPAS37273) is publicly available on the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register[17]. The study was conducted over the period 2017 to 2020, except for two databases in which the study ran over the years 2010-2013 for Danish registries (DCE-AU) and 2014-2017 for German Pharmacoepidemiological Research Database (GePaRD). The 10 population-based healthcare databases included data from ARS, PEDIANET (Italy), FISABIO, BIFAP and SIDIAP (Spain), PHARMO (Netherlands), CPRD (UK), GePaRD (Germany), SNDS (France) and Danish Registries. The databases differed in terms of population size, provenance of the diagnosis (e.g., emergency room, in and/or outpatient, specialist or general practitioners (GP)) and diagnostic coding systems (International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM), and ICD, Tenth Revision, Clinical Modification (ICD-10-CM), ICD-10 German Modification (ICD10-GM), CIM10 (Classification Internationale des Maladies), Read, SNOMED CT US Edition and Spanish Edition (SCTSPA)). Table 1 provides a summary of the main characteristics of the data sources. For three of them (BIFAP, SIDIAP and PHARMO), subpopulations were defined which included individuals with both primary care and hospital medical records (BIFAP_PC_HOSP, SIDIAP_PC_HOSP and PHARMO versus BIFAP_PC, SIDIAP_PC and PHARMO_PC_HOSP). The creation of subpopulation was necessary when diagnosis records from hospital discharge data and primary care had different source populations and/or lag times.

Study population

The source population comprised all individuals observed in one of the participating databases for at least one day during the study period and who had at least one year of data availability before study entry, except for individuals with data available since birth. Individuals were included in the study according to pre-defined inclusion and exclusion criteria. Reasons for exclusion were: invalid or missing birth date or missing sex record, exit before study entry (01 January 2017; 01 January 2010 for DCE-AU; 01 January 2014 for GePaRD), and less than one year of look-back period prior to study entry. Individuals at increased risk of severe COVID-19 disease were identified according to the presence of at least one of the following underlying conditions in the look-back period or during the study follow-up: cardiovascular disease, cancer, chronic lung disease, HIV, chronic kidney disease, type 2 diabetes, severe obesity (BMI ≥ 30), sickle cell disease or use of immunosuppressants.

Adverse Events of Special Interest (AESI)

As part of the harmonization of COVID-19 vaccine safety monitoring during clinical development phase, the Coalition for Epidemic Preparedness Innovations (CEPI) has created a preliminary list of AESIs for COVID-19 vaccine safety monitoring together with the Brighton Collaboration[18]. This list of AESIs has been defined based on events that are related or potentially related to marketed vaccines, events related to vaccine platforms or adjuvants, and events that may be associated with COVID-19. This preliminary list has been further extended and was reviewed and accepted by the European Medicines Agency advisory group monitoring committee. The final list included a total of 41 AESIs, *see Box*.

Box List of AESIs included in the study

Box. List of Adverse Events of Special Interest included in this study

- ***Auto-immune diseases***
  1. Guillain-Barré syndrome (GBS)
  2. Acute Disseminated Encephalomyelitis (ADEM)
  3. Narcolepsy
  4. Acute aseptic arthritis
  5. Type 1 diabetes mellitus
  6. Thrombocytopenia
- ***Circulatory system***
  7. Disseminated intravascular coagulation (DIC)
  8. Arterial thrombosis with thrombocytopenia
  9. Arterial thrombosis without thrombocytopenia
  10. Venous thromboembolism (VTE)
  11. Venous thrombosis with thrombocytopenia
  12. Venous thrombosis without thrombocytopenia
  13. Mixed arterial/venous thrombosis with thrombocytopenia
  14. Mixed arterial/venous thrombosis without thrombocytopenia
  15. Cerebral venous sinus thrombosis (CVST)
  16. Cerebral venous sinus thrombosis with thrombocytopenia
  17. Cerebral venous sinus thrombosis without thrombocytopenia
  18. Thrombotic microangiopathy
  19. Haemorrhagic stroke
  20. Ischemic stroke
  21. Single organ cutaneous vasculitis (SOCV)
- ***Respiratory system***
  22. Acute respiratory distress syndrome
- ***Cardiovascular system***
  23. Microangiopathy
  24. Heart failure
  25. Stress cardiomyopathy
  26. Coronary artery disease
  27. Arrhythmia
  28. Myocarditis
  29. Myocarditis/pericarditis
- ***Nerves and central nervous system***
  30. Generalized convulsion
  31. Meningoencephalitis
  32. Transverse myelitis
- ***Skin and mucous membrane, bone and joints system***
  33. Erythema multiforme
  34. Chilblain
- ***Hepato-gastrointestinal and renal system***
  35. Acute liver injury
  36. Acute kidney injury
- ***Other system***
  37. Anosmia-Ageusia
  38. Anaphylaxis
  39. Multisystem inflammatory syndrome
  40. Death (any causes)
  41. Sudden death

Data management workflow and data analysis

This study was conducted in a distributed manner using a common protocol, a ConcePTION common data model (CDM)[19] for syntactic harmonization, a common analytics program for semantic harmonization and data transformation/analysis[20]. Each data access provider (DAP) applied the Extract-Transform-Load process which led to a syntactic harmonization. The syntactic foundation transforms the structure of the data sets held by each DAP to a common format. To create the study variables semantic harmonization was needed to reconcile differences across different terminologies. A shared semantic foundation was built for each AESI by using a standardized event definition form. For each AESI and underlying condition, medical code lists have been created using the ADVANCE code mapper tool[21] and integrated coding systems: ICD-9-CM, ICD-10-CM/GM, CIM10, READv2, SNOMED CT US Edition and SCTSPA. DAPs were asked to review and update the proposed medical codes based

on local coding habits and prior experience. Narrow and broad algorithms were established for most AESIs allowing, respectively, for a specific and a sensitive clinical case definition. Event definition forms including medical code lists were made publicly available through the VAC4EU Zenodo community (https://www.zenodo.org/communities/vac4eu/?page=1&size=20). R scripts that included semantic harmonization and transformation of data in the CDM into incidence rates were coded in R using version ≥ 3.1.0 and distributed to the DAPs for local deployment. Aggregated data were uploaded by each DAP on the Digital Research Environment (https://www.andrea-cloud.eu/azure-dre), a secured Microsoft Azure cloud-based research environment, for final analysis and pooling. Demographic characteristics including age and person-time of follow-up were computed in each data source. Incidence rates (IR) and 95% exact confidence interval (95%CI) for each AESI and for each database were calculated for the study period, by year, age and sex and by dividing the number of incident cases by the total person-time at risk. Age-standardized IRs (according to the European population[22]) for the period 2017-2019 (or 2010-2013 for DCE-AU or 2014-2017 for GePaRD) were pooled using the DerSimonian and Laird meta-analytic approach for random effects models according to the provenance of the events (Table 1). Incidence rates were expressed per 100,000 person-years (PY). Percentage change between the years 2017-2019 *versus* 2020 were also computed to assess the change in health care utilization during the COVID-19 pandemic. Statistical analyses were performed in SAS v9.4 and STATA v17.

Table 1 Characteristics of the data sources

Country	Data sources	Population covered	Active population	Type of data source	Provenance of events	Coding system	Categories for analysis based on provenance of events
Denmark	Danish registries	National	5.9 million	Record linkage	In-and out-patient diagnoses	ICD-10	IN-OUTPATIENT
France	SNDS	National	7.5 million*	Insurance claims	Health insurance, inpatient (hospital discharge) and outpatient (from long-term disease registration) diagnoses	CIM-10	IN-OUTPATIENT
Germany	GePaRD	National	10.5 million**	Insurance claims	Health insurance, In- and out-patient*** diagnoses	ICD-10-GM	INPATIENT only

Italy	ARS	Tuscany	3.0 million	Record linkage	Inpatient diagnoses and emergency room department	ICD-9-CM	INPATIENT & EMR
	PEDIANET	National	0.2 million	Family pediatricians medical records	GP records	ICD-9-CM	GP only
Spain	FISABIO	Valencia	5.8 million	Record linkage	GP records, in-and out-patient discharge and emergency room	ICD-9-CM / ICD-10	GP & IN-OUTPATIENT
	BIFAP	8 regions†	10.3 million	GP medical records	GP records, in-hospital discharge diagnoses	ICD-9-CM/ ICD-10 / SCTSPA	GP only GP & IN-OUTPATIENT (subpopulation)
	SIDIAP	Catalonia	6.2 million	Record linkage	GP records, in-and out-patient specialist diagnoses emergency room	ICD-10-CM	GP only GP & IN-OUTPATIENT (subpopulation)
The Netherlands	PHARMO	Sub-sample	9.2 million	Record linkage	GP records, in-patient specialist diagnoses	ICD-9-CM	INPATIENT only GP & IN-OUTPATIENT (subpopulation)
UK	CPRD	Sub-sample	4.7 million	GP medical records	GP records	Read code	GP only

ICD: International Classification of Diseases; CIM: Classification Internationale des Maladies; CM: Clinical Modification; GM: German Modification; SNOMED: US Edition of SNOMED Clinical Terms; SCTSPA: SNOMED Clinical Terms, Spanish Language Edition
*A 1/10th sample of the SNDS representative of the French population over the study period was used.
†The 8 regions do not include Catalonia nor Valencia.
**Only one large statutory health insurance provider was included which represents 10.5 million people out of 16 million.
***Outpatient diagnoses were not used in this project. GePaRD was only used for a limited number of AESIs diagnosed in inpatient setting (Guillain Barre Syndrome, acute respiratory disease syndrome, heart failure, coronary artery disease, generalized convulsion, acute kidney injury, acute liver injury, anaphylaxis, multisystem inflammatory syndrome)
IN-OUTPATIENT: hospitalization including in and/or-outpatient setting; GP: general practitioners; EMR: Emergency Room

3. Results

Characteristics of the population

A total number of 63,456,074 individuals were included in the study, contributing to 211.7 million person-years. Demographic characteristics are available in Table 2. The largest contributions in person-time were from GePaRD (17.1%) and BIFAP (16.3%), followed by SNDS (13.7%), PHARMO (12.6%), Danish registries (10.6%), FISABIO (9.9%), SIDIAP (9.4%), CPRD (6.0%), ARS (4.3%) and PEDIANET (0.2%). Subpopulation sizes of data sources with both GP and hospital diagnoses were available (through linkage for part of the population) for 100%, 43.1%, 28.3% and 5.4% of the full included population for FISABIO, BIFAP, SIDIAP and PHARMO, respectively.

Table 2 Demographic characteristics

	Denmark		France		Germany		Italy				Spain										The Netherlands				UK	
	DCE-AU		SNDS		GePaRD		ARS		PEDIANET		FISABIO		BIFAP_PC		BIFAP_PC_HOSP		SIDIAP_PC		SIDIAP_PC_HOSP		PHARMO_HOSP		PHARMO_PC_HOSP		CPRD	
	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%
Total number of subjects	5 955 360	.	7 479 708	.	10 539 971	.	3 067 602	.	181 290	.	5 886 560	.	10 266 468	.	4 423 843	.	6 205 573	.	1 758 239	.	9 184 832	.	496 197	.	4 688 710	.
Person-time (in years) across follow-up period (per age group)																										
Overall	22 490 217	-	29 025 408	-	36 127 076	.	9 065 271	.	356 184	.	20 911 202	.	34 525 598	.	8 494 349	.	19 845 706	.	5 355 124	.	26 568 111	.	1 164 810	.	12 762 349	.
0-19	5 417 245	24.09	7 037 843	24.25	7 024 252	19.44	1 396 241	15.4	356 184	100	4 103 324	19.62	6 368 798	18.45	1 475 624	17.37	3 878 177	19.54	1 002 231	18.72	4 285 628	16.13	221 438	19.01	2 863 126	22.43
20-29	2 639 524	11.74	3 635 959	12.53	4 913 004	13.60	796 689	8.79	-	-	2 073 398	9.92	3 294 295	9.54	780 125	9.18	2 014 182	10.15	536 922	10.03	3 201 274	12.05	134 601	11.56	1 437 077	11.26
30-39	2 890 365	12.85	3 784 253	13.04	5 388 329	14.91	908 683	10.02	-	-	2 746 498	13.13	4 412 677	12.78	1 070 247	12.6	2 801 475	14.12	747 012	13.95	3 507 399	13.2	133 829	11.49	1 709 558	13.4
40-49	3 294 106	14.65	3 747 827	12.91	5 458 071	15.11	1 391 120	15.35	-	-	3 460 336	16.55	5 490 532	15.9	1 319 480	15.53	3 447 041	17.37	933 846	17.44	3 862 330	14.54	160 034	13.74	1 754 888	13.75
50-59	2 923 975	13	3 692 979	12.72	6 153 604	17.03	1 478 656	16.31	-	-	3 012 592	14.41	5 095 982	14.76	1 255 375	14.78	2 782 154	14.02	762 148	14.23	3 934 798	14.81	182 981	15.71	1 854 253	14.53
60-69	2 778 684	12.36	3 270 947	11.27	3 626 015	10.04	1 180 125	13.02	-	-	2 399 175	11.47	4 003 342	11.6	995 612	11.72	2 129 361	10.73	589 617	11.01	3 153 788	11.87	157 884	13.55	1 446 057	11.33
70-79	1 618 270	7.2	2 203 655	7.59	2 682 491	7.43	1 068 981	11.79	-	-	1 887 325	9.03	3 034 922	8.79	765 961	9.02	1 577 614	7.95	447 477	8.36	2 368 347	8.91	115 293	9.9	1 074 750	8.42
80+	928 047	4.13	1 651 944	5.69	881 311	2.44	844 776	9.32	-	-	1 228 553	5.88	2 825 050	8.18	831 925	9.79	1 215 702	6.13	335 871	6.27	2 254 547	8.49	58 751	5.04	622 638	4.88
Person-time (in years) across follow-up period (per sex)																										
Female	11 319 983	50.33	14 774 535	50.90	18 146 362	50.23	4 706 024	51.91	170 278	47.81	10 641 698	50.89	17 701 930	51.27	4 347 542	51.18	10 067 763	50.73	2 713 540	50.67	13 967 221	52.57	589 204	50.58	6 408 155	50.21
Male	11 170 234	49.67	14 250 873	49.10	17 980 714	49.77	4 359 247	48.09	185 906	52.19	10 269 503	49.11	16 823 667	48.73	4 146 807	48.82	9 777 943	49.27	2 641 584	49.33	12 600 891	47.43	575 606	49.42	6 354 194	49.79

Note: PEDIANET includes only pediatric population up to 16 years old. BIFAP_PC_HOSP, SIDIAP_PC_HOSP and PHARMO_PC_HOSP represents subpopulations for BIFAP_PC, SIDIAP_PC and PHARMO_HOSP, respectively.

The study flowchart is available in Supplementary materials (Figure 1). The proportion of individuals affected by conditions which increase the severity of COVID-19 varied across databases, cardiovascular diseases and chronic lung diseases were the most prevalent risk factor for serious COVID-19 (Figure 2 in Supplementary materials).

Incidence rates of AESIs

IRs per database, per year, age and sex are detailed in the final study report available on Zenodo website[23] and on the VAC4EU dashboard[24]. Incidence rates that are presented in this paper used the narrow clinical definitions and are for time periods that exclude the year 2020. Table 3 presents age-standardized pooled incidence rates for all AESIs according to the provenance of events over the study period.

Table 3 Pooled incidence rates and 95% confidence intervals for all AESIs (narrow definition) over the study period* according to the provenance of the events databases

		Incidence rate (/100,000 person-years) (95%CI)				
Body System	**AESIs**	**GP only**	**INPATIENT only**	**INPATIENT & EMR**	**GP & IN-OUTPATIENT**	**IN-OUTPATIENT**
Autoimmune diseases	ADEM	0.05 (0.00-0.14)	-	0.08 (0.00-0.38)	0.33 (0.06-0.59)	-
	Acute Aseptic Arthritis**	-	-	-	-	-
	Guillain Barre Syndrome	1.25 (0.27-2.23)	2.09 (0.46-3.74)	3.39 (2.16-4.63)	3.21 (1.00-4.42)	3.33 (2.48-4.17)
	Narcolepsy	1.44 (0.81-2.07)	0.31 (0.06-0.56)	0.57 (0.00-1.14)	1.58 (0.91-2.26)	2.29 (0.77-3.80)
	Thrombocytopenia	38.99 (7.23-70.76)	18.01 (16.31-19.70)	29.55 (26.03-33.08)	92.09 (42.47-141.71)	63.16 (0.00-147.83)
	Type 1 Diabetes Mellitus	9.14 (4.27-14.01)	7.12 (6.41-7.83)	7.11 (5.83-8.39)	13.12 (9.88-16.36)	19.85 (18.86-20.84)
Cardiovascular system	Arrhythmia	536.72 (82.87-990.58)	288.71 (282.78-294.64)	802.32 (786.92-817.72)	1199.31 (899.09-1499.53)	880.86 (662.45-1099.28)
	Coronary Artery Disease	113.17 (71.44-154.91)	139.93 (51.26-228.61)	218.81 (211.51-226.11)	162.45 (119.08-205.81)	201.96 (191.14-212.77)
	Heart Failure	154.28 (11.27-297.29)	189.99 (47.17-332.81)	453.08 (443.65-462.51)	416.76 (270.89-562.64)	404.93 (222.19-587.67)
	Microangiopathy	0.32 (0.03-0.61)	1.11 (0.66-1.56)	0.62 (0.01-1.22)	3.39 (0.00-7.31)	7.13 (0.10-14.16)
	Stress Cardiomyopathy	0.24 (0.10-0.37)	-	5.60 (4.39-6.80)	2.90 (0.99-4.80)	-
	Myocarditis	1.43 (0.38-2.48)	1.28 (0.80-1.77)	6.61 (4.81-8.40)	3.18 (1.73-4.62)	5.30 (2.00-8.61)

	Myocarditis or Pericarditis	11.86 (1.42-22.31)	3.96 (3.15-4.78)	30.04 (26.34-33.74)	20.63 (12.91-28.35)	21.24 (11.61-30.87)
Respiratory system	ARDS	18.58 (3.73-33.44)	13.20 (0.00-30.20)	23.86 (20.99-26.72)	68.33 (16.10-120.56)	86.24 (32.27-140.21)
Circulatory system	Arterial or VTE with TP	0.20 (0.09-0.30)	1.42 (0.96-1.88)	1.85 (1.02-2.68)	4.53 (0.00-9.94)	5.43 (0.00-14.79)
	Arterial or VTE without TP	328.12 (40.52-615.71)	194.81 (189.92-199.70)	532.38 (520.19-544.56)	606.15 (510.17-702.13)	580.75 (532.39-629.11)
	Arterial with TP	0.09 (0.01-0.16)	0.77 (0.45-1.08)	0.91 (0.34-1.49)	2.73 (0.00-6.12)	2.04 (0.00-5.35)
	Arterial without TP	187.94 (32.56-343.32)	157.57 (153.34-161.80)	380.58 (370.84-390.32)	384.18 (279.11-489.24)	381.92 (318.93-444.92)
	CVST with TP	0.00 (0.00-0.15)	0.00 (0.00-0.08)	0.03 (0.00-0.27)	0.06 (0.00-0.19)	0.00 (0.00-0.02)
	CVST without TP	0.13 (0.00-0.27)	0.81 (0.42-1.19)	1.29 (0.47-2.11)	0.82 (0.50-1.14)	1.98 (0.08-3.88)
	CVST	0.13 (0.00-0.27)	0.81 (0.42-1.19)	1.31 (0.49-2.14)	0.85 (0.53-1.17)	2.04 (0.04-4.04)
	Disseminated Intravascular Coagulation	0.11 (0.03-0.20)	0.68 (0.32-1.04)	1.47 (0.69-2.26)	2.65 (0.00-5.85)	5.68 (0.00-11.61)
	Hemorrhagic stroke	10.54 (0.91-20.17)	16.08 (14.67-17.49)	60.84 (6.76-64.93)	43.58 (26.44-60.73)	52.96 (41.27-64.64)
	Ischemic stroke	104.69 (14.84-194.53)	66.28 (63.55-69.00)	171.75 (165.30-178.20)	229.29 (159.11-299.46)	187.73 (138.78-236.69)
	SOCV	8.16 (5.09-11.23)	1.50 (0.99-2.01)	8.04 (6.28-9.79)	14.58 (2.47-26.68)	11.16 (4.74-17.59)
	Thrombotic microangiopathy	0.32 (0.00-0.65)	0.47 (0.18-0.76)	0.62 (0.20-1.03)	1.03 (0.75-1.32)	1.54 (0.34-2.74)
	VTE with TP	0.11 (0.02-0.19)	0.68 (0.34-1.02)	0.97 (0.32-1.62)	1.95 (0.00-4.24)	3.45 (0.00-9.59)
	VTE without TP	141.68 (9.68-273.68)	40.12 (37.73-42.51)	160.94 (153.74-168.14)	228.48 (206.26-250.71)	209.55 (88.61-230.48)
	VTE	141.77 (9.70-273.84)	40.66 (38.25-43.07)	161.66 (154.44-168.88)	229.67 (207.52-251.83)	211.85 (186.82-236.87)
Hepato-gastrointestinal and renal system	Acute Kidney Injury	190.25 (87.45-293.04)	138.47 (53.67-223.26)	222.62 (215.48-229.76)	544.24 (156.52-931.96)	421.03 (40.51-801.55)
	Acute Liver Injury	12.87 (1.54-24.19)	8.37 (5.82-10.91)	25.16 (21.91-28.42)	35.09 (19.87-50.31)	32.96 (8.38-57.55)
Nerves and central nervous system	Generalized Convulsion	73.64 (43.77-103.51)	80.68 (9.66-151.70)	142.56 (134.83-150.30)	152.35 (78.67-226.02)	194.28 (175.77-212.79)
	Meningoencephalitis	2.26 (0.33-4.19)	1.30 (0.81-1.78)	5.74 (4.11-7.36)	7.34 (4.19-10.49)	5.94 (2.43-9.45)
	Transverse Myelitis	0.40 (0.06-0.74)	0.27 (0.03-0.50)	1.11 (0.34-1.88)	0.48 (0.23-0.72)	0.69 (0.00-1.72)
Other system	Anaphylaxis	9.39 (3.16-15.61)	6.82 (0.00-13.71)	7.44 (5.54-9.33)	14.17 (7.46-20.87)	11.30 (10.04-12.56)
	Anosmia, Ageusia	13.48 (2.95-24.01)	0.12 (0.00-0.29)	0.08 (0.00-0.37)	24.50 (15.09-33.91)	1.70 (1.25-2.14)

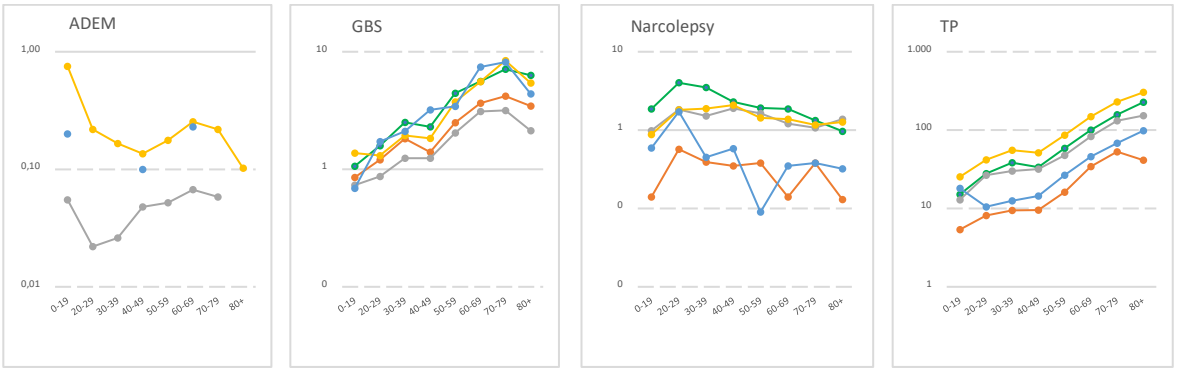
	Death	642.94 (87.87-1198.01)	-	1150.09 (1134.88-1165.30)	812.34 (720.03-904.64)	1022.92 (661.34-1384.50)
	MIS	0.52 (0.33-0.72)	0.59 (0.41-0.78)	1.08 (0.56-1.59)	1.18 (0.23-2.13)	0.79 (0.31-1.28)
	Sudden death	52.96 (41.25-64.67)	-	1.97 (1.21-2.73)	81.62 (34.21-129.03)	24.30 (0.00-64.32)
Skin and mucous membrane system	Chilblain like lesions	13.66 (1.01-26.32)	0.01 (0.00-0.09)	0.17 (0.00-0.54)	22.25 (2.70-41.79)	0.21 (0.00-0.65)
	Erythema multiforme	5.99 (2.23-9.76)	0.31 (0.06-0.56)	9.65 (7.52-11.78)	8.72 (4.33-13.11)	2.64 (0.00-5.87)

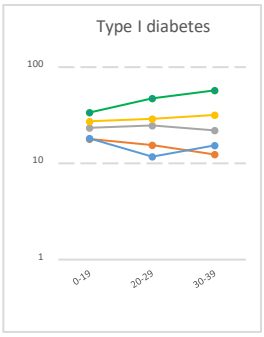
*Study period for Danish registries: 2010-2013 and for GePaRD: 2014-2017. **No narrow clinical definition for acute aseptic arthritis available. GePaRD: only the following events were included in the study: GBS, ARDS, HF, CAD, Generalized convulsion, Acute Kidney Injury, Acute Liver Injury, anaphylaxis, MIS. GPs: general practitioners. ADEM: Acute Disseminated Encephalomyelitis, ARDS: Acute Respiratory Distress Syndrome, CVST: Cerebral Venous Sinus Thrombosis, DIC: Disseminated Intravascular Coagulation, MIS: Multisystem Inflammatory Syndrome, SOCV: Single Organ Cutaneous Vasculitis, TP: Thrombocytopenia, VTE: Venous Thromboembolism. GP only: PEDIANET, BIFAP, SIDIAP, CPRD; INPATIENT only: PHARMO; INPATIENT & EMR: ARS; GP & IN-OUTPATIENT: FISABIO, BIFAP subpopulation, SIDIAP subpopulation, PHARMO subpopulation; IN-OUTPATIENT: Danish registries, SNDS.

Plots in Figure 1 depict the incidence rates per age and according to the provenance of events. Age- and sex-stratified incidence rates for all AESIs according to the ACCESS recommendations are presented in Supplementary materials (Table 1).

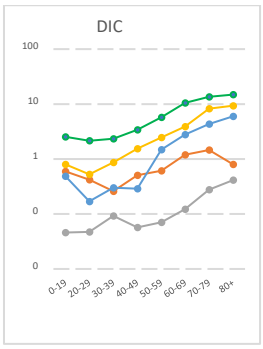
Figure 1 Age-stratified incidence rates for AESIs per body system over the study period* (per 100,000 person-years)

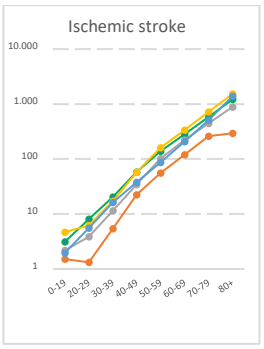
Autoimmune diseases

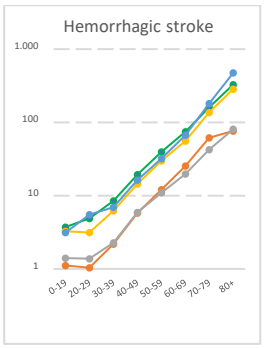


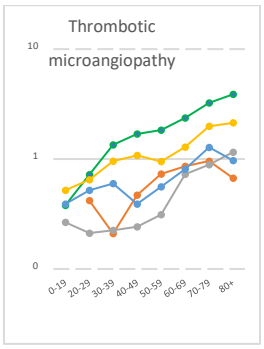


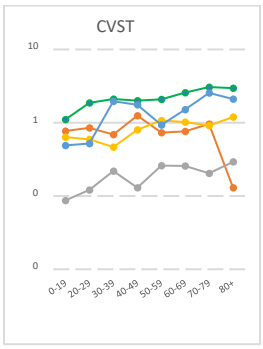
Circulatory system

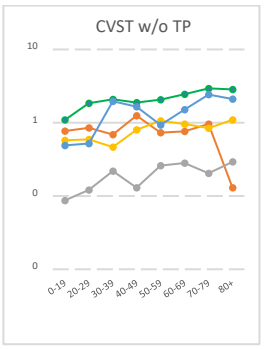


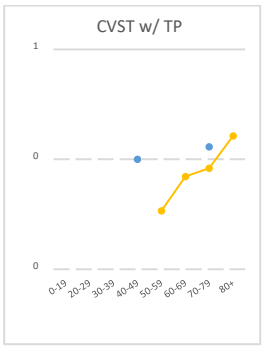


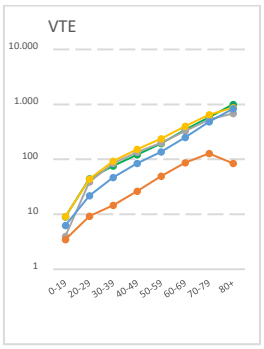


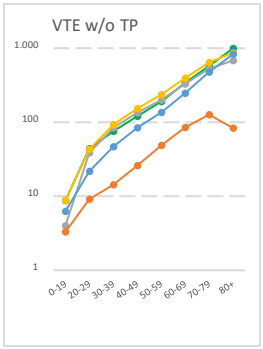


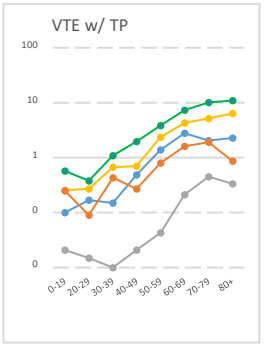


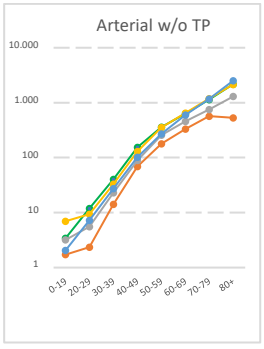


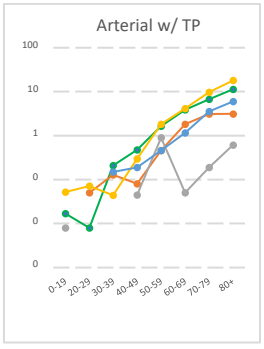


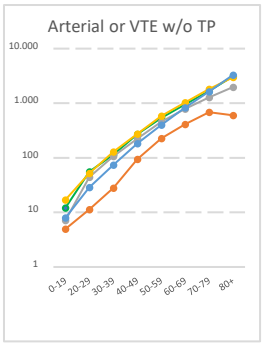


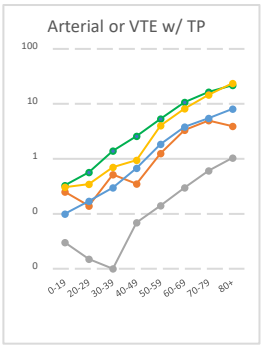




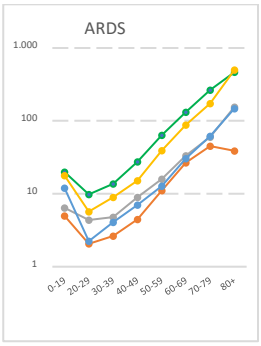






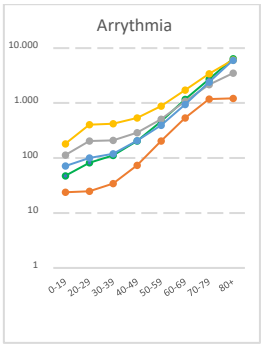


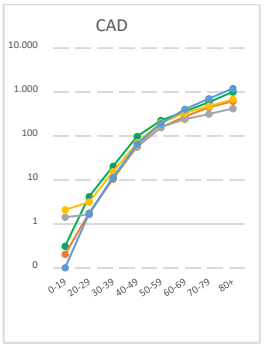
Respiratory system

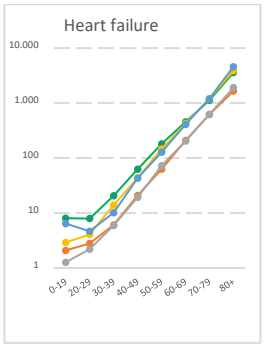


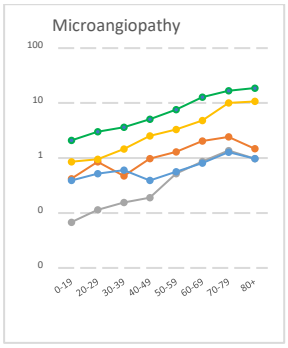
Cardiovascular system

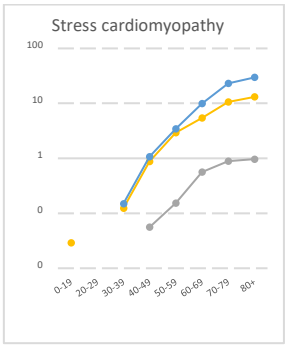
Nerves and central nervous system

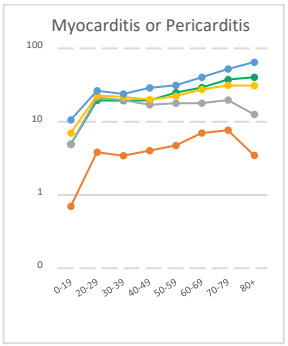


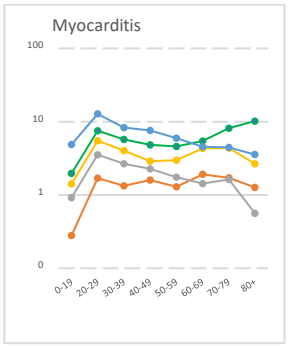


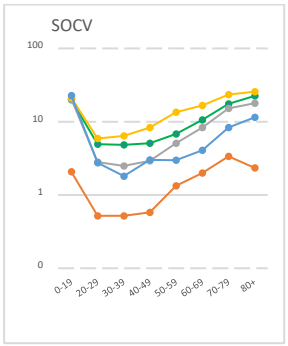


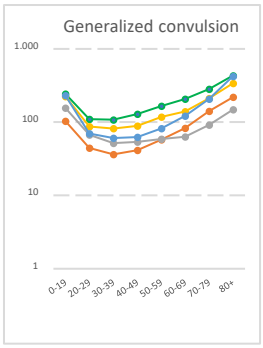


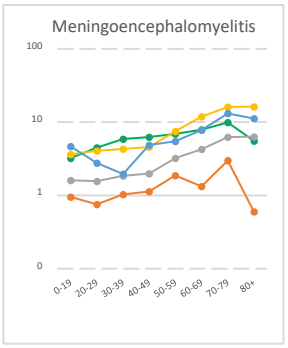


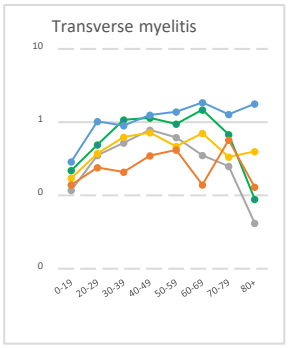




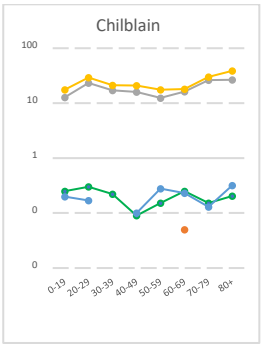


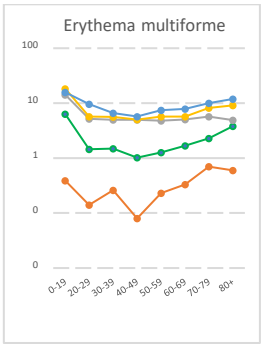




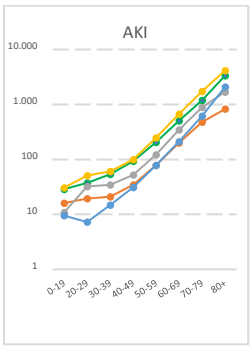


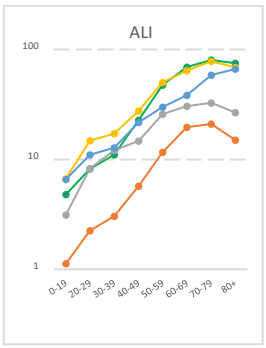
Skin and mucous membrane, bone and joints system



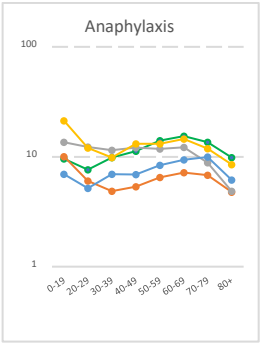


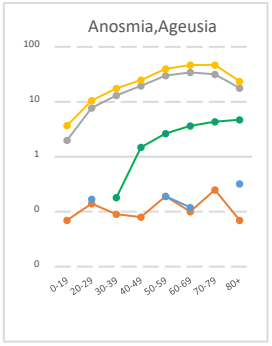
Hepato-gastrointestinal and renal system

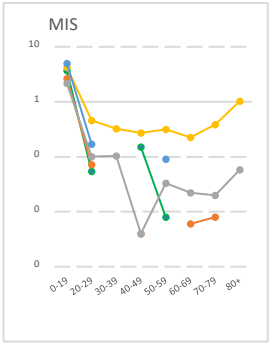


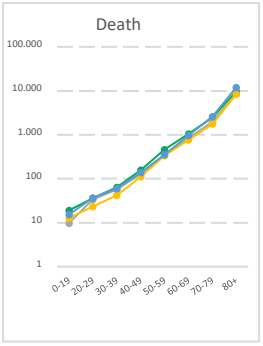


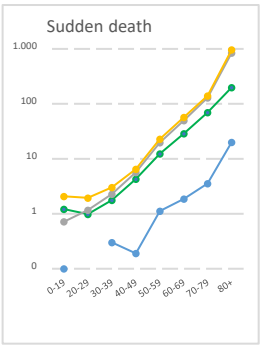
Other system











*The study period includes the year 2017 to 2019, except for for two databases in which the study ran over the years 2010-2013 for Danish registries (DCE-AU) and 2014-2017 for German Pharmacoepidemiological Research Database (GePaRD). Note: Log scale was used to highlight the age-pattern. The log scale was automatically generated based on the magnitude of the incidence rates and varied across AESIs. No narrow clinical definition for acute aseptic arthritis available. ADEM: Acute Disseminated Encephalomyelitis, AKI: Acute Kidney Injury, ALI: Acute Liver Injury, ARDS: Acute Respiratory Distress Syndrome, CVST: Cerebral Venous Sinus Thrombosis, DIC: Disseminated Intravascular Coagulation, MIS: Multisystem Inflammatory Syndrome, SOCV: Single Organ Cutaneous Vasculitis, TP: Thrombocytopenia, VTE: Venous Thromboembolism.

For the autoimmune diseases, pooled IRs for ADEM, GBS and narcolepsy were the lowest rates. Provenance of diagnoses impacted substantially the observed rates with diagnoses of narcolepsy, GBS and diabetes most frequently reported in settings including in-outpatient and/or GPs records. A clear age and sex-pattern was shown for GBS and TP. IRs for GBS and TP were slightly elevated in males. Cardiovascular disorders were more frequently reported in the hospital setting. Microangiopathy and stress cardiomyopathy showed the lowest rates compared to other cardiovascular disorders. A peak of myocarditis and myocarditis/pericarditis was observed in the 20-29 age category and higher rates of SOCV were observed in the younger population (0-19). IRs for myocarditis and coronary artery disease were higher in males, while IR for stress cardiomyopathy was higher in females. For circulatory disorders, IRs were higher for diagnoses from hospital records as compared to diagnoses in GPs records. Rates ranged from 229.67/100,000 PY for venous thromboembolism (VTE) to 0.85/100,000 PY for CVST in databases including GPs and hospital medical records. TTS rates were extremely low ranging from 0.06/100,000 PY for CVST with TP to 4.53/100,000 PY for mixed venous and arterial thrombosis with TP. Circulatory disorders were shown to increase with age, except for CVST for which

an age-pattern was not detected. IRs for disseminated intravascular coagulation, arterial thrombosis and microangiopathy were higher in males compared to females. Hepato-gastrointestinal disorders were more frequently reported in hospitals or GPs settings with rates increasing with age and a slight decrease for acute liver injury in the elderly (80+). Similarly, nerves and central nervous disorders were more frequently reported in hospital setting. Rates for generalized convulsion peaked in the younger population (20-29) and in the elderly (80+). No clear age-pattern was observed for meningoencephalitis and rates for transverse myelitis dropped in the 80+. IR for transverse myelitis was slightly elevated in females. Anaphylaxis and anosmia-ageusia diagnoses were more frequently reported in settings including GPs records. Rates for anaphylaxis and multisystem inflammatory disorders peaked in the younger ages (0-19). Rates for death and sudden death showed a clear age-pattern across study setting but could not be detected in settings including exclusively inpatient medical records. ARDS was more frequently reported in the hospital setting with rates declining in 20-29 year-olds and increasing again with age. Chilblain-like lesion and erythema multiforme diagnoses were more frequently reported in settings including GPs medical records. Rates of chilblain-like lesion peaked in 20-29 year-olds; erythema multiforme peaked in ages 0-19. Both AESIs showed higher rates in females compared to males.

Incidence rates in 2020 and in population with underlying conditions

For the year 2020, all AESIs, except anaphylaxis and ARDS, were less frequently reported in setting with emergency room visit. Anosmia-ageusia, sudden death, ARDS and thrombosis (CVST and VTE) were more frequently reported in settings with both GP and hospital medical records (Figure 3, Supplementary materials). IRs in population with underlying conditions showed significantly higher rates for all AESIs compared to the general population (data not shown).

4. Discussion

Based on data from 63 million European individuals, this cohort study generated age-and-sex specific background incidence rates with high precision for a pre-specified list of 41 AESIs, necessary for monitoring the safety of COVID-19 vaccines. We generated background incidence rates using a

distributed data network with common protocol, common data model and common analytics using 10 diverse healthcare databases across 7 European countries. These rates have been reported from January 2021 onwards, periodically and were used throughout 2021 by the European Medicines Agency and vaccine manufacturers for observed/expected analyses (personal communication).

Gubernot et al. (2021)[25] recently conducted a literature review of incidence rates of 22 AESIs, as well as the Brighton Collaboration (9 events); our overall rates are consistent with the literature derived data although we could not compare age and sex strata. Li et al. (2021)[26] recently published a study on AESI incidence rates from the OHDSI network, which covered general practice or claims data from eight countries (USA, UK, Australia, France, Germany, Spain, Netherlands and Japan) and reported on 15 AESIs. In general, our results differed substantially for several of the 12 common AESIs, which may be explained by the fact that incidence rates from the 8 countries were pooled regardless that the provenance of the events that went into the numerator differed substantially: 5 of the OHDSI data sources only captured GP recorded diagnosis data, whereas US and Japanese data captured claims. Our approach and strength were to pool results only across similar provenance of the event and to present the rates by provenance, independently. We considered the different provenances in the analysis as this is crucial for the correct interpretation of real-world evidence derived from heterogeneous data sources, several AESIs are only diagnosed in secondary care and are underestimated in primary care medical records, such as cardiovascular and thrombotic events. We would recommend that rates are presented by provenance and that this diversity is preserved in the pooling for the observed/expected analyses.

To give examples we briefly describe and compare the rates for selected AESIs with published data focusing on AESI that have been identified as safety risks following administration of COVID-19 vaccines. More detailed contextualization of the rates for each of the different AESI against published references is available in our final study report[23]. Our VTE rates (pulmonary embolism and deep vein thrombosis) were of similar magnitude compared to literature data retrieved by Gubernot et al. (2021) (108-117/100,000 PY)(25), Huang et al. (2014) (133/100,000 PY)[27] and Pottegard et al. (2021) (126-

158/100,000 PY)[28], with a notable increase of incidence with age. For TTS, we operationalized the Brighton Collaboration case definition after a public webinar by VAC4EU & Brighton Collaboration (https://youtu.be/-Sp5GKfzB2I) establishing four subcategories of thromboembolic events, i.e., venous thrombosis (VTE), arterial thrombosis (AMI and stroke), CVST and the combination of all (mixed venous and arterial), each of the thromboembolic conditions was stratified by the co-occurrence of a thrombocytopenia diagnosis within 10 days around the thromboembolic diagnosis. Our observations suggested that CVST is extremely rare, as are any of the combinations with thrombocytopenia, with rates estimated at <1 to 5/100,000 PY. These observations are consistent with the recent study from Burn (2021)[29]. Our clinical definition for thrombocytopenia included both immune thrombocytopenia and secondary thrombocytopenia and showed higher rates compared to other published references such as Li et al. [26]which restricted the concept definition to immune diseases (448/100,000 PY versus 56/100,000 PY in males of older ages). Our incidence rates for the composite endpoint myocarditis/pericarditis were slightly lower compared to data from Li et al. (2021)[26], since we excluded chronic conditions and causes such as rheumatism. Our rates of myocarditis were much lower than our composite of myocarditis/pericarditis, showing that the composite endpoint was mainly driven by pericarditis medical conditions. Our rates for myocarditis differed by age and sex and were comparable with Gubernot et al. (2021)[25] which reported rates ranging from 1 to 10 cases/100,000 PY. The impact of the COVID-19 pandemic on healthcare seeking and recording was clearly highlighted in the year 2020 with a sharp increase in rates in medical events directly related to COVID-19 such as ARDS, sudden death and anosmia-ageusia.

How to use the background rates

In the context of readiness for real-world monitoring of COVID-19 vaccines, the background incidence rates, which had been released periodically and openly, have been proven useful for observed-to-expected (O/E) analyses by EMA and vaccine manufacturers. In vaccine pharmacoepidemiology, signal detection methods are preliminary assessments allowing identification of potential safety concerns, but background rates are required to interpret them[30,31]. Health authorities usually request O/E

analysis to refine detected safety signals before implementing any further assessments[32]. The O/E analysis relies on exposure data and published background incidence rates. Since mass vaccinations campaigns usually roll out in a channeled manner, it is of crucial importance to have rates stratified by age, sex, and underlying comorbidity, which usually is poorly documented in the literature. In this study, age, sex-stratified and comorbidity specific rates were generated from 10 existing large electronic healthcare databases in 7 European countries, with semantically harmonized data. Because each data source has its own characteristics with regards to provenance of the events (GPs only, in or outpatient settings, emergency room visit or specialist referrals), we provided pooled estimates according to the provenance of the events. Background rates can be generated prior to vaccination roll-out when electronic health data are available, but the users should be aware of the nature of the event, the setting in which it is diagnosed, and evaluate whether the data source appropriately captures the data. Data sources that contain data from the setting where the disease is typically diagnosed should be preferred. In this study, given the nature of the AESIs included in this study, we recommend using background rates from data banks that show the highest level of completeness of identification of these events in terms of the type of diagnoses (such as GP and hospital-based data sources) which includes all data sources with such subpopulation. For some events, such as CVST, data sources including emergency and outpatient visits may be preferred, while for anosmia-ageusia or chilblain-like lesions, data sources including GPs setting would be recommended (see Table 1 in Supplementary materials).

Strengths and Limitations

ACCESS was a project funded by the EMA to prepare European infrastructure to monitor COVID-19 vaccines. The project ran from May 2020 to July 2021 and delivered background rates of AESIs, template protocols for implementation of observational studies, and feasibility assessments in each country to participate in studies and analyses performed by EMA for its Scientific Committees and ECDC. All deliverables have been made publicly available immediately to the scientific community through the EU PAS register (https://www.encepp.eu/encepp/studiesDatabase.jsp), the VAC4EU

website (https://vac4eu.org) and Zenodo (https://www.zenodo.org). European data sources are quite heterogeneous because of different coding systems, health care practices, provenance of diagnosis and systems. To standardize the analytical process, we applied a two-step approach, first a syntactic harmonization, putting all data in the same structure, and secondly a semantic harmonization, which was conducted transparently and centrally through a R-script. Semantic harmonization is complex, and infinite. It comprises harmonization of different coding systems with different granularity levels, coding practices in different settings. The harmonization process across terminologies was organized through the use of the Unified Medical Language System using the Codemapper[21] followed by extensive review of codes by the DAPs. This harnesses the expertise of the local data sources. It is acknowledged that while a rigorous harmonization process has been applied, residual heterogeneity may persist within and between data sources which would impact pooled results. Therefore, it is our recommendation to consider, in addition to pooled incidence rates, data source-specific incidence rates for further used of the generated data. The question on heterogeneity paths the way for the development of metrics to measure heterogeneity in data sources and the development of guidance to define acceptable thresholds when conducting distributed data network studies. Our study stressed the importance of an appropriate study setting to conduct future safety research's studies. Due to the nature and resource constraints for this study, case validation could not be conducted; we attempted to assess and reveal the impact of potential misclassification by using narrow and broad clinical definitions for most of the AESIs, and by stratifying by the provenance of diagnosis. In some instances, the governance approval can be a lengthy process, especially in a pandemic situation. For this reason, the Danish DAP decided to prioritize the use of a set of data for which ethics approval was previously obtained. For the other DAPs, we obtained governance approvals from scientific and ethics committees within a few weeks after submission of the protocol. Access to data was also facilitated with pre-agreement with DAPs. Ultimately, we could generate background incidence rates for newly identified syndrome like TTS in a few days showing the strength of the network in rapid response to specific research questions.

5. Conclusion

The ACCESS project started at an early stage of the COVID-19 pandemic as a component of the EMA readiness strategy for the times where vaccines would be authorized. ACCESS was successful in delivering these data on time as the first set of background rates were made available to EMA in December 2020, providing support to the safety monitoring of vaccines as soon as they were available in the EU. A large population of 63 million European individuals was included in the study, without restrictions beyond study period, to ensure representativeness to the European population and generalizability of the background incidence rates.

References

[1] Ahmed SF, Quadeer AA, McKay MR. Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies. Viruses 2020;12(3). Available from: https://www.mdpi.com/1999-4915/12/3/254

[2] Shrotri M, Swinnen T, Kampmann B, Parker EPK. An interactive website tracking COVID-19 vaccine development. Lancet Glob Heal 2021;9(5):e590–2. Available from: https://doi.org/10.1016/S2214-109X(21)00043-7

[3] Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. Nat Hum Behav 2021;5(7):947–53. Available from: https://doi.org/10.1038/s41562-021-01122-8

[4] Scully M, Singh D, Lown R, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021;384(23):2202–11. Available from: https://doi.org/10.1056/NEJMoa2105385

[5] Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021;384(22):2124–30. Available from: https://doi.org/10.1056/NEJMoa2104882

[6] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021;384(22):2092–101. Available from: https://doi.org/10.1056/NEJMoa2104840

[7] See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA 2021;325(24):2448–56. Available from: https://doi.org/10.1001/jama.2021.7517

[8] European Medicines Agency. EMA's safety committee continues investigation of COVID-19 Vaccine AstraZeneca and thromboembolic events – further update [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://www.ema.europa.eu/en/news/emas-safety-committee-continues-investigation-covid-19-vaccine-astrazeneca-thromboembolic-events

[9] U.S. Food & Drug Administration. FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough

[10] Brighton Collaboration. Interim Case Definition of Thrombosis with Thrombocytopenia Syndrome (TTS) [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-

definition/

[11] Brighton Collaboration. Myocarditis/Pericarditis Case Definition [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://brightoncollaboration.us/myocarditis-case-definition-update/

[12] Vogel G, Couzin-Frankel J. Israel reports link between rare cases of heart inflammation and COVID-19 vaccination in young men. Science [Internet]. 2021 Jun 1 [cited 2022 Feb 2]; Available from: https://www.science.org/content/article/israel-reports-link-between-rare-cases-heart-inflammation-and-covid-19-vaccination

[13] European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 June 2021 [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-7-10-june-2021

[14] Centers for Disease Control and Prevention. ACIP Presentation Slides: July 22, 2021 Meeting [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://www.cdc.gov/vaccines/acip/meetings/slides-2021-07-22.html

[15] Sturkenboom M, Bahri P, Chiucchiuini A, et al. Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines. Vaccine 2020;38:B1–7. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X19310023

[16] European Medicines Agency. EMA commissions independent research to prepare for real-world monitoring of COVID-19 vaccines [Internet]. 2020 [cited 2022 Feb 2]. Available from: https://www.ema.europa.eu/en/news/ema-commissions-independent-research-prepare-real-world-monitoring-covid-19-vaccines

[17] European Network for Centres for Pharmacoepidemiology and Pharmacovigilance. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines [Internet]. 2020 [cited 2022 Feb 2]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=37274

[18] Brighton Collaboration. Priority List of Adverse Events of Special Interest: COVID-19 [Internet]. 2020 [cited 2022 Feb 2]. Available from: https://brightoncollaboration.us/priority-list-aesi-covid/

[19] Thurin NH, Pajouheshnia R, Roberto G, et al. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clin Pharmacol Ther 2022;111(1):321–31. Available from: https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.2476

[20] Gini R, Sturkenboom MCJ, Sultana J, Cave A, Landi A, Pacurariu A, et al. Different Strategies to Execute Multi-Database Studies for Medicines Surveillance in Real-World Setting: A Reflection on the European Model. Clin Pharmacol Ther 2020;108:228–35.

[21] Becker BFH, Avillach P, Romio S, et al. CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiol Drug Saf 2017;26(8):998–1005.

[22] Eurostat. Population change - Demographic balance and crude rates at national level [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://ec.europa.eu/eurostat/databrowser/view/DEMO_GIND__custom_1110718/bookmark/table?lang=en&bookmarkId=39d70859-90b3-4d58-ba1e-5096d89d608d

[23] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo. 2021.

[24] VAC4EU. Dashboard Background rates of Adverse Events of Special Interest for COVID-19 vaccines [Internet]. 2021 [cited 2022 Feb 2]. Available from: https://vac4eu.org/covid-19-tool/

[25] Gubernot D, Jazwa A, Niu M, et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine 2021;39(28):3666–77. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X21005788

[26] Li X, Ostropolets A, Makadia R, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: Multinational network cohort study. BMJ 2021;373:n1435.

[27] Huang D, Chan P-H, She H-L, et al. Secular trends and etiologies of venous thromboembolism in Chinese from 2004 to 2016. Thromb Res 2018;166:80–5. Available from: https://doi.org/10.1016/j.thromres.2018.04.021

[28] Pottegård A, Lund LC, Karlstad Ø, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114. Available from: http://www.bmj.com/content/373/bmj.n1114.abstract

[29] Burn E, Li X, Kostka K, et al. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: incidence between 2017 and 2019 and patient profiles from 20.6 million people in six European countries. medRxiv 2021;2021.05.12.21257083. Available from: http://medrxiv.org/content/early/2021/05/13/2021.05.12.21257083.abstract

[30] Black S, Eskola J, Siegrist C-A, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009;374(9707):2115–22. Available from: https://doi.org/10.1016/S0140-6736(09)61877-8

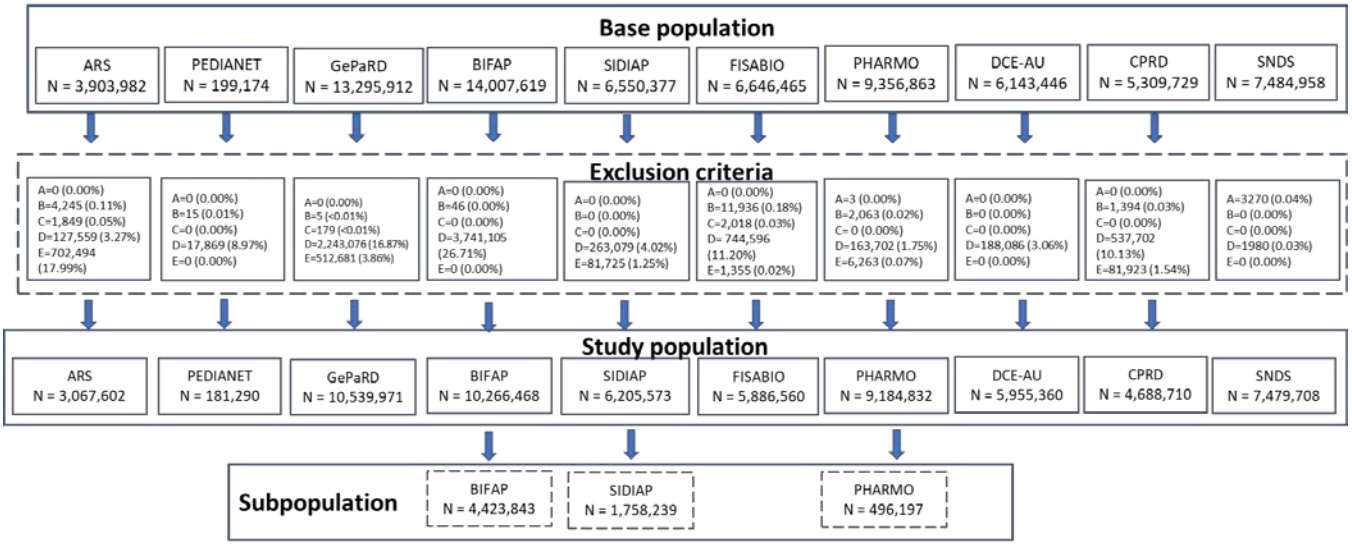
[31] Black SB, Law B, Chen RT, Dekker CL, Sturkenboom M, Huang W-T, et al. The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety.

Vaccine 2021;39(19):2712–8. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X2100284X

[32] Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Vol. 25, Pharmacoepidemiol Drug Saf 2016;25:215–22.

Supplementary materials

Figure 1 Study flowchart



Exclusion criteria: A=no record for sex or birth date; B=invalid birth date; C=death date before study entry; D=no overlap in observation period; E=insufficient look-back period

Table 1 Pooled sex-and-age stratified incidence rates according to the provenance of the events
Incidence rates for all AESIs, except anosmia-ageusia should rely on hospital databanks (GP and INOUTPATIENT databases). Incidence rates for anosmia-ageusia should rely on data generated using GPs databanks (GP only databases). Note: rates for acute aseptic arthritis were not available because no narrow clinical definition could be developed.

Autoimmune diseases

AESIs	Age group	Female	Male
Guillain Barre Syndrome	0-19	1.20 (0.74-1.65)	1.54 (1.05-2.03)
	20-29	0.92 (0.34-1.50)	1.63 (0.90-2.37)
	30-39	1.51 (0.65-2.37	2.11 (1.21-3.01)
	40-49	1.95 (1.28-2.62)	2.23 (1.30-3.16)
	50-59	2.60 (1.87-3.34)	4.85 (3.87-5.84)
	60-69	4.78 (2.18-7.38)	6.13 (3.50-8.66)
	70-79	6.12 (4.18-8.06)	11.07 (4.52-17.63)
	80+	3.64 (0.07-7.21)	8.29 (1.70-14.88)
	Overall	2.46 (1.871-3.041)	3.77 (2.94 (4.60)
ADEM	0-19	0.71 (0.22-1.19)	0.80 (0.00-1.83)
	20-29	0.35 (0.00-0.76)	0.13 (0.00-0.43)
	30-39	0.23 (0.00-0.52)	0.11 (0.00-0.34)

	40-49	0.16 (0.00-0.39)	0.13 (0.00-0.42)
	50-59	0.11 (0.00-0.32)	0.23 (0.00-0.51)
	60-69	0.22 (0.00-0.53)	0.20 (0.00-0.50)
	70-79	0.28 (0.00-0.65)	0.19 (0.00-0.59)
	80+	0.06 (0.00-0.33)	0.08 (0.00-0.51)
	Overall	0.21 (0.11-0.31)	0.21 (0.08-0.34)
Narcolepsy	0-19	0.88 (0.22-1.49)	0.89 (0.39-1.38)
	20-29	1.99 (1.00-2.99)	1.80 (0.21-3.38)
	30-39	1.73 (1.09-2.37)	2.23 (1.51-2.94)
	40-49	2.07 (0.74-3.40)	2.66 (1.77-3.56)
	50-59	1.63 (0.29-2.98)	1.61 (0.76-2.46)
	60-69	1.52 (0.88-2.17)	1.38 (0.74-2.02)
	70-79	1.23 (0.56-1.89)	1.11 (0.00-2.42)
	80+	1.26 (0.56-1.96)	1.28 (0.35-2.21)
	Overall	1.50 (1.18-1.82)	1.54 (1.18-1.90)
Type 1 Diabetes Mellitus	0-19	25.53 (22.46-28.60)	29.14 (26.26-32.01)
	20-29	25.18 (18.11-32.25)	30.82 (20.34-41.31)
	30-39	26.83 (14.57-39.08)	35.90 (19.99-51.82)
	Overall	25.50 (21.20-29.80)	31.76 (26.54-36.97)
Thrombocytopenia	0-19	23.93 (10.86-36.40)	26.85 (11.59-42.11)
	20-29	48.98 (19.39-78.58)	34.43 (13.21-55.64)
	30-39	70.61 (32.36-108.86)	41.16 (23.25-59.08)
	40-49	50.28 (21.19-79.37)	52.98 (25.72-80.24)
	50-59	68.78 (36.02-101.54)	103.57 (47.33-159.82)
	60-69	108.04 (60.26-155.83)	192.73 (90.04-295.42)
	70-79	160.84 (81.57-240.10)	312.17 (139.05-485.29)
	80+	315.15 (68.80-361.50)	447.69 (167.23-728.14)
	Overall	92.40 (74.79-110.00)	147.17 (123.45-170.89)

ADEM: Acute Diseminated Encephalomyelitis

Circulatory system

AESIs	Age group	Female	Male
Disseminated Intravascular Coagulation	0-19	0.59 (0.00-1.25)	1.00 (0.00-2.28)
	20-29	0.17 (0.00-0.51)	0.81 (0.09-1.54)
	30-39	1.00 (0.50-1.51)	0.78 (0.00-1.82)
	40-49	1.50 (0.08-2.92)	1.49 (0.00-3.50)
	50-59	1.50 (0.00-3.82)	3.52 (0.00-7.77)
	60-69	2.89 (0.00-6.39)	5.12 (0.00-12.05)
	70-79	6.62 (0.00-13.61)	10.25 (0.00-22.99)
	80+	7.98 (0.00-16.77)	11.93 (0.00-27.60)
	Overall	1.99 (1.39-2.60)	2.98 (2.23-3.73)
Arterial without TP	0-19	7.08 (2.36-11.80)	6.83 (1.86-11.80)
	20-29	8.29 (6.73-9.85)	9.72 (6.72-12.71)
	30-39	23.27 (18.09-28.46)	40.06 (33.77-46.35)
	40-49	71.50 (52.55-90.45)	177.89 (140.22-215.57)
	50-59	182.01 (133.17-230.84)	525.51 (418.99-632.02)
	60-69	384.45 (276.80-492.11)	940.52 (669.50-1211.54)
	70-79	847.71 (603.91-1091.53)	1570.60 (1109.83-2031.37)
	80+	1919.06 (1289.11-2549.01)	2540.80 (1657.11-3424.50)
	Overall	377.21 (347.95-406.48)	634.06 (597.68-670.44)
Arterial with TP	0-19	0.07 (0.00-0.23)	0.04 (0.00-0.17)
	20-29	0.07 (0.00-0.34)	0.11 (0.00-0.41)
	30-39	0.08 (0.00-0.30)	0.00 (0.00-0.15)
	40-49	0.19 (0.00-0.43)	0.40 (0.00-0.94)
	50-59	0.85 (0.00-1.82)	2.86 (0.00-6.13)
	60-69	1.69 (0.00-4.13)	6.84 (0.00-15.82)
	70-79	6.21 (0.00-13.33)	13.78 (0.00-32.57)
	80+	9.11 (0.00-21.69)	32.22 (0.00-66.73)
	Overall	0.78 (0.42-1.14)	1.73 (1.20-2.25)
VTE	0-19	8.42 (6.56-10.28)	9.26 (7.33-11.18)
	20-29	52.71 (41.33-64.08)	31.58 (25.62-37.55)
	30-39	114.50 (88.34-140.66)	67.67 (60.35-74.78)
	40-49	163.18 (124.85-201.52)	138.64 (119.97-157.31)
	50-59	218.50 (167.47-269.53)	256.36 (233.86-278.86)
	60-69	375.08 (299.99-450.16)	417.74 (383.29-452.19)
	70-79	691.70 (583.62-799.78)	600.21 (543.64-656.77)

	80+	930.17 (821.18-1039.15)	785.79 (629.18-942.39)
	Overall	313.88 (277.73-350.04)	281.22 (249.93-312.52)

VTE without TP	0-19	8.39 (6.49-10.29)	9.00 (7.26-10.74)
	20-29	52.51 (40.95-64.08)	31.42 (25.48-37.35)
	30-39	114.12 (87.85-140.40)	67.37 (60.04-74.71)
	40-49	163.05 (124.04-202.07)	138.01 (119.25-156.77)
	50-59	217.25 (165.98-268.53)	254.61 (232.21-277.00)
	60-69	373.78 (298.60-448.95)	413.65 (380.99-446.30)
	70-79	690.07 (580.87-799.27)	595.15 (541.37-648.93)
	80+	926.42 (819.98-1032.87)	780.74 (627.85-933.63)
	Overall	312.73 (276.74-348.72)	279.11 (248.14-310.08)
VTE with TP	0-19	0.09 (0.00-0.27)	0.37 (0.00-0.87)
	20-29	0.24 (0.00-0.61)	0.22 (0.00-0.57)
	30-39	0.72 (0.00-1.71)	0.56 (0.00-1.30)
	40-49	0.39 (0.00-1.07)	1.01 (0.00-2.33)
	50-59	1.71 (0.29-3.65)	2.94 (0.00-6.85)
	60-69	2.20 (0.29-4.12)	6.67 (0.00-13.41)
	70-79	2.85 (0.00-7.00)	7.96 (0.00-17.70)
	80+	5.50 (0.00-11.50)	7.83 (0.00-17.39)
	Overall	1.03 (0.67-1.39)	1.89 (1.35-2.42)
Mixed arterial/venous thrombosis without TP	0-19	16.97 (10.71-23.22)	9.00 (7.26-10.74)
	20-29	61.54 (48.14-74.93)	31.42 (25.48-37.35)
	30-39	141.45 (112.33-170.56)	67.37 (60.04-74.71)
	40-49	229.28 (193.63-264.94)	138.01 (119.25-156.77)
	50-59	385.20 (342.67-427.73)	254.61 (232.21-277.00)
	60-69	733.62 (665.56-801.68)	413.65 (380.99-446.30)
	70-79	1512.92 (1336.20-1689.65)	595.15 (541.37-648.93)
	80+	2798.34 (2133.64-3463.03)	780.74 (627.85-933.63)
	Overall	716.89 (647.92-785.86)	279.11 (248.14-310.08)
Mixed arterial/venous thrombosis with TP	0-19	0.19 (0.00-0.41)	0.37 (0.00-0.87)
	20-29	0.29 (0.00-0.72)	0.22 (0.00-0.57)
	30-39	0.79 (0.00-1.88)	0.56 (0.00-1.30)
	40-49	0.54 (0.00-1.34)	1.01 (0.00-2.33)
	50-59	2.49 (0.00-5.25)	2.94 (0.00-6.85)

	60-69	3.53 (0.00-7.43)	6.67 (0.00-13.41)
	70-79	9.07 (0.00-19.98)	7.96 (0.00-17.70)
	80+	13.77 (0.00-31.22)	7.83 (0.00-17.39)
	Overall	2.10 (1.49-2.71)	1.89 (1.35-2.42)
CVST	0-19	0.56 (0.03-1.09)	0.60 (0.13-1.08)
	20-29	0.61 (0.00-1.25)	0.46 (0.02-0.90)
	30-39	0.41 (0.00-0.85)	0.51 (0.13-0.89)
	40-49	0.97 (0.52-1.41)	0.55 (0.21-0.89)
	50-59	0.82 (0.39-1.25)	1.27 (0.74-1.79)
	60-69	0.97 (0.03-1.91)	1.15 (0.56-1.75)
	70-79	0.49 (0.04-0.94)	1.11 (0.00-2.38)
	80+	1.08 (0.07-2.10)	1.28 (0.35-2.21)
	Overall	0.67 (0.49-0.85)	0.68 (0.53-0.84)
CVST without TP	0-19	0.56 (0.03-1.09)	0.52 (0.21-0.82)
	20-29	0.61 (0.00-1.25)	0.46 (0.02-0.90)
	30-39	0.41 (0.00-0.85)	0.51 (0.13-0.89)
	40-49	0.97 (0.52-1.41)	0.55 (0.21-0.89)
	50-59	0.82 (0.39-1.25)	1.23 (0.71-1.75)
	60-69	0.83 (0.00-1.70)	1.15 (0.56-1.75)
	70-79	0.38 (0.00-0.80)	1.07 (0.00-2.24)
	80+	0.99 (0.10-1.89)	1.19 (0.29-2.10)
	Overall	0.64 (0.46-0.81)	0.66 (0.51-0.82)
CVST with TP	0-19	0.00 (0.00-0.12)	0.17 (0.00-0.41)
	20-29	0.00 (0.00-0.23)	0.00 (0.00-0.23)
	30-39	0.00 (0.00-0.17)	0.00 (0.00-0.17)
	40-49	0.00 (0.00-0.14)	0.00 (0.00-0.13)
	50-59	0.00 (0.00-0.16)	0.08 (0.00-0.30)
	60-69	0.13 (0.00-0.41)	0.00 (0.00-0.21)
	70-79	0.02 (0.00-0.25)	0.13 (0.00-0.53)
	80+	0.14 (0.00-0.58)	0.23 (0.00-0.94)
	Overall	0.01 (0.00-0.07)	0.03 (0.00-0.11)
Thrombotic microangiopathy	0-19	0.32 (0.00-0.66)	1.14 (0.00-2.32)
	20-29	0.99 (0.39-1.60)	1.04 (0.00-2.40)
	30-39	1.21 (0.66-1.76)	1.44 (0.00-3.03)

	40-49	1.50 (0.86-2.14)	1.99 (0.00-4.31)
	50-59	1.07 (0.21-1.93)	4.24 (0.00-9.21)
	60-69	1.57 (0.92-2.22)	6.03 (0.00-13.83)
	70-79	1.88 (1.09-2.66)	12.20 (0.00-26.76)
	80+	2.13 (0.81-3.45)	12.43 (0.00-30.26)
	Overall	1.18 (0.87-1.50)	3.80 (2.85-4.76)
Hemorrhagic stroke	0-19	2.58 (0.48-4.69)	4.01 (0.73-7.29)
	20-29	2.37 (0.75-3.99)	3.97 (1.21-6.73)
	30-39	5.28 (3.31-7.24)	7.02 (3.27-10.78)
	40-49	11.17 (7.23-15.11)	17.39 (10.20-24.58)
	50-59	21.69 (12.03-3.35)	38.67 (23.15-54.19)
	60-69	39.15 (23.46-54.84)	74.20 (42.44-105.95)
	70-79	100.22 (66.08-134.36)	180.45 (118.98-523.36)
	80+	239.51 (138.29-340.74)	361.26 (199.56-523.36)
	Overall	43.65 (37.43-49.87)	69.60 (61.06-78.13)
Ischemic stroke	0-19	4.83 (2.46-7.19)	4.39 (1.71-7.07)
	20-29	6.48 (5.09-7.87)	4.61 (2.26-6.87)
	30-39	15.75 (10.97-20.53)	16.73 (13.27-20.19)
	40-49	45.28 (31.00-59.55)	64.12 (47.13-81.11)
	50-59	109.96 (71.64-148.27)	207.99 (148.35-267.62)
	60-69	238.87 (165.25-312.50)	441.75 (294.49-589.00)
	70-79	580.62 (408.91-752.32)	893.76 (622.30-1165.22)
	80+	1445.03 (963.33-1926.73)	1663.21 (1087.73-2238.47)
	Overall	266.03 (244.12-287.94)	342.28 (1087.73-2238.69)
SOCV	0-19	22.87 (9.38-36.36)	19.90 (8.07-31.73)
	20-29	8.00 (0.74-15.26)	3.93 (0.00-8.70)
	30-39	8.30 (0.19-16.40)	4.58 (0.00-9.76)
	40-49	9.28 (0.70-17.86)	7.25 (1.38-13.12)
	50-59	15.24 (1.25-29.24)	11.51 (1.15-21.88)
	60-69	19.51 (1.57-37.44)	13.77 (0.00-27.76)
	70-79	24.97 (1.51-48.43)	21.93 (2.05-41.81)
	80+	25.57 (0.00-52.76)	26.26 (0.00-53.94)
	Overall	16.47 (12.16-20.77)	13.26 (10.01-16.51)

CVST: Cerebral Venous Sinus Thrombosis; TP: Thrombocytopenia; VTE: Venous Thromboembolism

Cardiovascular system

AESIs	Age group	Female	Male
Microangiopathy	0-19	0.52 (0.00-1.19)	1.14 (0.00-2.32)
	20-29	0.84 (0.00-1.87)	1.04 (0.00-2.40)
	30-39	1.70 (0.14-3.26)	1.44 50.00-3.03)
	40-49	2.94 (0.49-5.39)	1.99 (0.00-4.31)
	50-59	2.49 (0.00-5.37)	4.24 (0.00-9.21)
	60-69	3.85 (0.00-8.03)	6.03 (0.00-13.83)
	70-79	8.18 (0.04-16.31)	12.20 (0.00-26.76)
	80+	9.64 (0.00-21.37)	12.43 (0.00-30.26)
	Overall	2.94 (2.13-3.76)	3.80 (2.85-4.76)
Heart Failure	0-19	2.93 (0.85-5.01)	2.96 (0.74-5.18)
	20-29	3.16 (0.05-6.27)	4.93 (3.31-6.54)
	30-39	10.14 (4.79 (15.48)	15.60 (7.252-23.94)
	40-49	26.97 (14.48-39.49)	57.00 (32.63-81.34)
	50-59	94.96 (57.04-132.87)	195.14 (108.03-282.26)
	60-69	318.22 (204.15-432.28)	544.72 (334.13-755.31)
	70-79	1003.47 (667.84-1339.10)	1436.01 (963.51-1908.52)
	80+	3725.21 (2347.51-5102.91)	4191.25 (2845.65-5536.85)
	Overall	494.23 (471.12-517.33)	579.16 (553.14-605.19)
Stress Cardiomyopathy	0-19	0.04 (0.00-0.18)	0.04 (0.00-0.17)
	20-29	0.00 (0.00-0.21)	0.00 (0.00-0.20)
	30-39	0.16 (0.00-0.42)	0.09 (0.00-0.31)
	40-49	1.53 (0.76-2.29)	0.15 (0.00-0.48)
	50-59	4.51 (2.03-6.99)	1.32 (0.21-2.25)
	60-69	8.62 (4.85-12.38)	1.95 (0.00-4.16)
	70-79	15.18 (6.80-23.56)	4.80 (0.33-9.27)
	80+	16.62 (3.29-29.94)	6.69 (0.91-12.48)
	Overall	3.29 (2.62-3.96)	0.56 (0.29-0.82)
Coronary Artery Disease	0-19	2.02 (0.00-4.05)	2.12 (0.25-3.98)
	20-29	1.61 (0.72-2.50)	4.49 (2.00-6.99)
	30-39	7.56 (5.13-9.99)	23.12 (20.24-26.00)
	40-49	23.50 (18.08-28.92)	112.72 (89.80-135.65)
	50-59	70.52 (55.64-85.40)	322.24 (265.10-379.38)
	60-69	149.66 (108.94-190.39)	517.54 (370.30-664.79)

	70-79	280.98 (192.72-369.24)	709.67 (480.70-938.63)
	80+	511.29 (326.26-696.31)	938.67 (572.51-1304.82)
	Overall	94.78 (86.70-102.86)	256.243.09-269.08)
Myocarditis	0-19	0.54 (0.00-1.11)	2.24 (1.10-3.39)
	20-29	1.16 (0.53-1.79)	9.48 (6.05-12.91)
	30-39	1.46 (0.59-2.34)	6.04 (3.32-8.76)
	40-49	1.16 (0.37-1.94)	4.16 (2.03-6.29)
	50-59	1.98 (0.69-3.26)	3.23 (0.90-5.56)
	60-69	2.59 (1.07-4.11)	5.26 (1.71-8.81)
	70-79	2.95 (1.35-4.55)	5.06 (1.14-8.97)
	80+	1.99 (0.00-4.38)	2.80 (0.00-5.93)
	Overall	1.59 (1.18-2.01)	4.49 (3.56-5.43)
Myocarditis or Pericarditis	0-19	1.88 (1.16-2.61)	11.20 (4.78-17.63)
	20-29	5.60 (4.30-6.90)	39.05 (18.21-59.90)
	30-39	9.15 (3.27-15.03)	33.54 (15.58-51.50)
	40-49	10.07 (4.94-15.20)	28.72 (15.31-42.14)
	50-59	14.39 (8.23-20.54)	29.13 (18.93-39.33)
	60-69	17.16 (10.92-23.40)	36.87 (24.96-48.78)
	70-79	22.50 (13.26-31.75)	40.17 (24.82-55.53)
	80+	22.80 (11.55-34.05)	4.34 (22.19-60.48)
	Overall	11.87 (9.84-13.91)	31.44 (26.98-35.89)
Arrhythmia	0-19	183.82 (145.87-221.76)	178.01 (146.12-209.90)
	20-29	451.35 (338.88-563.83)	342.74 (285.77-399.72)
	30-39	466.71 (371.31-562.12)	356.05 (305.15-406.95)
	40-49	556.99 (451.07-662.90)	504.62 (426.96-582.28)
	50-59	814.11 (645.05-983.17)	931.89 (756.70-1107.09)
	60-69	1413.36 (1118.46-3426.96)	2052.72 (1553.12-2552.33)
	70-79	2777.08 (2127.20-3426.96)	4144.27 (3044.16-5244.38)
	80+	5346.36 (3324.70-7368.01)	7349.09 (1744.53-2131.65)
	Overall	1490.59 (1308.53-1672.65)	1938.09 (1744.53-2131.65)

Respiratory system

AESIs	**Age group**	**Female**	**Male**
Acute Respiratory Distress Syndrome	0-19	17.10 (5.85-28.35)	18.67 (8.44-28.90)
	20-29	4.67 (2.21-7.14)	7.68 (5.93-9.43)

	30-39	7.12 (1.64-12.59)	10.33 (6.91-13.75)
	40-49	12.26 (4.41-20.10)	18.32 (7.60-29.05)
	50-59	32.69 (10.09-55.30)	45.83 (14.62-77.04)
	60-69	70.69 (25.83-115.54)	106.44 (30.87-182.01)
	70-79	127.54 (32.63-222.44)	227.31 (54.23-400.40)
	80+	467.15 (82.40-851.90)	555.06 (110.65-999.47)
	Overall	87.88 (73.77-101.99)	114.67 (98.83-130.51)

Nerves and central nervous system

AESIs	Age group	Female	Male
Generalized Convulsion	0-19	209.71 (127.03-292.40)	239.80 (142.18-337.43)
	20-29	85.05 (35.60-134.51)	90.08 (43.14-137.01)
	30-39	77.72 (34.73-120.71)	85.76 (40.83-130.69)
	40-49	80.00 (36.32-123.68)	98.20 (49.56-146.68)
	50-59	99.94 (49.19-150.69)	136.42 (69.41-203.43)
	60-69	116.31 (52.68-179.93)	166.43 (73.89-258.97)
	70-79	182.96 (89.66-276.26)	245.41 (109.51-381.31)
	80+	324.55 (126.69-522.42)	367.48 (114.66-620.29)
	Overall	146.27 (119.18-173.36)	177.72 (146.67-208.77)
Meningoencephalitis	0-19	3.33 (1.57-5.09)	4.13 (1.48-6.77)
	20-29	4.83 (3.62-6.04)	3.30 (2.29-4.31)
	30-39	4.31 (0.86-7.76)	4.62 (2.12-7.13)
	40-49	4.90 (1.25-8.55)	4.70 (2.54-6.86)
	50-59	7.17 (4.98-9.36)	8.24 (4.77-11.70)
	60-69	9.19 (2.83-15.56)	13.63 (9.64-17.61)
	70-79	16.72 (7.49-25.95)	16.09 (8.73-23.45)
	80+	17.32 (4.54-30.11)	16.06 (8.04-24.09)
	Overall	7.98 (6.16-9.80)	8.12 (6.45-9.79)
Transverse Myelitis	0-19	0.19 (0.00-0.41)	0.08 (0.00-0.24)
	20-29	0.50 (0.05-0.96)	0.21 (0.00-0.54)
	30-39	0.76 (0.22-1.29)	0.45 (0.09-0.82)
	40-49	0.92 (0.25-1.60)	0.39 (0.09-0.68)
	50-59	0.49 (0.01-0.96)	0.32 (0.00-0.81)
	60-69	0.64 (0.20-1.08)	0.67 (0.00-1.40)
	70-79	0.35 (0.00-0.87)	0.18 (0.00-0.55)
	80+	0.34 (0.00-0.75)	0.37 (0.00-1.22)
	Overall	0.42 (0.29-0.55)	0.22 (0.11-0.33)

Skin and mucous membrane system

AESIs	Age group	Female	Male
Chilblain like lesions	0-19	23.09 (4.29-41.88)	12.39 (0.86-23.92)
	20-29	43.46 (2.84-84.09)	15.81 (3.20-28.42)
	30-39	31.74 (1.78-61.69)	10.54 (1.46-19.63)
	40-49	31.20 (0.92-61.47)	11.07 (1.65-20.49)

	50-59	20.59 (1.51-39.67)	14.64 (2.39-26.88)
	60-69	21.30 (2.26-40.35)	14.60 (2.69-26.52)
	70-79	35.90 (3.86-67.94)	22.99 (5.37-40.61)
	80+	42.08 (3.62-80.54)	34.03 (6.65-61.41)
	Overall	31.12 (22.59-39.64)	16.76 (12.68-20.85)
Erythema multiforme	0-19	16.72 (4.50-28.95)	20.04 (9.89-30.20)
	20-29	6.53 (3.27-9.80)	5.48 (2.72-8.17)
	30-39	7.01 (3.07-10.96)	4.45 (1.57-7.33)
	40-49	6.61 (3.23-9.99)	3.93 (1.40-6.46)
	50-59	6.10 (2.18-10.12)	5.55 (1.67-9.42)
	60-69	6.63 (1.06-12.21)	4.95 (0.99-8.91)
	70-79	7.69 (2.32-13.06)	7.58 (3.56-11.60)
	80+	6.96 (0.00-14.48)	11.97 (4.95-18.98)
	Overall	7.89 (5.92-9.86)	7.68 (5.65-9.72)

Hepatogastrointestnal and renal system

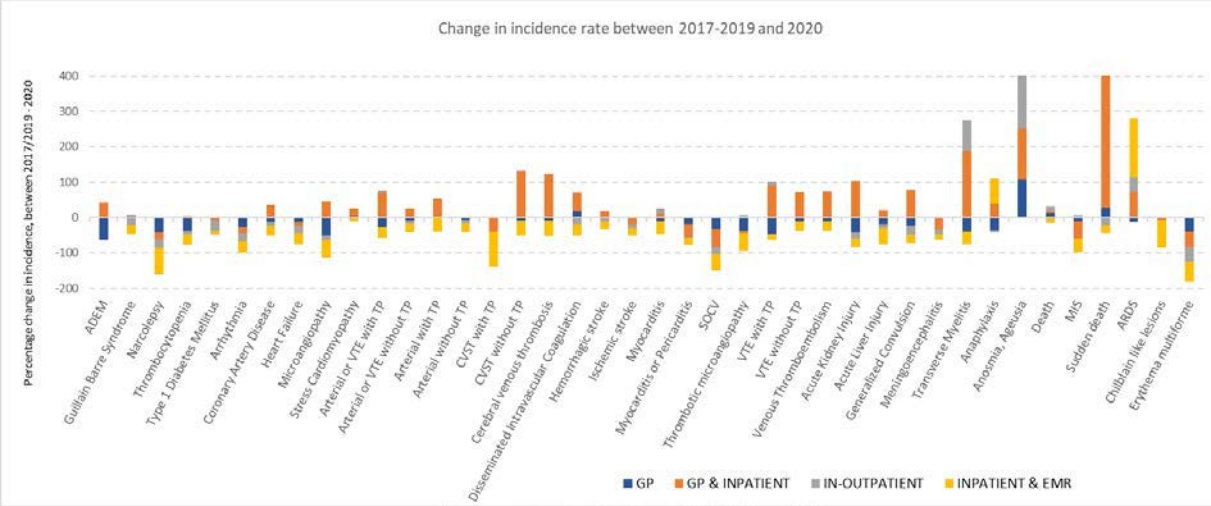
AESIs	**Age group**	**Female**	**Male**
Acute Liver Injury	0-19	7.80 (4.99-10.61)	5.26 (2.48-8.04)
	20-29	11.97 (8.30-15.63)	16.48 (11.72-21.23)
	30-39	14.49 (11.32-17.67)	19.80 (17.77-21.82)
	40-49	21.85 (15.31-28.40)	32.34 (23.37-41.32)
	50-59	37.94 (26.74-49.15)	60.84 (30.70-90.98)
	60-69	43.89 (27.36-60.42)	86.00 (41.10-130.89)
	70-79	58.82 (30.40-87.23)	101.29 (40.27-162.30)
	80+	56.74 (11.02-102.27)	88.68 (18.45-158.90)
	Overall	31.58 (26.04-37.12)	50.21 (41.29-59.13)
Acute Kidney Injury	0-19	37.12 (18.81-55.43)	23.76 (11.13-36.38)
	20-29	67.92 (25.96-109.88)	33.93 (15.30-52.56)
	30-39	67.07 (27.03-107.11)	53.97 (21.03-86.92)
	40-49	92.45 (33.81-151.09)	105.08 (36.50-173.66)
	50-59	187.61 (73.95-301.27)	306.43 (101.47-511.40)
	60-69	487.78 (183.23-792.33)	871.63 (291.63-1451.63)
	70-79	1354.54 (490.20-2218.88)	2162.32 (686.31-3638.32)
	80+	3733.87 (744.63-6723.11)	4860.15 (1001.93-8718.36)
	Overall	699.55 (643.13-755.98)	926.44 (866.29-986.58)

Other system

AESIs	Age group	Female	Male
Anosmia, Ageusia	0-19	2.35 (1.00-3.70)	1.79 (0.74-2.85)
	20-29	9.02 (4.73-13.32)	6.30 (3.42-9.19)
	30-39	15.02 (8.34-21.71)	10.92 (5.36-16.47)
	40-49	22.12 (12.71-31.54)	16.68 (9.62-23.73)
	50-59	37.41 (23.59-51.23)	22.62 (11.63-33.62)
	60-69	40.34 (25.20-55.49)	27.66 (12.66-42.66)
	70-79	39.15 (19.56-58.75)	22.46 (12.50-32.43)
	80+	18.60 (8.72-28.49)	15.60 (8.08-23.12)
	Overall	21.96 (17.82-26.11)	14.72 (11.95-17.50)
Anaphylaxis	0-19	17.26 (10.05-24.48)	25.16 (13.11-37.21)
	20-29	13.26 (2.65-23.80)	11.16 (4.49-17.83)
	30-39	11.99 (2.88-21.10)	7.93 (2.37-13.49)
	40-49	13.56 (4.99-22.14)	12.61 (7.14-18.09)
	50-59	13.92 (6.48-21.37)	12.64 (8.58-16.71)
	60-69	13.47 (6.74-20.20)	15.57 (13.03-18.12)
	70-79	11.21 (4.91-17.33)	12.90 (8.71-17.10)
	80+	7.84 (3.27-12.42)	8.80 (5.26-12.35)
	Overall	12.96 (10.43-15.50)	13.31 (10.73-15.89)
Multisystem Inflammatory Sydrome	0-19	3.08 (0.69-5.46)	5.23 (2.69-7.76)
	20-29	0.51 (0.04-0.98)	0.39 (0.00-1.12)
	30-39	0.34 (0.00-0.97)	0.31 (0.00-0.90)
	40-49	0.28 (0.00-0.80)	0.27 (0.00-0.77)
	50-59	0.30 (0.00-0.68)	0.36 (0.00-1.02)
	60-69	0.21 (0.00-0.61)	0.26 (0.00-0.77)
	70-79	0.21 (0.00-0.62)	0.60 (0.00-1.72)
	80+	0.78 (0.00-2.11)	1.43 (0.00-3.81)
	Overall	0.56 (0.29-84)	0.83 (0.46-1.19)
Death (any causes)	0-19	10.24 (6.77-13.71)	15.19 (9.98-20.40)
	20-29	14.49 (10.30-18.67)	31.33 (27.46-35.20)
	30-39	31.02 (27.00-35.05)	52.61 (43.53-61.69)
	40-49	81.08 (73.26-88.90)	139.37 (120.22-158.52)
	50-59	219.76 (196.62-242.90)	453.43 (391.82-515.05)
	60-69	453.84 (417.02-490.66)	1088.14 (970.08-1206.21)
	70-79	1167.28 (1081.25-1253.31)	2481.12 (2250.09-2712.16)

	80+	7664.66 (6629.84-8699.49)	9398.47 (1526.20-10000.00)
	Overall	1147.16 (1074.96-1219.35)	1619.47 (1526.20-1712.74)
Sudden death	0-19	2.38 (0.08-4.68)	1.69 (0.00-3.56)
	20-29	2.22 (0.00-4.90)	1.40 (0.00-3.13)
	30-39	2.34 (0.11-4.57)	3.32 (0.08-6.56)
	40-49	5.23 (0.94-9.52)	7.17 (1.21-13.22)
	50-59	14.78 (4.28-25.28)	30.07 (11.96-48.19)
	60-69	31.09 (10.38-51.80)	83.98 (37.66-130.30)
	70-79	94.12 (38.98-149.26)	193.75 (86.57-300.93)
	80+	936.56 (443.10-1430.02)	1004.02 (477.93-1530.11)
	Overall	27.43 (23.97-30.88)	30.29 (26.84-33.75)

Figure 3 Percentage change in health care utilization in the pre- versus during the COVID-19 pandemic period (2017-2019 versus 2020)



Only databases with data in 2020 were included. ADEM: Acute Disseminated Encephalomyelitis, ARDS: Acute Respiratory Distress Syndrome, CVST: Cerebral Venous Sinus Thrombosis, DIC: Disseminated Intravascular Coagulation, MIS: Multisystem Inflammatory Syndrome, SOCV: Single Organ Cutaneous Vasculitis, TP: Thrombocytopenia, VTE: Venous Thromboembolism. No data for acute aseptic arthritis because no narrow clinical definition could be developed.

Chapter 3: Overview of methods for vaccine safety signal evaluation

3.1 Systematic review and meta-analysis of post-licensure observational studies on HPV vaccination and autoimmune and other rare adverse events

Corinne Willame, Kartini Gadroen, Wichor Bramer, Daniel Weibel, Miriam Sturkenboom

Pediatric Infectious Disease Journal. 2020 Apr;39(4):287-293. doi:0.1097/INF.0000000000002569.

Abstract

Background: Because of the limited number of subjects in pre-licensure studies, autoimmune diseases and other rare adverse effects of vaccines may go undetected. Since 2006, millions of human papillomavirus (HPV) vaccine doses have been distributed and a considerable amount of post-licensure safety data have been generated. The objective of this study was to review available HPV post-licensure safety studies and to summarize risk estimates of autoimmune and other rare diseases.

Methods: For this systematic review and meta-analysis, we searched literature databases to identify any post-licensure safety studies related to HPV vaccination and autoimmune adverse events from inception to the 16th of April 2019. Pooled risk estimates were computed using fixed or random effect models if at least two estimates per disease and per HPV vaccine were available.

Results: Twenty-two studies met our inclusion criteria. The studies applied various methodologies and used different types of data sources and outcome definitions. Quadrivalent HPV vaccine (4vHPV) was most commonly assessed. Type 1 diabetes mellitus, immune thrombocytopenia purpura (ITP) and thyroiditis diseases were most frequently reported. The meta-analysis was conducted on 35 diseases corresponding to 48 pooled risk estimates. Majority of the pooled estimates showed no significant effect (n=43). Three negative (paralysis, ITP and Chronic Fatigue Syndrome) and two positive (Hashimoto and Raynaud diseases) associations were detected.

Conclusion: Our study demonstrated an absence of clear association between HPV vaccines and autoimmune and other rare diseases. The review also highlights the need for more systematic collaborations to monitor rare safety adverse events.

1. Introduction

HPV vaccines are effective in reducing HPV infections [1,2] and in preventing cervical cancer, caused by certain HPV genotypes [3]. Currently three licensed HPV vaccines are available. A quadrivalent vaccine (4vHPV, Gardasil®, Merck, United States) and a bivalent vaccine (2vHPV, Cervarix®, GSK, Belgium) licensed in 2006 and 2007 respectively, followed in late 2014 by nine-valent vaccine (9vHPV, Gardasil9®, Merck, United States). **Table 1** summarizes the characteristics of the three vaccines.

Table 1 Characteristics of HPV vaccines

		Cervarix [Recombinant, adjuvanted, adsorbed]	Gardasil [Recombinant, adsorbed]	Gardasil9 [Recombinant, adsorbed]
Recommended route of administration		Intramuscular	Intramuscular	Intramuscular
Characteristics by dose (0.5 ml)	Formulation	Suspension	Suspension	Suspension
	L1 virus-like particle types	HPV-16 (20µg), 18 (20µg)	HPV-6 (20µg), 11 (40µg), 16 (40µg), 18 (20µg)	HPV-6 (30µg), 11 (40µg), 16 (60µg), 18 (40µg), 31 (20µg), 33 (20µg), 45 (20µg), 52 (20µg), 58 (20µg)
	Cross-protection	HPV-31, 33, 45	HPV-31	None
	Adjuvant	Adsorbed on aluminium hydroxide, hydrated (Al(OH)3) (0.5 mg) Al3+ in total Adjuvanted by AS04 containing: 3- -desacyl-4'- monophosphoryl lipid A (MPL) (50 µg)	Adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (0.225 mg Al).	Adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (0.5 mg Al).
	Expression system	Baculovirus-insect cell	Yeast cells	Yeast cells

All three HPV vaccines were initially licensed and marketed using a 3-dose vaccination schedule. However, a 2-dose schedule was subsequently approved for all three vaccines. HPV vaccines are

available in more than 100 countries [4] and over 80 countries have included the HPV vaccine into their national immunization programmes mainly targeting young adolescent girls [5]. As of 2014 it is estimated that 59 million women have received at least one dose of HPV vaccine [6]. Routine vaccination of boys is currently implemented in several countries worldwide.

To enhance the immune response, HPV vaccines contain adjuvanted systems, such as toll like receptors or oil-based emulsions. These adjuvants vaccines enhance a general immune response and may potentially trigger autoimmune reactions (responses against bodies own tissue) [7]. The safety of vaccines and its adjuvants require assessment pre-licensure and continuous monitoring post-licensure. This is done by passive surveillance of case reports and active surveillance studies, aiming to detect rare reactions or associations with diseases that have low incidences. As part of post-marketing commitments and requests several studies were conducted aiming to estimate the risks of developing autoimmune diseases following HPV vaccination [8,9][9]. To date, available meta-analysis of HPV vaccine and autoimmune diseases have largely synthesised results of clinical trials [10] or a mixed of post-licensure studies and clinical trials [11]. To address the need to analyse available post-licensure safety data, we carried out a systematic review of post-licensure observational safety studies assessing the risk of autoimmune and rare adverse events following HPV vaccination; we describe the methodological approaches used; and we summarize the risk estimates.

2. Materials and Methods

We used a comprehensive three-step search strategy to identify relevant studies. No language restrictions were placed on the searches or search results. The study conforms to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [12] and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [13] (ENCePP) guidelines.

Search strategy and selection criteria

First, we searched Embase.com, Medline (Ovid), ISI Web-of-Science, Cochrane Central from inception to 16th of April 2019 for any post-licensure observational safety studies assessing the risk of autoimmune adverse events following HPV vaccination. A search strategy was developed for each

database with a combination of free text and controlled vocabulary (ie. MeSh terms). Additional search terms were included in consultation with a reference librarian (WB). The detailed search strategies for each database are presented in **Supplementary Table S1**. Second, we screened reference lists of publications retrieved to identify additional relevant studies. Third, we searched web-based platforms including the EnCePP register [14] and manual searches in health authorities' websites and Google Scholar.

Two reviewers (CW, KG) independently screened titles and abstracts followed by the retrieval and, reviewed full-text articles according to the pre-defined eligibility criteria described below. Disagreements were resolved through discussion. The following inclusion criteria were applied: (1) HPV vaccination; (2) post-licensure studies; (3) epidemiologic or Phase IV studies; (4) healthy population; and (5) risk/safety assessment. Commentaries, meeting reports, letters to editors, case reports, biological or animal studies, were excluded. Eligible papers, as well as papers which could not be excluded right away, were then included in the full-text assessment. Selected papers were assessed by reviewing the full-text according to the following inclusion criteria: (1) HPV related adverse events, (2) autoimmune diseases and rare safety outcomes assessment, (3) no assessment using spontaneous reporting database.

Data abstraction and quality assessment

For each of the eligible studies we extracted the following data as a minimum: first author and year of publication, study design, objective and period, data source, geographical area, age of subjects, type of vaccine, adverse events reported either as individual or composite endpoints, method for identification and validation of cases, disease onset, risk window and risk estimates.

The study quality was assessed by the two same reviewers using an adapted quality checklist combining the Newcastle-Ottawa Scale [15] and the Scottish Intercollegiate Guidelines Network [16] quality criteria for cohort and case-control studies. The adapted quality checklist, including assessment of case-only design, is presented in **Supplementary Table S2**. To assess the quality of the studies, we scored each of the studies following four parameters: the selection of study groups (2 points),

confounding factors (1 point), assessment of the outcome (3 points) and assessment of the exposure (1 point). The total score represented the sum of scores for each parameter. This score was used as a relative measure of data quality, no threshold for exclusion was applied.

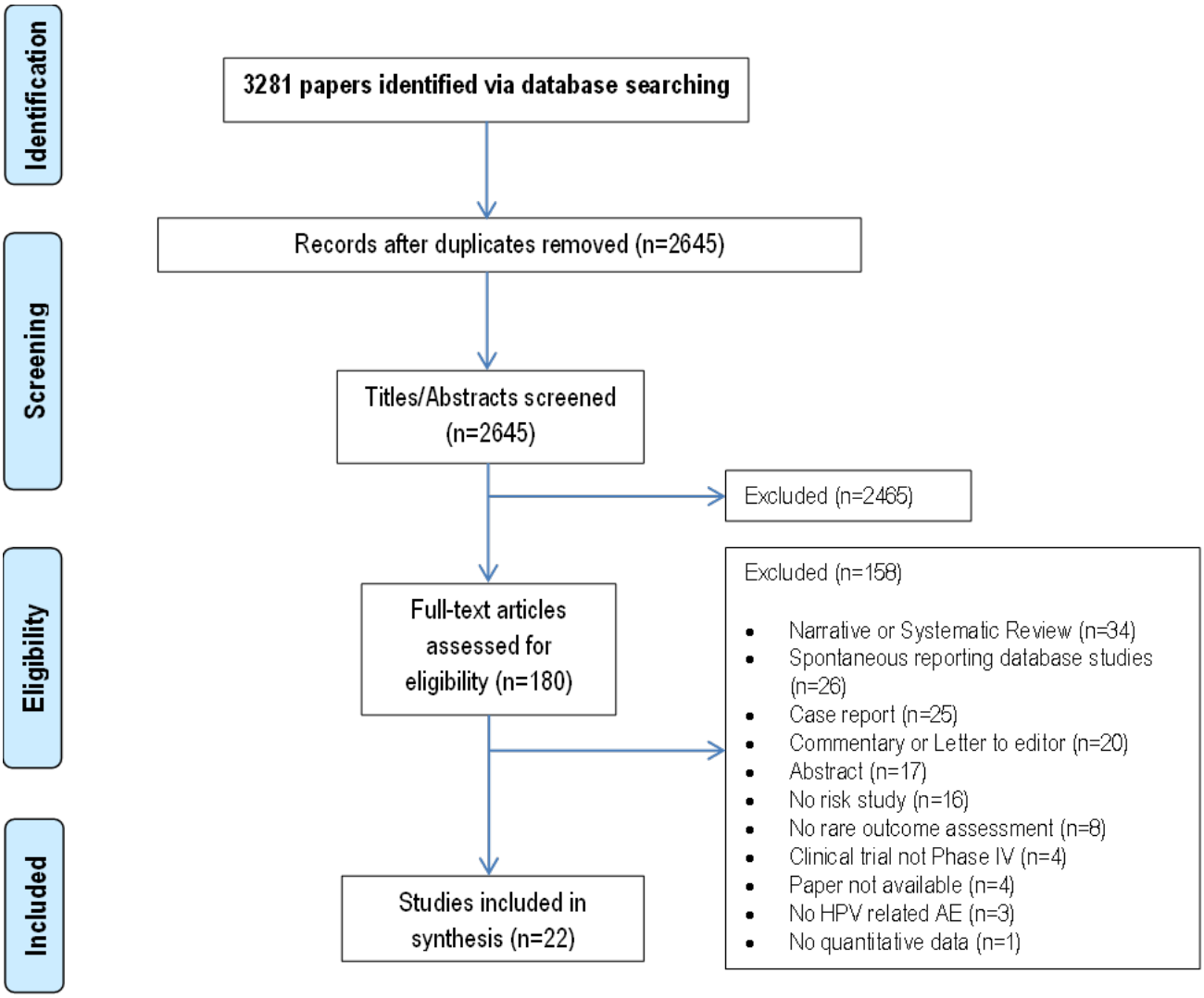
Data analysis

Pooled risk estimates (odds ratios) and their respective 95% confidence intervals (CI) for individual autoimmune diseases were calculated if at least two risk estimates per outcome and per HPV vaccine type were available. Under the rare disease assumption, the odds ratio and relative risk can be treated as approximately equal. Therefore, the pooled estimate was computed by pooling any risk estimates, independently of the type of risk measurement (relative risk, odds ratio or hazard ratio) and by using fixed (Mantel Haenszel-method) or random (Der Simonian-Laird method) effect models. To determine the extent of variation between studies, we computed heterogeneity tests with Higgins I^2 statistic to measure the proportion of observed variance that reflects true effect sizes. I^2 values over 50% were considered as relevant inconsistency between studies. Statistical analyses were performed using Stata software [17].

3. Results

Of the 3281 papers, 180 potentially relevant full-text articles were independently reviewed. From these, 22 studies (<1%) were identified as relevant for our review. **Figure 1** depicts the PRISMA flowchart. Consultation of the ENCePP register and other websites did not identify additional studies of interest.

Figure 1 PRISMA Flowchart of the selection procedure



HPV = Human Papillomavirus Vaccine, AE = Adverse Event

Supplementary Table S3 shows the main characteristics of the 22 post-licensure observational studies meeting the inclusion criteria. Studies were published from 2012 to 2019. Fourteen studies were conducted in Europe (Denmark and Sweden (5), Finland (1), France (3), Norway (1), The Netherlands (1) and United Kingdom (3)) and eight in North America (Canada (2) and United States (6)). Most studies used a retrospective study design and a variety of types of data sources: registers in Nordic countries, general practitioners and hospital databases in UK and Canada, and claims databases in France and US. Two prospective studies were conducted in France by using the Pharmacoepidemiologic General Research Extension (PGRx) methodology, a research platform recruiting prospectively and routinely autoimmune disorder cases through a network of specialists.

Most studies included females only with ages ranging from 9 to 44 years, 1 study included males only, and 2 studies included males and females of any age. Various types of study designs were implemented to assess the risk of autoimmune diseases after HPV vaccination; 3 case-control studies including 1 matched [18], 1 unmatched [19] and 1 nested case-control [20]; 7 case-only designs including 5 self-controlled case series [21-25] and 2 case-centered method [26,27]; and 12 cohort studies [8,9,28-37] including a surveillance study [8]. More than 60 different autoimmune and rare adverse events were studied. Some studies focused on any autoimmune diseases (n=4) [28,31,32,35], others (n=18) [8,9,18-27,29,30,33,34,36,37] targeted specific outcomes. Type 1 diabetes mellitus was the most frequently studied (in 11 studies) [8,9,18,19,24,28,31-33,35,37]. Autoimmune thyroiditis (AIT) diseases [8,9,19,24,28,32,35,37] including Hashimoto and Grave's diseases, hypothyroidism and other hyperthyroidism, and immune thrombocytopenia purpura [8,9,18,19,24,28,32,35] (ITP) were assessed in 8 studies; Crohn's disease [21,24,28,32,35,37] in 6 studies; Bell's palsy [24,28,31,32,35], coeliac disease [9,28,31,32,35], juvenile rheumatoid arthritis [8,9,24,35], optic neuritis [8,24,27,28,36], rheumatoid arthritis [8,9,28,31,32], ulcerative colitis [24,28,31,32,35] and systemic lupus erythematosus [8,9,28,32,35] in 5 studies; acute disseminated encephalomyelitis [8,20,26,24], chronic fatigue syndrome [22,25,30,35], epilepsy [28,31,32,35], Henoch-Schonlein's purpura [28,31,32,35], pancreatitis [9,28,32,35], paralysis [28,31,32,35], psoriasis [28,31,32,35], vasculitis [9,28,31,32], venous thrombocytopenia [23,28,31,35] and vitiligo [28,31,32,35] in 4 studies; ankylosing spondylitis [28,31,32], erythema nodosum [28,32,35], haemolytic anemia [8,24,32], multiple sclerosis [8,20,34], myositis [28,32,35], narcolepsy [28,31,32], Raynaud disease [28,32,35], scleroderma [9,28,32] in 3 studies. Four studies [9,19,21,29] among 7 including data on Guillain Barre Syndrome (GBS) provided risk estimates. Fourteen studies [8,18,20,23,24,26-32,34,36] concerned 4vHPV vaccine exposure, while 4 studies [22,25,35,37] assessed 2vHPV vaccine exposure. Two studies [9,21] provided risk estimates separately for 4vHPV and 2vHPV vaccine exposures. Two studies [19,33] assessed a combined exposure to both 2v-and 4vHPV and both 4v- and 9vHPV vaccines.

Based on the adapted quality checklist, the 22 studies included in this review were considered to have a satisfactory methodological quality. The quality assessment scores for each study are reported in **Supplementary Table S3**.

Methodological approaches

Methodological considerations of the 22 studies including methods for identification and validation of cases, diagnostic criteria, onset of the diseases and analytical parameters are further detailed in **Supplementary Table S4**.

Definition of outcome: Five studies [8,9,20,27,37] developed complex algorithms combining diagnosis codes and additional clinical information such as medications, laboratory test results and referral to specialists to identify cases. Fifteen studies [19,21-26,28-36] identifying cases by diagnosis codes only implemented a review of all medical charts or contacted health care providers (6 studies) [21,24,26,27,33,36]. Three studies [8,20,37], in addition to elaborated algorithms, put in place a case ascertainment process with a panel of specialist physicians. In most of the studies, the disease onset was the date of the first diagnosis, whereas in 2 studies [20,37] using case ascertainment process, the criteria of first clinical sign or symptom was used.

Analytical parameters: In some studies [18,19,24,34,37], the researchers created composite endpoints including multiple disease conditions such as for demyelinating diseases, connective tissue disorders or neuroinflammatory diseases. Two studies [24,37] analysed composite endpoints as primary objective while all other studies assessed individual endpoint as their primary objective. Several time frames, most often disease-specific, were evaluated in case-control designs ranging from 14 days until 3 years prior to disease onset. In cohort designs the follow-up time varied from 180 days until 10 years after the last exposure irrespective of the disease. Case-only study designs were usually applied for individual endpoints only. In those studies, risk windows were defined according to the disease varying from 42-days to 1-year after disease onset. Detailed risk windows are presented in **Supplementary Table S4**.

Risk estimates

We computed pooled risk estimates for the following categories of autoimmune diseases: dermatological (including erythema nodosum, psoriasis, scleroderma, systemic lupus erythematosus and vitiligo); haematological (including ITP); gastrointestinal (including coeliac, Crohn disease, pancreatitis and ulcerative colitis); musculoskeletal or systemic diseases (including ankylosing spondylitis, Henoch-Schonlein's purpura, juvenile rheumatoid arthritis, myositis, rheumatoid arthritis and vasculitis); neurological (Bell's palsy, epilepsy, GBS, chronic fatigue syndrome, narcolepsy and paralysis); ophthalmic (optic neuritis); other demyelinating diseases (including central nervous system disorders and multiple sclerosis); thyroiditis disorders (including Hashimoto, Graves' disease and other hyperthyroidism); other disorders (including Raynaud's disease, Sjogren syndrome, and venous thrombocytopenia) and type 1 diabetes. Pooled estimates were computed for 35 disease conditions corresponding to 48 pooled estimates. Pooled estimates are reported in **Table 2**.

Table 2: Summary of pooled estimates (ORs) for 35 autoimmune diseases and/or other rare adverse events

Outcomes	HPV vaccine exposure	Pooled estimates* [OR (95%CI)]	I^2 statistics
Dermatological			
Erythema nodosum	4vHPV	1.26 (0.89; 1.79)	0.0%
Psoriasis	4vHPV	1.03 (0.87; 1.23)	0.0%
Scleroderma	4vHPV	1.04 (0.64; 1.69)	29.7%
Systemic Lupus Erythematosus	4vHPV	1.04 (0.82; 1.33)	0.0%
	2vHPV	1.20 (0.39; 3.68)	20.5%
Vitiligo	4vHPV	1.31 (0.91; 1.87)	25.6%
Diabetes			
Diabetes Type 1 Diabetes Mellitus	4vHPV	0.93 (0.65; 1.34)	86.5%
	2vHPV	0.80 (0.50; 1.26)	58.5%
Haematological			
Idiopathic Thrombocytopenia Purpura	4vHPV	1.06 (0.85; 1.33)	40.2%
	2vHPV	**0.55 (0.34; 0.88)**	0.0%
Gastroinstestinal			
Coeliac disease	4vHPV	1.16 (0.87; 1.56)	67.3%
	2vHPV	1.05 (0.80; 1.38)	0.0%
Crohn's disease	4vHPV	1.04 (0.73; 1.47)	69.3%
	2vHPV	1.17 (0.77; 1.78)	0.0%
Pancreatitis	4vHPV	0.87 (0.69; 1.08)	0.0%
	2vHPV	1.68 (0.85; 3.33)	0.0%
Ulcerative colitis	4vHPV	0.93 (0.58; 1.50)	80.7%
	2vHPV	0.57 (0.15; 2.23)	80.7%

Musculoskeletal/Systemic			
Ankylosing spondylitis	4vHPV	0.98 (0.65; 1.48)	0.0%
Behcet syndrome	4vHPV	1.52 (0.29; 7.96)	69.4%
Henoch-Schonlein's purpura	4vHPV	1.03 (0.66; 1.60)	0.0%
Juvenile Rheumatoid Arthritis	4vHPV	0.73 (0.36; 1.47)	77.7%
	2vHPV	1.03 (0.82; 1.29)	6.2%
Myositis	4vHPV	0.92 (0.50; 1.69)	0.0%
Polymyositis/Dermatomyositis	4vHPV	0.83 (0.46; 1.51)	0.0%
Rheumatoid Arthritis	4vHPV	0.92 (0.72; 1.17)	0.0%
Vasculitis	4vHPV	1.11 (0.86; 1.42)	0.0%
Neurological			
Bell's palsy	4vHPV	0.79 (0.46; 1.35)	73.8%
	2vHPV	1.37 (0.83; 2.26)	0.0%
Epilepsy	4vHPV	0.81 (0.54; 1.24)	87.7%
Guillain Barre Syndrome	4vHPV	1.79 (0.65; 4.94)	64.0%
	2vHPV	2.89 (0.58; 14.40)	69.7%
Chronic Fatigue Syndrome	2vHPV	**0.77 (0.62; 0.97)**	11.5%
Narcolepsy	4vHPV	1.08 (0.64; 1.84)	19.3%
Paralysis	4vHPV	**0.52 (0.35; 0.77)**	0.0%
Ophthalmic			
Optic neuritis	4vHPV	1.20 (0.84; 1.71)	19.8%
Other demyelinating diseases			
Central Nervous system demyelinating syndrome	4vHPV	1.02 (0.77; 1.33)	0.0%
Multiple sclerosis	4vHPV	0.96 (0.77; 1.21)	0.0%
Other disorders			
Raynaud's disease	4vHPV	**1.63 (1.21; 2.20)**	0.0%
Sjogren syndrome	4vHPV	1.34 (0.71; 2.51)	0.0%
Venous Thrombocytopenia	4vHPV	0.80 (0.60; 1.07)	0.0%
Thyroid			
Hashimoto disease	4vHPV	**1.25 (1.09; 1.44)**	0.0%
	2vHPV	0.88 (0.57; 1.36)	0.0%
Grave's disease	4vHPV	0.88 (0.73; 1.07)	3.7%
	2vHPV	1.12 (0.56; 2.24)	63.3%
Autoimmune thyroiditis	4vHPV	1.10 (0.94; 1.27)	0.0%
	2vHPV	1.76 (0.65; 4.77)	83.3%
Other hyperthyroidism	4vHPV	0.98 (0.79; 1.22)	0.0%

2vHPV = bivalent HPV vaccine; 4vHPV = quadrivalent HPV vaccine.

*Pooled estimates were computed using fixed or random (I^2 > 50%) effect models in Stata v14.0.

Bold estimates are statistically significant.

Risk estimates for all autoimmune diseases and other rare events are reported in **Supplementary Table S5**. Most of them were computed for 4vHPV (n=34) and the remaining for 2vHPV (n=14). Majority of the pooled estimates did not show significant association (n=43). Three pooled estimates showed a

protective effect for ITP (OR= 0.55 [95%CI: 0.34-0.88]) and CFS (OR= 0.77 [95%CI: 0.62-0.97]) after 2vHPV vaccine and for paralysis (OR=0.52 [95%CI: 0.55-0.77]) after 4vHPV vaccine. Two pooled estimates showed a statistically significant increased risk for Hashimoto disease (OR=1.25 [95%CI: 1.09-1.44]) and Raynaud's disease (OR=1.63 [95%CI: 1.21-2.20]) after 4vHPV vaccine.

For diseases reported in a single study, 9 risk estimates showed statistically significant associations (**Supplementary Table S5**). Increased risks with relatively large 95%CI were observed in males following 9vHPV for narcolepsy (RR=3.44 [95%CI: 1.08-11.0]) and vitiligo (RR=4.70 [95%CI: 1.13-19.5]).

4. Discussion and Conclusions

Following large scale use of HPV vaccines rare, serious adverse events have been reported which prompted additional investigations [38-40]. Further to this, several post-licensure studies were conducted to estimate associations between HPV vaccination and autoimmune and other rare adverse events. The present review is to our knowledge the first comprehensive review aiming to describe the methodological approaches used in HPV vaccine post-licensure observational studies. In addition, we aimed to summarize risk estimates of autoimmune and other rare events following immunization with HPV from the available evidence. Among the 22 post-licensure observational safety studies included we identified two important elements informing on the validity and robustness of post-licensure studies assessing rare adverse events.

The first element is related to the validity of the clinical outcomes and determination of onset of disease. In the eligible studies, simple to more complex algorithms were developed to identify and validate cases of autoimmune diseases. The level of granularity of the clinical case definition may generate, if not consistent across studies, an important source of heterogeneity restricting direct comparison between studies. As an example, one study [9] broadly defined autoimmune thyroiditis diseases including in its definition codes for disease of non-autoimmune origin while other studies [8,24,28,32,35] targeted specific medical conditions such as Hashimoto disease. In addition, algorithm-based approach should ensure a high specificity of the outcome definition and therefore avoid inclusion of false positive subjects. Algorithm-based search only is deemed sufficiently robust to detect

acute events such as GBS. However, for diseases with insidious onset such approach may introduce bias on the true onset date.

Second important element is related to the analytical parameters including risk period, endpoints and sample size. While a long and sufficient follow-up time is required for long-latency diseases to be detected, risk period must be adequately defined to establish accurate evidence of a causal relationship. Some autoimmune events are known to occur within few weeks after vaccine exposure such as GBS detected between 6 to 8 weeks after swine flu vaccine [41,42]. For some other autoimmune diseases, evidence of time to disease onset (i.e. multiple sclerosis) [43] or lag time between onset of symptoms and disease diagnosis (i.e. rheumatoid arthritis) [44] are not well clearly established. In such circumstances, risk periods should be defined as much as possible using epidemiologic and mechanistic evidence or by expert opinion. Sensitivity analyses using different risk periods and clustering analyses are complementary methods to highlight potential windows of risk. A disease-specific time frame should be the preferred approach when different kind of clinical events are under assessment. In case-only study design, a wash-out period between risk and control periods should also be preferably considered, to avoid misclassification [45]. In the studies, sample sizes limitations were overcome by creating composite endpoints or by combining multiple healthcare databases. With intrinsic limitations such as heterogeneity between databases or lack of specificity of the outcome of interest both alternative approaches emphasize the need for collaboration to increase sample size and develop common clinical definitions. Because of the rarity of autoimmune diseases, some of the studies included in our review may not be adequately powered to detect a potential increased or decreased risk. This possible lack of statistical power may suggest an unreliable absence of risk. In addition, 2vHPV vaccine was less frequently studied and therefore no estimation of risk could be generated for some of the diseases.

Our review also provides pooled risk estimates. Pooled findings in females suggested that 4vHPV vaccination significantly increased the risk of both Hashimoto and Raynaud's diseases. The slightly elevated risk of Hashimoto disease was mainly driven by the Chao *et al.* [8] study. After further

evaluation, the researchers demonstrated that most of the new onset cases were likely pre-existing cases and that no consistent evidence for a safety signal for autoimmune thyroid conditions in general was observed among vaccinated subjects. Similarly, the increased risk of Raynaud's disease was driven by the Arnheim *et al.* [28] study. The researchers discriminated this safety signal based on pre-specified causality criteria including the strength of the association (rate ratio < 3.0). On the contrary a protective effect was observed for paralysis after 4vHPV and for ITP and CFS after 2vHPV. By using criteria such as the strength of the association, the consistency of the reported risks and the level of significance to interpret the risk estimates, we noticed a lack of clear association for all protective and risk effects with regards to HPV vaccines. In addition, the pooled analysis has several limitations due to heterogeneity of clinical definitions, targeted age categories and variation in risk periods across studies. Two studies [28,32] conducted in Sweden and Denmark used same sources of data but targeted 2 different age categories (10-17 and 18-44 years old). Therefore, the pooled estimate for Raynaud disease and paralysis does not bring any added-value and only the individual studies can confirm the observed risks. Similarly, a higher risk of Hashimoto disease was observed from a pool of 3 studies for which the age of the populations did not necessarily overlap. Moreover, the small number of studies included in our analysis did not allow stratification by type of study design or risk estimates. The pooling of any risk estimates did not affect drastically the pooled estimates because for rare events odds ratio and relative risk are virtually similar. However, while each individual study was fit-for-purpose for the stated objectives, the variability of methods across studies may impact the ability to validly characterize risks. The risk evaluation in our review should be considered as an indicator of possible harms after HPV vaccination for which enhanced and continuous surveillance should be maintained or implemented. A recently published meta-analysis [11] also showed a small increased risk of Hashimoto disease after HPV vaccination. However, the authors did not provide analysis by type of HPV vaccine. Because the mechanisms of action of adjuvant systems may perform differently, a critical evaluation by type of vaccine may help to discriminate any potential triggering effect.

This review also underlines the need for harmonization of outcome definitions and collaboration in assessing vaccine safety, which is one of the efforts currently done in the ADVANCE project [46] in the European Union and was possible globally for assessing safety of the pandemic influenza vaccine [47]. In conclusion, this systematic review emphasizes the diversity of methodological approaches to assess the risk of developing rare adverse events after HPV vaccination. Results show that many events have been studied but not systematically for the different HPV vaccines. The review highlights that positive and negative associations were observed with autoimmune diseases. However, these estimates should be interpreted with caution due to the diversity in methodological approaches used by the studies included in this review. More systematic collaborations and harmonization of event clinical definitions are needed to monitor rare safety events.

References

[1] Mesher D, Panwar K, Thomas SL, et al: Continuing reductions in HPV 16/18 in a population with high coverage of bivalent HPV vaccination in England: an ongoing cross-sectional study. *BMJ Open* 2016;6: e009915.

[2] Herweijer E, Sundström K, Ploner A, et al: Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study. *Int J Cancer* 2016; Jun 15;138(12):2867-74.

[3] Kash N, Lee MA, Kollipara R, et al: Safety and efficacy data on vaccines and immunization to human papillomavirus. *J Clin Med* 2015; 4:614-633.

[4] Haupt RM, Sings HL: The efficacy and safety of the quadrivalent human papillomavirus 6/11/16/18 vaccine Gardasil. *J Adolesc Health* 2011; 49: 467–475.

[5] Gallagher KE, LaMontagne DS, Watson-Jones D. Status of HPV vaccine introduction and barriers to country uptake. *Vaccine*, 2018: 36; 4761-4767.

[6] Bruni L, Diaz M, Barrionuevo-Rosas L, et al: Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health* 2016; 4: e453–63.

[7] Batista-Duharte A, Tellez Martinez D, Zeppone Carlos I. Efficacy and safety of immunological adjuvants. Where is the cut-off? *Biomed Pharmacother* 2018; 105: 616-624.

[8] Chao C, Klein NP, Velicer CM, et al: Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. *J Intern Med* 2012;271: 193-203.

[9] Miranda S, Chaignot C, Collin C, et al: Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study over 2 million young girls in France. Vaccine 2017; 35: 4761-4768.

[10] Genovese C, La Fauci V, Squeri A et al: HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature. *J Prev Med Hyg*, 2018; 59:E194-E199.

[11] Jiang H, Shi Y, Zhang X et al: Human papillomavirus vaccination and the risk of autoimmune disorders: A systematic review and meta-analysis. *Vaccine*, 2019: 37; 3031-3039.

[12] Moher D, Liberati A, et al: *Preferred Reporting Items for Systematic Reviews and Meta-Analyses:* The PRISMA Statement. *J Clin Epidemiol* 2009; 62: 1006-12.

[13] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 6). EMA/95098/2010. Available from: http://www.encepp.eu/standards_and_guidances [Accessed 07 June 2019].

[14] The European Union electronic register of post-authorisation studies (EU PAS Register). Available from: http://www.encepp.eu/encepp_studies/indexRegister.shtml [Accessed 07 June 2019].

[15] Wells GA, Shea B, O'Connell O, et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 07 June 2019].

[16] Scottish Intercollegiate Guidelines Network. Critical appraisal: notes and checklists. Available from: http://www.sign.ac.uk/checklists-and-notes.html [Accessed 07 June 2019].

[17] StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

[18] Grimaldi-Bensouda L, Guillemot D, Godeau B, et al: Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. *J Intern Med* 2014; 275: 398-408.

[19] Grimaldi-Bensouda L, Rossignol M, Koné-Paut I, et al: Risk of autoimmune diseases and human papillomavirus (HPV) vaccines: Six years of case-referent surveillance. *J Autoimmun* 2017; 79: 84-90.

[20] Langer-Gould A, Qian L, Tartof SY, et al: Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. *JAMA Neurol* 2014; 71: 1506-13.

[21] Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. *Vaccine* 2017; 35: 1729-1732.

[22] Donegan K, Beau-Lejdstrom R, King B, et al: Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine* 2013; 31: 4961-7.

[23] Scheller NM, Pasternak B, Svanstrom H, et al: Quadrivalent Human Papillomavirus Vaccine and the Risk of Venous Thromboembolism. *JAMA* 2014; 312: 187-8.

[24] Liu E, Smith L, Ellis A, et al: Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV vaccine cohort study. *CMAJ* 2018; May 28; 190: E648-55.

[25] Schurink-van't Klooster T, Kemmeren J, van der Maas N, et al: No evidence found for an increased risk of long-term fatigue following human papillomavirus vaccination of adolescent girls. *Vaccine* 2018; 36: 6796-6802.

[26] Baxter R, Lewis E, Goddard K, et al: Acute demyelinating events following vaccines: A case-centered analysis. Clinical Infectious Diseases 2016; 63(11): 1456-62.

[27] Baxter R, Lewis E, Fireman B, et al: Case-centered analysis of optic neuritis after vaccines. *Clin Infec Dis* 2016; 63(1): 79-81.

[28] Arnheim-Dahlström L, Pasternak B, Svanström H. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ* 2013; 347: f5906.

[29] Deceuninck G, Sauvageau C, Gilca V, et al: Absence of association between Guillain-Barré syndrome hospitalizations and HPV-vaccine. *Expert Rev Vaccines* 2018; 17 (1): 99-102.

[30] Feiring B, Laake I, Bakken IJ, et al: HPV vaccination and risk of chronic fatigue syndrome/myalgic

encephalomyelitis: A nationwide register-based study from Norway. *Vaccine* 2017; 35: 4203-4212.

[31] Frisch M, Besson A, Bjerring Clemmensen K, et al: Quadrivalent human papillomavirus vaccination in boys and risk of autoimmune diseases, neurological diseases and venous thromboembolism. *Int J Epidemiol* 2018; 634-641.

[32] Hviid A, Svanstrom H, Scheller NM, et al: Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases. *J Intern Med* 2018; 283: 154-65.

[33] Klein N, Goddard K, Lewis E, et al: Long term risk of developing type 1 diabetes after HPV vaccination in males and females. *Vaccine* 2019; 37: 1938-1944.

[34] Scheller NM, Svanström H, Pasternak B, et al: Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA* 2015; 313: 54-61.

[35] Skufca J, Ollgren J, Artama M, et al: The association of adverse events with bivalent human papilloma virus vaccination: A nationwide register based cohort study in Finland. *Vaccine* 2018; 36: 5926-33.

[36] Sridhar G, Tian F, Forshee R, et al: Evaluation of optic neuritis following human papillomavirus vaccination. *HV&I* 2017; 13 (7): 1705-1713.

[37] Willame C, Rosillon D, Zima J, et al: Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Hum Vaccin Immunother* 2016, 12 (11): 2862-71.

[38] Colafrancesco S, Perricone C, Tomljenovic L, et al: Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced adjuvants. *Am J Reprod Immunol* 2013; 70: 309-316.

[39] Kinoshita T, Abe R, Hineno A, et al: Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. *Intern Med* 2014, 53(19):2185-200.

[40] European Medicines Agency. EMA to further clarify safety profile of human papillomavirus (HPV) vaccines. July 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/07/WC500189481.pdf [Accessed 07 June 2019].

[41] Schonberger L, Bregman D, Sullivan-Bolyai J, al: Guillain-Barré syndrome following vaccination in the national influenza immunization program, United States, 1976-1977. *Am J Epidemiol* 1979; 110(2): 105-23.

[42] Wise M, Viray M, Sejvar J, et al: Guillain-Barré syndrome during the 2009-2010 H1N1 influenza vaccination campaign: population-based surveillance among 45 million americans. *Am J*

Epidemiol 2012; 175(11): 1110-9.

[43] Institute of Medicine: Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: The National Academies Press. 2012.

[44] Chan K-W, Felson D, Yood R, et al: The lag time between onset of symptoms and diagnosis of rheumatoid arthritis. *Arthritis Rheum* 1994; 37 (6): 814-20.

[45] Li R, Stewart B, Weintraub E. Evaluating efficiency and statistical power of self-controlled case series and self-controlled risk interval designs in vaccine safety. *J Biopharm Stat* 2016; 26 (4): 686-93.

[46] ADVANCE. Available from: http://www.advance-vaccines.eu/ [Accessed 07 June 2019]

[47] Dodd C, Romio S, Black S, et al. International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. *Vaccine* 2013; 31: 4448-58.

Supplementary materials

Table S1: Search strategy per database

The following list of autoimmune diseases was used to develop the search strategy: Addison disease, ankylosing spondylitis, arthritis, autoimmune hepatitis, Basedow disease, Behet disease, Bell's palsy, Crohn disease, demyelinating disease, diabetes mellitus, encephalomyelitis, Graves' disease, Guillain Barre syndrome, Hashimoto disease, hemolytic anemia, inflammatory bowel disease, lupus erythematosus, Miller Fisher syndrome, multiple sclerosis, postural orthostatic tachycardia syndrome, psoriasis, Raynaud disease, thyroiditis, thrombocytopenia, transverse myelitis, optic neuritis, uveitis.

Embase:
('autoimmune disease'/exp OR autoantibody/exp OR autoimmunity/exp OR 'inflammatory bowel disease'/exp OR 'Raynaud phenomenon'/exp OR 'psoriatic arthritis'/exp OR 'ankylosing spondylitis'/exp OR 'autoimmune hemolytic anemia'/exp OR psoriasis/de OR 'Bell palsy'/exp OR 'demyelinating disease'/exp OR 'nervous system inflammation'/exp OR 'diabetes mellitus'/exp OR 'Addison disease'/exp OR thyroiditis/exp OR 'postural orthostatic tachycardia syndrome'/exp OR 'autoimmune hepatitis'/de OR 'autoinflammatory disease'/exp OR (autoimmun* OR autoantibod* OR (inflammator* NEAR/3 bowel*) OR ibd OR crohn* OR (ulcerat* NEAR/3 colit*) OR behcet* OR ((systemic OR disseminated OR visceralis) NEAR/3 lupus NEAR/3 erythematos*) OR Raynaud* OR ((rheumat* OR deforman* OR inflammator* OR juvenile OR chronic) NEAR/3 (arthrit* OR polyarthrit* OR arthropath*)) OR (still* NEAR/3 disease*) OR (ankyl* NEAR/3 spondyl*) OR (idiopath* NEAR/3 (thrombocytop* OR purpura)) OR psoria* OR (Guillain NEAR/3 Barre) OR (Miller NEAR/3 Fisher) OR (Bell* NEAR/3 palsy) OR ((idiopath* OR inflammat* OR herpe*) NEAR/3 facial NEAR/3 neuropath*) OR ((multipl* OR disseminat*) NEAR/3 sclerosis) OR (transverse NEAR/3 myelit*) OR demyelinat* OR (acute NEAR/3 disseminated NEAR/3 encephal*) OR adem OR (encephal* NEAR/3 (postvaccin* OR vaccin*)) OR ('nervous system' NEAR/3 inflammat*) OR neuritis OR uveitis OR diabet* OR Addison* OR thyroiditis OR

Ophthalmic* OR Endocrin* OR Hashimoto OR Grave* OR Basedow* OR (postural NEAR/3 tachycard*) OR pots OR autoinflammat* OR (auto NEXT/1 inflammat*) OR (asia NEAR/3 syndrome*)):ab,ti) AND (((Alphapapillomavirus/exp OR 'uterine cervix cancer'/de OR papilloma/de OR Papillomaviridae/exp OR 'papillomavirus infection'/exp OR 'condyloma acuminatum'/exp OR (papillomavir* OR papilloma OR (papilloma NEXT/1 vir*) OR hpv OR (cervi* NEAR/3 (cancer* OR malign*)) OR (genital* NEAR/3 wart*) OR (condylom* NEAR/3 acuminat*)):ab,ti) AND (vaccine/de OR 'cancer vaccine'/de OR vaccination/de OR 'vaccination reaction'/exp OR 'cancer immunotherapy'/de OR (vaccin* OR postvaccin* OR immunization* OR immunisation* OR immunotherap*):ab,ti)) OR ('Wart virus vaccine'/exp OR ((Wart* NEAR/3 virus* NEAR/3 vaccin*) OR cervarix OR gardasil OR silgard):ab,ti))
Medline ovid:
(exp "autoimmune diseases"/ OR exp Autoantibodies/ OR exp Autoimmunity/ OR exp "Inflammatory Bowel Diseases"/ OR "Raynaud Disease"/ OR "Arthritis, Psoriatic"/ OR "Arthritis, Juvenile"/ OR "Spondylitis, Ankylosing"/ OR "Anemia, Hemolytic, Autoimmune"/ OR exp psoriasis/ OR "Bell palsy"/ OR exp "Demyelinating Diseases"/ OR exp "Central Nervous System Infections"/ OR exp "diabetes mellitus"/ OR exp thyroiditis/ OR "Postural Orthostatic Tachycardia Syndrome"/ OR (autoimmun* OR autoantibod* OR (inflammator* ADJ3 bowel*) OR ibd OR crohn* OR (ulcerat* ADJ3 colit*) OR behcet* OR ((systemic OR disseminated OR visceralis) ADJ3 lupus ADJ3 erythematos*) OR Raynaud* OR ((rheumat* OR deforman* OR inflammator* OR juvenile OR chronic) ADJ3 (arthrit* OR polyarthrit* OR arthropath*)) OR (still* ADJ3 disease*) OR (ankyl* ADJ3 spondyl*) OR (idiopath* ADJ3 (thrombocytop* OR purpura)) OR psoria* OR (Guillain ADJ3 Barre) OR (Miller ADJ3 Fisher) OR (Bell* ADJ3 palsy) OR ((idiopath* OR inflammat* OR herpe*) ADJ3 facial ADJ3 neuropath*) OR ((multipl* OR disseminat*) ADJ3 sclerosis) OR (transverse ADJ3 myelit*) OR demyelinat* OR (acute ADJ3 disseminated ADJ3 encephal*) OR adem OR (encephal* ADJ3 (postvaccin* OR vaccin*)) OR ("nervous system" ADJ3

inflammat*) OR neuritis OR uveitis OR diabet* OR Addison* OR thyroiditis OR Ophthalmic* OR Endocrin* OR Hashimoto OR Grave* OR Basedow* OR (postural ADJ3 tachycard*) OR pots OR autoinflammat* OR (auto ADJ inflammat*) OR (asia ADJ3 syndrome*)).ab,ti.) AND (((exp Alphapapillomavirus/ OR "Uterine Cervical Neoplasms"/ OR papilloma/ OR Papillomaviridae/ OR exp "Papillomavirus Infections"/ OR (papillomavir* OR papilloma OR (papilloma ADJ vir*) OR hpv OR (cervi* ADJ3 (cancer* OR malign*)) OR (genital* ADJ3 wart*) OR (condylom* ADJ3 acuminat*)).ab,ti.) AND (vaccines/ OR "cancer vaccines"/ OR exp vaccination/ OR (vaccin* OR postvaccin* OR immunization* OR immunisation* OR immunotherap*).ab,ti.)) OR ("Papillomavirus Vaccines"/ OR ((Wart* ADJ3 virus* ADJ3 vaccin*) OR cervarix OR gardasil OR silgard).ab,ti.))
Cochrane:
((autoimmun* OR autoantibod* OR (inflammator* NEAR/3 bowel*) OR ibd OR crohn* OR (ulcerat* NEAR/3 colit*) OR behcet* OR ((systemic OR disseminated OR visceralis) NEAR/3 lupus NEAR/3 erythematos*) OR Raynaud* OR ((rheumat* OR deforman* OR inflammator* OR juvenile OR chronic) NEAR/3 (arthrit* OR polyarthrit* OR arthropath*)) OR (still* NEAR/3 disease*) OR (ankyl* NEAR/3 spondyl*) OR (idiopath* NEAR/3 (thrombocytop* OR purpura)) OR psoria* OR (Guillain NEAR/3 Barre) OR (Miller NEAR/3 Fisher) OR (Bell* NEAR/3 palsy) OR ((idiopath* OR inflammat* OR herpe*) NEAR/3 facial NEAR/3 neuropath*) OR ((multipl* OR disseminat*) NEAR/3 sclerosis) OR (transverse NEAR/3 myelit*) OR demyelinat* OR (acute NEAR/3 disseminated NEAR/3 encephal*) OR adem OR (encephal* NEAR/3 (postvaccin* OR vaccin*)) OR ('nervous system' NEAR/3 inflammat*) OR neuritis OR uveitis OR diabet* OR Addison* OR thyroiditis OR Ophthalmic* OR Endocrin* OR Hashimoto OR Grave* OR Basedow* OR (postural NEAR/3 tachycard*) OR pots OR autoinflammat* OR (auto NEXT/1 inflammat*) OR (asia NEAR/3 syndrome*)):ab,ti) AND ((((papillomavir* OR papilloma OR (papilloma NEXT/1 vir*) OR hpv OR (cervi* NEAR/3 (cancer* OR malign*)) OR (genital* NEAR/3 wart*) OR (condylom*

NEAR/3 acuminat*)):ab,ti) AND ((vaccin* OR postvaccin* OR immunization* OR immunisation* OR immunotherap*):ab,ti)) OR (((Wart* NEAR/3 virus* NEAR/3 vaccin*) OR cervarix OR gardasil OR silgard):ab,ti))
Web-of-Science:
TS=(((autoimmun* OR autoantibod* OR (inflammator* NEAR/2 bowel*) OR ibd OR crohn* OR (ulcerat* NEAR/2 colit*) OR behcet* OR ((systemic OR disseminated OR visceralis) NEAR/2 lupus NEAR/2 erythematos*) OR Raynaud* OR ((rheumat* OR deforman* OR inflammator* OR juvenile OR chronic) NEAR/2 (arthrit* OR polyarthrit* OR arthropath*)) OR (still* NEAR/2 disease*) OR (ankyl* NEAR/2 spondyl*) OR (idiopath* NEAR/2 (thrombocytop* OR purpura)) OR psoria* OR (Guillain NEAR/2 Barre) OR (Miller NEAR/2 Fisher) OR (Bell* NEAR/2 palsy) OR ((idiopath* OR inflammat* OR herpe*) NEAR/2 facial NEAR/2 neuropath*) OR ((multipl* OR disseminat*) NEAR/2 sclerosis) OR (transverse NEAR/2 myelit*) OR demyelinat* OR (acute NEAR/2 disseminated NEAR/2 encephal*) OR adem OR (encephal* NEAR/2 (postvaccin* OR vaccin*)) OR ("nervous system" NEAR/2 inflammat*) OR neuritis OR uveitis OR diabet* OR Addison* OR thyroiditis OR Ophthalmic* OR Endocrin* OR Hashimoto OR Grave* OR Basedow* OR (postural NEAR/2 tachycard*) OR pots OR autoinflammat* OR (auto NEAR/1 inflammat*) OR (asia NEAR/2 syndrome*))) AND ((((papillomavir* OR papilloma OR (papilloma NEAR/1 vir*) OR hpv OR (cervi* NEAR/2 (cancer* OR malign*)) OR (genital* NEAR/2 wart*) OR (condylom* NEAR/2 acuminat*))) AND ((vaccin* OR postvaccin* OR immunization* OR immunisation* OR immunotherap*))) OR (((Wart* NEAR/2 virus* NEAR/2 vaccin*) OR cervarix OR gardasil OR silgard))))
Pubmed publisher:
("autoimmune diseases"[mh] OR Autoantibodies[mh] OR Autoimmunity[mh] OR "Inflammatory Bowel Diseases"[mh] OR "Raynaud Disease"[mh] OR "Arthritis, Psoriatic"[mh] OR "Arthritis, Juvenile"[mh] OR "Spondylitis, Ankylosing"[mh] OR "Anemia, Hemolytic, Autoimmune"[mh] OR

psoriasis[mh] OR "Bell palsy"[mh] OR "Demyelinating Diseases"[mh] OR "Central Nervous System Infections"[mh] OR "diabetes mellitus"[mh] OR thyroiditis[mh] OR "Postural Orthostatic Tachycardia Syndrome"[mh] OR (autoimmun*[tiab] OR autoantibod*[tiab] OR (inflammator*[tiab] AND bowel*[tiab]) OR ibd OR crohn*[tiab] OR (ulcerat*[tiab] AND colit*[tiab]) OR behcet*[tiab] OR ((systemic OR disseminated OR visceralis) AND lupus AND erythematos*[tiab]) OR Raynaud*[tiab] OR ((rheumat*[tiab] OR deforman*[tiab] OR inflammator*[tiab] OR juvenile OR chronic) AND (arthrit*[tiab] OR polyarthrit*[tiab] OR arthropath*[tiab])) OR (still*[tiab] AND disease*[tiab]) OR (ankyl*[tiab] AND spondyl*[tiab]) OR (idiopath*[tiab] AND (thrombocytop*[tiab] OR purpura)) OR psoria*[tiab] OR (Guillain AND Barre) OR (Miller AND Fisher) OR (Bell*[tiab] AND palsy) OR ((idiopath*[tiab] OR inflammat*[tiab] OR herpe*[tiab]) AND facial AND neuropath*[tiab]) OR ((multipl*[tiab] OR disseminat*[tiab]) AND sclerosis) OR (transverse AND myelit*[tiab]) OR demyelinat*[tiab] OR (acute AND disseminated AND encephal*[tiab]) OR adem OR (encephal*[tiab] AND (postvaccin*[tiab] OR vaccin*[tiab])) OR ("nervous system" AND inflammat*[tiab]) OR neuritis OR uveitis OR diabet*[tiab] OR Addison*[tiab] OR thyroiditis OR Ophthalmic*[tiab] OR Endocrin*[tiab] OR Hashimoto OR Grave*[tiab] OR Basedow*[tiab] OR (postural AND tachycard*[tiab]) OR pots OR autoinflammat*[tiab] OR (auto inflammat*[tiab]) OR (asia AND syndrome*[tiab]))) AND (((Alphapapillomavirus[mh] OR "Uterine Cervical Neoplasms"[mh] OR papilloma[mh] OR Papillomaviridae[mh] OR "Papillomavirus Infections"[mh] OR (papillomavir*[tiab] OR papilloma OR (papilloma vir*[tiab]) OR hpv OR (cervi*[tiab] AND (cancer*[tiab] OR malign*[tiab])) OR (genital*[tiab] AND wart*[tiab]) OR (condylom*[tiab] AND acuminat*[tiab]))) AND (vaccines[mh] OR "cancer vaccines"[mh] OR vaccination[mh] OR (vaccin*[tiab] OR postvaccin*[tiab] OR immunization*[tiab] OR immunisation*[tiab] OR immunotherap*[tiab]))) OR ("Papillomavirus Vaccines"[mh] OR ((Wart*[tiab] AND virus*[tiab] AND vaccin*[tiab]) OR cervarix OR gardasil OR silgard))) AND publisher[sb]
Google scholar:

autoimmune|"auto immune"|autoimmunity|"auto immunity"|autoantibody
papillomavirus|"papilloma|papilloma virus"
vaccination|vaccin|postvaccination|immunization|immunisation|immunotherapy

Table S2. Quality criteria adapted from NOS and SIGN checklists.

	Criteria	**Score**
	Selection of the study groups	
1.	The exposed/non-exposed or cases/controls are taken from comparable population (Not Applicable for case-only design) Yes No	 1 0
2.	The inclusion and exclusion criteria are described and are comparable for both study groups (Not Applicable for case-only design) Yes No	 1 0
3.	If Case-Only design: representativeness of the cases Consecutive or obviously representative series of cases Potential for selection biases or not stated	 2 0
	Outcome Assessment	
4.	Case identification & validation from: Secure electronic medical records completed with a review by physicians/specialists or disease registries Only based on electronic medical records	 1 0
5.	Disease onset based on: First symptom and/or first clinical signs Disease diagnosis	 1 0
6.	Demonstration that the outcome of interest was not present at the study start Yes	 1

	No	0
	Exposure Assessment	
7.	Ascertainment of exposure from: Documented source: validated electronic medical records or vaccine card Interviews, reimbursement data source or no description	 1 0
	Confounding factors	
8.	The study controlled for: the most important and any additional confounders or self-adjustment no adjustment	 1 0

NOS: Newcastle Ottawa Scale; SIGN: Scottish Intercollegiate Guidelines Network

Table S3 Characteristics of the studies assessing the risk of autoimmune diseases and rare adverse events post-HPV vaccination

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
Andrews[21], 2017	To assess the risk of GBS after HPV vaccination	SCCS	Sep2007-Mar2016	England	Hospital database: HES	12-18 y-o, females	**Distinct 4vHPV** & **2vHPV**	GBS	7
Arnheim-Dahlstrom[28], 2013	To identify potential safety signal of serious adverse outcome after HPV vaccination	Cohort study using concurrent control cohort	Oct2006-Dec2010	Denmark & Sweden	Registers: Demographic and national patients registers	10-17 y-o, females	**4vHPV**	29 outcomes including*: - 23 ADs (Graves'disease, Hashimoto disease, ITP, T1D etc.) and - 6 neurological diseases (Bell's palsy, Epilepsy, Narcolepsy, Optic neuritis, Paralysis, VTE)	6
Baxter[26], 2016(a)	To analyze the association of immunization and	Case-centered	Jan2007-Dec2012	US	Claims data: Vaccine Safety Datalink	Any age, females and males	**4vHPV**	TM/ADEM	6

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
	transverse myelitis or ADEM								
Baxter[27], 2016(b)	To detect an association between optic neuritis and any vaccine (including HPV)	Case-centered	Jan2007-Dec2012	US, California	Claims data: Kaiser Permanente Northern California	Any age, females and males	**4vHPV**	Optic neuritis	6
Chao[8], 2012	Surveillance of AD post- HPV vaccination	Cohort study	Aug2006-Mar2008	US, California	Claims data: Kaiser Permanente Northern & Southern California	9-26 y-o, females	**4vHPV**	- 5 Rheumatologic diseases (ITP, AI haemolytic anaemia, SLE, RA, JRA) - 3 Endocrine diseases (T1D, Hashimoto's disease, Graves'disease) - 7 Neurological/Ophthalmic	7

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
								diseases (MS, ADEM, other demyelinating diseases of CNS, GBS, Optic neuritis, Uveitis)	
Deceuninck[29], 2017	To assess an association between HPV vaccination and GBS hospitalization	Cohort study	Oct1999-Mar2014	Canada, Quebec	Hospital database: provincial hospital discharge database	7-17 y-o, females and males	**4vHPV**	GBS	2
Donegan[22], 2013	To estimate the risk of fatigue syndromes in the year after 1st HPV vaccination	SCCS	Oct2008-Dec2011	UK	General practices database: CPRD	12-20 y-o, females	**2vHPV**	CFS/Myalgic encephamyelitis/post-viral fatigue syndrome	6

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
Feiring[30], 2017	To assess the link between HPV vaccination and CFS/ Myalgic encephalomyelitis	Cohort study	Sep2009-Dec2014	Norway	Registers: Norvegian Patient Registry and Norvegian Immunisation Registry	12-18 y-o, females	**4vHPV**	CFS/Myalgic encephalomyelitis	4
Frisch[31], 2018	To investigate whether 4vHPV is associated with AID, neurological disorders and VTE	Cohort study	Oct2006-Nov2016	Denmark	Registers: National demographic and healthcare registers	10-17 y-o, males	**4vHPV**	52 outcomes including*: -39 ADs (Basedow disease, Hashimoto, coeliac and Crohn diseases, ulcerative colitis, SLE, myositis, etc.) -12 neurologic disorders (ADEM, Bell's palsy, GBS, etc.) -VTE	4

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
Grimaldi-Bensouda[18], 2014	To assess the risk of ADs after HPV vaccination	Matched case-control (1:3)	Dec2006-Dec2010 for Central demyelination Dec2006-Apr2011 for Other ADs	France	PGRx programme	14-26 y-o, females	**4vHPV**	AIT (including Graves & Hashimoto) / Central demyelination & MS / Connective tissues disorders (SLE, JRA, RA, dermato-myositis) / T1D GBS / ITP	6
Grimaldi-Bensouda[19], 2017	To assess the risk of ADs following HPV vaccines exposure	Case-control study	Apr2008-Oct2014	France	PGRx programme	11-25 y-o, females	**Combined 4vHPV & 2vHPV**	-Central demyelination and multiple sclerosis - Connective tissue diseases including: lupus, chronic inflammatory arthritis, JRA, RA, myositis, and undetermined connective tissue	6

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
								disease -Other ADs : GBS / T1D / AIT / ITP	
Hviid[32], 2017	To compare rates of serious chronic diseases after HPV vaccination	Cohort study (main analysis) and SCCS	Oct2006-Jul2013 in Denmark Oct2006-Dec2012 in Sweden	Sweden and Denmark	Registers: Demographic and national patients registers	18-44 y-o, females	**4vHPV**	45 outcomes including*: - 38 AD (Graves'disease, Hashimoto disease, T1D etc.) and - 7 neurological diseases (Bell's palsy, Epilepsy, GBS, Myasthenia gravis, Narcolepsy, Other encephalitis, Paralysis)	5
Klein[33], 2019	To evaluate whether receipt of 4v/9vHPV is associated with	Cohort study	July2006-Dec2015	US, California	Claims data: Kaiser Permanente Southern	From 10 y-o, females and males	**Combined 4vHPV & 9vHPV**	T1D	5

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
	subsequent increased risk of T1D				California database				
Langer-Gould[20], 2014	To assess link between first onset of CNS AD and HPV vaccine	Matched nested case-control (1:5)	Jan2008-Dec2011	US, Southern California	Claims data: Kaiser Permanente Southern California database	9-26 y-o, females	**4vHPV**	- Multiple Sclerosis - Other Central Nervous System Diseases	7
Liu[24], 2018	To assess the risk of autoimmune disorders after 4vHPV vaccination	SCCS	Sep2007-Mar2013	Canada, Ontario	Hospital database: Discharge and emergency admission	13 y-o, females	**4vHPV**	18 outcomes including* ITP, JRA, MS, ADEM, TM, GBS, optic neuritis, T1D, Bell's palsy, Hashimoto disease, Grave disease, Crohn disease, UC, AD hepatitis	6

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
Miranda[9], 2017	To assess the risk of AD after HPV vaccination	Cohort study using concurrent control cohort	Jan2008-Dec2013	France	Claims data: National health insurance information system including hospitalization	13-16 y-o, females	**Distinct 4vHPV** & **2vHPV**	Caeliac disease / Demyelinaing disease of CNS / GBS / ITP / IBD / Myositis/poly-dermato-myositis / Pancreatitis RA/JRA / Sjogren'syndrome SLE / Systemic Scleroderma Vasculitis / T1D / Thyroiditis	4
Scheller[23], 2014	To study the potential link between HPV vaccination and venous thromboembolism	SCCS	Oct2006-Jul2013	Denmark	Registers: National demographic and healthcare registers	10-44 y-o, females	**4vHPV**	VTE	6

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
Scheller[34], 2015	To assess the risk of multiple sclerosis & Other demyelinating diseases after HPV vaccination	Cohort study using concurrent control cohort (Main analysis) and SCCS	Oct2006-Jul2013 in Denmark Oct2006-Dec2012 in Sweden	Sweden and Denmark	Registers: Nationwide health and demographic registers	10-44 y-o, females	**4vHPV**	- Multiple Sclerosis - Demyelinating diseases including: optic neuritis, neuromyelitis optica, transverse myelitis, ADEM, other central demyelinating diseases	6
Schurink-van't Klooster[25], 2018	To investigate occurrence of CFS	SCCS	Jan2007-Dec2014	The Netherlands	General practice database: IPCI	12-16 y-o, females	**2vHPV**	CFS	5
Skufca[35], 2018	To evaluate the association between 2vHPV and numerous AEFIs	Cohort study using concurrent control cohort	Nov2013-Dec2016	Finland	Registers: National hospital discharge register and National	11-15 y-o, females	**2vHPV**	38 outcomes including* Bells palsy, caeliac disease, GBS, ITP, complex regional pain syndrome etc.	5

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
					vaccination register				
Sridhar[36], 2017	To evaluate the association between HPV and optic neuritis	Cohort study using concurrent matched control cohort	Jan2007-Apr2012	US	Claims data: HealthCore Integrated Research Database	9-26 y-o, females	**4vHPV**	Optic neuritis	4
Willame[37], 2016	To evaluate the risk of new onset of AD after HPV vaccination	Cohort study using historical control cohort and males control cohorts (Main analysis) and SCCS	Sep2008-Aug2010	UK	General practices and hospital databases: CPRD + HES	9-25 y-o, females	**2vHPV**	-Neuroinflammatory/ Ophthalmic diseases including: MS, transverse myelitis, optic neuritis, GBS, AD uveitis, other acute demyelinating diseases -Other AD including: SLE, RA, JRA, Still's disease,	7

Author, year of publication	Study objective	Study design	Study period	Country, Region	Data source	Study population (age, gender)	HPV Vaccine Exposure	Autoimmune and rare adverse events under assessment	Study quality assessment score (from 0 to 7)
								psoriatic arthritis, ankylosing spondylitis, ITP, haemolytic anaemia, T1D, AIT, Crohn's disease, UC and AD hepatitis	

*The full list of diseases is available in **Supplementary Table S5**.

AD = Autoimmune Diseases; ADEM = Acute Disseminated Encephalomyelitis; AEFI = Adverse Events Following Immunization; AI = Autoimmune; AIT = Autoimmune Thyroiditis; Al = Aluminium hydroxyphosphate sulphate; AS04 = Adjuvant System 04; CFS = Chronic Fatigue Syndrome; CNS = Central Nervous System; GBS = Guillain Barré Syndrome; HES = Hospital Episode Statistics; HPV = Human Papillomavirus Vaccine; IBD = Inflammatory Bowel Diseases; IPCI = ; ITP = Immune Thrombocytopenia Purpura; JRA = Juvenile Rheumatoid Arthritis; PGRx = Pharmacoepidemiologic General Research eXtension; RA = Rheumatoid Arthritis; SLE = Systemic Lupus Erythematous; T1D = Type 1 Diabetes Mellitus; SCCS = Self-Controlled-Case Series; UC = Ulcerative Colitis; UK = United Kingdom; US = United States; VTE = Venous Thromboembolism; y-o = years old; 4vHPV = quadrivalent Human Papillomavirus Vaccine; 2vHPV = bivalent Human Papillomavirus vaccine.

Table S4 Methodological approaches used in the studies

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
Andrews[21], 2017	**Identification:** EMR searches using diagnosis codes **Validation:** confirmation by GPs questionnaire	-	Earliest onset date based on GP	Individual endpoint	IRR	Self-and time-varying covariates adjustment	Risk period: 90 days after exposure to each dose (92–183, 184–365, 0–183, and 0–365)	At least 90% power to detect a RR of 2.0	Number of cases included: 100 corresponding to 101 episodes of GBS
Arnheim-Dahlstrom[28], 2013	**Identification:** EMR searches using diagnosis codes **Validation:** NP	-	First disease diagnosis	Individual endpoint	RR	Multivariate modelling	Risk period: 180 days after exposure to each dose For VTE: risk period 90 days after exposure to each dose	NR	Number of exposed: 296,826 Number of non-exposed: 700,759

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
Baxter[26], 2016(a)	**Identification:** EMR searches using diagnosis codes **Validation:** medical charts review by neurologist	Brighton collaboration criteria & TM Consortium Working group criteria	Neurologist first diagnosis within 3 months of EMR	Individual endpoint	OR	Matched design, no additional adjustment	Risk period: 5-28 days after exposure to any dose (and 2-42 days)	NR	Number of cases: 6 (ADEM)/ 3 (TM) Number of controls: 56,846 (ADEM)/ 7273 (TM)
Baxter[27], 2016(b)	**Identification:** EMR searches using diagnosis codes **Validation:** medical charts review by trained medical reviewers	-	New onset and symptoms	Individual endpoint	OR	Matched design, no additional adjustment	Risk period: 2-42 days after exposure to any dose (and 5-28 days)	NR	Number of cases: 5 Number of controls: 42,063

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
Chao[8], 2012	**Identification:** EMR searches using diagnosis and treatment/medication codes. **Validation:** medical charts review by a panel of experts	Clinical judgment	First disease diagnosis based on clinical judgment	Individual endpoint	IRR	Multivariate modelling	Risk period: 180 days after exposure to each dose	NR	Number of subjects included: 189,629
Deceuninck[29], 2017	**Identification:** EMR searches using diagnosis codes **Validation:** NP	-	First disease diagnosis	Individual endpoint	RR	Multivariate modelling	Risk period: not specified	82% power to detect a RR of 2.5	Females follow-up time: 6,715,209 person-years

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
									Males follow-up time: 7,020,960 person-years
Donegan[27], 2013	**Identification:** EMR based on disease diagnosis, test results, referrals. **Validation:** NP	-	First disease diagnosis	Individual endpoint	IRR	Self-and time-varying covariates adjustment	Risk period: 1 year after 1st dose Control period: all other observed time periods	NR	Number of cases included: 187
Feiring[30], 2017	**Identification:** EMR searches using diagnosis codes **Validation:** NP	Fukuda criteria: national guidelines	First disease diagnosis	Individual endpoint	HR	Multivariate modelling	Risk period: from 90 days post-vaccination until end of study period	NR	Number of exposed: 145,195 Number of non-exposed: 31,258

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
Frisch[31], 2018	**Identification:** EMR searches using diagnosis codes **Validation:** NP	-	First disease diagnosis	Individual endpoints	RR	Multivariate modelling	Risk period: any time after each dose, 180 days and > 181 days in sensitivity analysis	-	Number of exposed: 7,384 Number of non-exposed: 561,026
Grimaldi-Bensouda[18], 2014	Cases recruited from clinical registries via networks of specialized centres	According to international conventions	First clinical sign (index date)	Individual and composite endpoints	OR	Matching	Time frames before index date: 2 months for GBS; 6 months for ITP; 24 months for other ADs	Assuming 80% power and alpha 0,05, the min. detectable OR was 1.6 for composite endpoints and between 2.2 and 2.8 for individual endpoints	Number of cases: 269 Number of controls: 1,096

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
Grimaldi-Bensouda[19], 2017	Cases recruited from clinical registries via networks of specialized centres	According to international conventions	First clinical sign (index date)	Individual and composite endpoints	OR	Matching	Time frames before index date: 2 months for GBS; 6 months for ITP; 24 months for other ADs	NR	Number of cases: 510 Number of controls: 1953
Hviid[32], 2017	**Identification:** EMR searches using diagnosis codes **Validation:** NP	-	First disease diagnosis	Individual endpoints	RR	Multivariate modelling	Risk period: acute period of 180 days after each dose and long-term period after the first 180 days	NR	Number of exposed: 242,720 Number of non-exposed: 2,884,070
Klein[33], 2019	**Identification:** EMR searches using diagnosis codes	-	First disease diagnosis minus a 6-	Individual endpoint	HR	Multivariate modelling	Risk period: entire study period (10 years)	-	Number of exposed: 330,200 Number of non-exposed: 907,300

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
	Validation: medical charts review on a sample of cases		month lag period						
Langer-Gould[20], 2014	**Identification:** EMR searches using diagnosis codes and additional clinical details. **Validation:** medical charts review and validation by specialists	Revised Mc Donald criteria & consensus by specialists	First symptom (index date)	Individual endpoints	OR	Matching	Time frames before index date: 14 days, 30 days, 42 days, 90 days, 180 days, 1 year, 3 years	NR	Number of cases: 780 Number of controls: 3,885

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
Liu[24], 2018	**Identification:** EMR searches using diagnosis codes **Validation:** by specialists	-	First disease diagnosis	Composite endpoints and individual endpoints (exploratory analysis)	IRR	Self-age, seasonality and other vaccination adjustment	7-60 days after exposure to each dose	90% power to detect a RR of 2.0	Number of cases included in SCCS: 681 (any diseases)
Miranda[8], 2017	**Identification**: EMR searches using diagnosis codes and treatment/medication codes. **Validation**: NP	-	First disease diagnosis	Individual endpoints	HR	Multivariate modelling	Risk period: 2 years after 1st dose	NR	Number of exposed: 842,120 Number of non-exposed: 1,410,596

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
Scheller[23], 2014	**Identification:** EMR searches using diagnosis codes **Validation:** NP	-	First disease diagnosis	Individual endpoints	IRR	Self-and age adjustment	Risk period: 42 days and shorter periods (1-14 days, 15-28 days and 29-42 days) from vaccination Control period: all other observed time periods	NR	Number of cases included: 4,375
Scheller[34], 2015	**Identification:** EMR searches using diagnosis codes **Validation:** NP	-	First disease diagnosis	Individual endpoint for MS and composite endpoints for	RR	Multivariate modelling and Self-and age adjustment	Risk period: 2-year after exposure to each dose SCCS: 2-year risk period after exposure	NR	Number of exposed: 789,082 Number of non-exposed: 3,194,742

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
				demyelinating diseases			to each dose / all other observed time periods for control period		Number of cases included in SCCS: 4,322 (MS) and 3,300 (demyelinating disease)
Schurink-van't Klooster[25], 2018	**Identification:** EMR searches using diagnosis codes **Validation:** NP	-	First disease diagnosis	Individual endpoint	IRR	Self and age adjustment	Risk period: 12 (6 and 18) month after exposure to each dose	-	Number of cases included in SCCS: 16
Skufca[35], 2018	**Identification:** EMR searches using diagnosis codes	-	First disease diagnosis	Individual endpoint	HR	Multivariate modelling	Risk period: 0-180, 181-365, > 365 days and entire follow-up	NR	Number of exposed: 134,615 Number of non-exposed: 105,990

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
	Validation: NP								
Sridhar[36], 2017	**Identification:** EMR searches using diagnosis codes **Validation:** medical charts review and validation by specialists	International headache society case definition	First disease diagnosis	Individual endpoint	IRR	Multivariate modelling	Risk period: 60-days after exposure to each dose	NR	Number of exposed: 327,918 Number of matched non-exposed: 327,918
Willame[37], 2016	**Identification:** EMR searches using diagnosis and treatment/medication codes.	Clinical judgment	First symptom	Composite endpoints and individual endpoints for AIT, Crohn's	IRR	Multivariate modelling and Self-adjustment	Risk period: 1 year after 1st dose SCCS: 1-year risk period after 1st dose /	Assuming 80% power, the min. detectable RR was between 18.7 and 3.7 for Neuroinflammatory/Ophthalmic disease and between 2.0 and	Number of exposed: 65,000 Number of non-exposed: 195,000 (one historical

	Definition of outcome			Analytical parameters					
Author, year of publication	**Cases Identification & Validation**	**Diagnostic criteria**	**Disease onset**	**Disease study endpoints**	**Statistical Estimates**	**Adjustment for potential confounders**	**Risk windows**	**Detectable risk**	**Sample Size**
	Validation: medical charts review and validation by specialists			disease and diabetes			6 months buffer period / 1-year control period after buffer period	1.6 for other AD (composite endpoints)	female control cohort and two male control cohorts) Number of cases included in SCCS: 68 (any diseases)

AD = Autoimmune diseases; AIT = Autoimmune Thyroiditis; EMR = Electronic Medical Records; GP = General Practitioners; NP = Not Performed; NR = Not Reported; OR = Odds Ratio; RR = Risk Ratio; IRR = Incidence Rate Ratio; HR = Hazard Ratio; ITP = Immune Thrombocytopenia Purpura; GBS = Guillain-Barré Syndrome; SCCS = Self-Controlled-Case Series; TM = Transverse myelitis.

Table S5: Pooled estimates (ORs) for individual autoimmune diseases of the 22 studies included in the systematic review

Autoimmune diseases and/or other rare outcomes	Author, year of publication	HPV vaccine exposure	Parameter	N*	Estimates (95%CI)	Pooled estimates** [OR (95%CI)]
Dermatological						
Erythema nodosum	Arnheim, 2013	4vHPV	RR	19	1.05 (0.63; 1.73)	1.26 (0.89; 1.79)
	Hviid, 2018	4vHPV	RR	17	1.50 (0.92; 2.46)	
	Skufca, 2018	2vHPV	HR	9	8.37 (0.85; 82.54)	-
Psoriasis	Arnheim, 2013	4vHPV	RR	80	1.01 (0.80; 1.28)	1.03 (0.87; 1.23)
	Hviid, 2018	4vHPV	RR	57	1.06 (0.82; 1.38)	
	Frisch, 2018[£]	4vHPV	RR	2	0.66 (0.16-2.64)	-
	Skufca, 2018	2vHPV	HR	45	1.10 (0.69; 1.74)	-
Localized scleroderma	Hviid, 2018	4vHPV	RR	6	2.07 (0.90; 4.75)	-
	Skufca, 2018	2vHPV	HR	8	1.00 (0.33; 3.07)	-
Scleroderma	Arnheim, 2013	4vHPV	RR	6	1.04 (0.44; 2.48)	1.04 (0.64; 1.69)
	Miranda, 2017	4vHPV	HR	11	0.73 (0.36; 1.50)	
	Hviid, 2018	4vHPV	RR	4	2.13 (0.77; 5.91)	
	Miranda, 2017	2vHPV	NC	0	-	-
Pemphigoid	Hviid, 2018	4vHPV	RR	1	2.80 (0.37; 21.47)	-
Pemphigus foliaceus	Hviid, 2018	4vHPV	NC	0	-	-

Pemphigus vulgaris	Hviid, 2018	4vHPV	RR	1	**8.75 (1.04; 73.99)**	-
Localized lupus erythematosus	Hviid, 2018	4vHPV	RR	8	1.71 (0.84; 3.51)	-
Systemic Lupus Erythematosus	Chao, 2012	4vHPV	RR	10	1.07 (0.69; 1.60)	1.04 (0.82; 1.33)
	Arnheim, 2013	4vHPV	RR	11	1.35 (0.69; 2.67)	
	Miranda, 2017	4vHPV	HR	44	1.04 (0.71; 1.52)	
	Hviid, 2018	4vHPV	RR	8	0.73 (0.36; 1.47)	
	Miranda, 2017	2vHPV	HR	1	0.48 (0.07; 3.47)	1.20 (0.39; 3.68)
	Skufca, 2018	2vHPV	HR	7	1.88 (0.48; 7.45)	
Vitiligo	Arnheim, 2013	4vHPV	RR	24	1.13 (0.73; 1.74)	1.31 (0.91; 1.87)
	Hviid, 2018	4vHPV	RR	10	1.78 (0.94; 3.34)	
	Frisch, 2018[£]	4vHPV	RR	2	**4.70 (1.13-19.5)**	-
	Skufca, 2018	2vHPV	HR	5	0.41 (0.13; 1.28)	-
Diabetes						
Diabetes Type 1 Diabetes Mellitus	Chao, 2012	4vHPV	RR	9	**0.57 (0.47; 0.73)**	0.93 (0.65; 1.34)
	Arnheim, 2013	4vHPV	RR	99	**1.29 (1.03; 1.62)**	
	Grimaldi-Bensouda, 2014	4vHPV	OR	9	1.20 (0.40; 3.60)	
	Miranda, 2017	4vHPV	HR	142	1.09 (0.88; 1.33)	
	Hviid, 2018	4vHPV	RR	28	0.85 (0.58; 1.24)	
	Frisch, 2018[£]	4vHPV	RR	8	0.80 (0.40-1.60)	-
	Willame, 2016	2vHPV	RR	8	**0.30 (0.11; 0.83)**	0.80 (0.50; 1.26)

	Miranda, 2017	2vHPV	HR	7	0.91 (0.43; 1.94)	
	Skufca, 2018	2vHPV	HR	83	1.16 (0.82; 1.64)	
	Liu, 2018	2vHPV	IRR	NR	0.73 (0.44; 1.22)	
	Grimaldi-Bensouda, 2017	4vHPV & 2vHPV	OR	14	0.61 (0.32; 1.17)	-
	Klein, 2019	4vHPV & 9vHPV	RR	123	1.21 (0.94; 1.57)	-
Haematological						
Hemolytic anemia	Chao, 2012	4vHPV	NC	0	-	-
	Hviid, 2018	4vHPV	RR	2	1.89 (0.45; 7.92)	-
	Liu, 2018	2vHPV	IRR	NR	0.80 (0.08; 8.21)	-
Idiopathic Thrombocytopenia Purpura	Chao, 2012	4vHPV	RR	6	1.16 (0.85; 1.83)	
	Arnheim, 2013	4vHPV	RR	14	1.18 (0.65; 2.17)	
	Grimaldi-Bensouda, 2014	4vHPV	OR	6	1.00 (0.40; 2.60)	1.06 (0.85; 1.33)
	Miranda, 2017	4vHPV	HR	35	0.72 (0.48; 1.08)	
	Hviid, 2018	4vHPV	RR	14	1.70 (0.98; 2.94)	
	Miranda, 2017	2vHPV	HR	2	0.85 (0.31; 3.47)	
	Skufca, 2018	2vHPV	HR	21	0.56 (0.31; 1.03)	**0.55 (0.34; 0.88)**
	Liu, 2018	2vHPV	IRR	103	0.35 (0.12; 1.04)	
	Grimaldi-Bensouda, 2017	4vHPV & 2vHPV	OR	11	1.17 (0.56; 2.41)	-
Pernicious anemia	Hviid, 2018	4vHPV	RR	5	2.04 (0.82; 5.10)	-
Gastroinstestinal						

Coeliac disease	Arnheim, 2013	4vHPV	RR	107	1.11 (0.90; 1.36)	
	Miranda, 2017	4vHPV	HR	38	0.86 (0.57; 1.29)	1.16 (0.87; 1.56)
	Hviid, 2018	4vHPV	RR	53	**1.54 (1.16; 2.03)**	
	Frisch, 2018[£]	4vHPV	RR	2	0.72 (0.18-2.89)	-
	Miranda, 2017	2vHPV	HR	2	0.78 (0.19; 3.21)	
	Skufca, 2018	2vHPV	HR	125	1.06 (0.80; 1.40)	1.05 (0.80; 1.38)
Crohn's disease	Arnheim, 2013	4vHPV	RR	47	0.85 (0.62; 1.17)	
	Hviid, 2018	4vHPV	RR	77	1.22 (0.97; 1.54)	1.04 (0.73; 1.47)
	Frisch, 2018[£]	4vHPV	RR	6	0.63 (0.28; 1.41)	-
	Willame, 2016	2vHPV	RR	6	1.21 (0.37; 3.95)	
	Skufca, 2018	2vHPV	HR	29	1.45 (0.78; 2.70)	1.17 (0.77; 1.78)
	Liu, 2018	2vHPV	IRR	NR	0.92 (0.48; 1.76)	
Inflammatory Bowel Disease	Miranda, 2017	4vHPV	HR	281	**1.21 (1.03; 1.41)**	-
	Miranda, 2017	2vHPV	HR	12	0.89 (0.50; 1.59)	-
Pancreatitis	Arnheim, 2013	4vHPV	RR	10	1.19 (0.60; 2.35)	
	Miranda, 2017	4vHPV	HR	61	0.81 (0.59; 1.11)	0.87 (0.69; 1.08)
	Hviid, 2018	4vHPV	RR	31	0.87 (0.61; 1.24)	
	Miranda, 2017	2vHPV	HR	7	1.75 (0.81; 3.78)	
	Skufca, 2018	2vHPV	HR	5	1.43 (0.32; 6.44)	1.68 (0.85; 3.33)
Primary biliary cirrhosis	Hviid, 2018	4vHPV	NC	0	-	-

Ulcerative colitis	Arnheim, 2013	4vHPV	RR	35	0.71 (0.49; 1.03)	0.93 (0.58; 1.50)
	Hviid, 2018	4vHPV	RR	100	1.16 (0.95; 1.42)	
	Frisch, 2018[£]	4vHPV	RR	6	0.68 (0.30; 1.51)	-
	Skufca, 2018	2vHPV	HR	55	0.97 (0.63; 1.47)	0.57 (0.15; 2.23)
	Liu, 2018	2vHPV	IRR	NR	0.23 (0.05; 1.03)	
Musculoskeletal/Systemic						
Abnormalities of gait and mobility	Skufca, 2018	2vHPV	HR	26	1.00 (0.54; 1.83)	-
Ankylosing spondylitis	Arnheim, 2013	4vHPV	RR	8	0.94 (0.44; 2.01)	0.98 (0.65; 1.48)
	Hviid, 2018	4vHPV	RR	17	1.00 (0.62; 1.63)	
	Frisch, 2018[£]	4vHPV	RR	2	2.01 (0.49; 8.16)	-
Behcet syndrome	Arnheim, 2013	4vHPV	RR	5	**3.37 (1.05; 10.8)**	1.52 (0.29; 7.96)
	Hviid, 2018	4vHPV	RR	2	0.62 (0.15; 2.56)	
Henoch-Schonlein's purpura	Arnheim, 2013	4vHPV	RR	17	0.89 (0.52; 1.52)	1.03 (0.66; 1.60)
	Hviid, 2018	4vHPV	RR	7	1.40 (0.64; 3.04)	
	Frisch, 2018[£]	4vHPV	RR	5	1.58 (0.65; 3.83)	-
	Skufca, 2018	2vHPV	HR	14	**0.46 (0.23; 0.95)**	-
Juvenile Arthritis	Frisch, 2018[£]	4vHPV	RR	2	0.68 (0.17; 2.73)	-
Juvenile Rheumatoid Arthritis	Chao, 2012	4vHPV	RR	3	**0.48 (0.26; 0.91)**	0.73 (0.36; 1.47)
	Arnheim, 2013	4vHPV	RR	86	0.99 (0.78; 1.26)	
	Skufca, 2018	2vHPV	HR	118	0.94 (0.71; 1.25)	1.03 (0.82; 1.29)

	Liu, 2018	2vHPV	IRR	323	1.20 (0.83; 1.73)	
Myositis	Arnheim, 2013	4vHPV	RR	8	1.07 (0.50; 2.31)	0.92 (0.50; 1.69)
	Hviid, 2018	4vHPV	RR	4	0.71 (0.26; 1.92)	
	Skufca, 2018	2vHPV	HR	5	1.52 (0.29; 7.97)	-
Nervous and musculoskeletal system symptoms	Skufca, 2018	2vHPV	HR	83	1.10 (0.76; 1.58)	-
Polymyositis/ dermatomyositis	Hviid, 2018	4vHPV	RR	2	0.68 (0.17; 2.83)	0.83 (0.46; 1.51)
Myositis/polymyositis/ dermatomyositis	Miranda, 2017	4vHPV	HR	15	0.87 (0.45; 1.69)	
	Miranda, 2017	2vHPV	NC	0	-	-
Polyarteritis nodosa	Hviid, 2018	4vHPV	RR	1	0.74 (0.10; 5.59)	-
Polyarteritis nodosa and related conditions	Skufca, 2018	2vHPV	HR	5	1.42 (0.31; 6.57)	-
Rheumatoid Arthritis	Chao, 2012	4vHPV	RR	4	0.71 (0.39; 1.45)	0.92 (0.72; 1.17)
	Arnheim, 2013	4vHPV	RR	27	1.01 (0.66; 1.54)	
	Hviid, 2018	4vHPV	RR	38	0.92 (0.66; 1.27)	
	Frisch, 2018[£]	4vHPV	RR	3	2.29 (0.73; 7.24)	-
Rheumatoid Arthritis and Juvenile Rheumatoid Arthritis combined	Miranda, 2017	4vHPV	HR	93	1.12 (0.49; 2.55)	-
	Miranda, 2017	2vHPV	HR	6	1.09 (0.48; 2.48)	-
Systemic autoimmune rheumatoid diseases	Liu, 2018	2vHPV	IRR	111	1.21 (0.57; 2.57)	-
Vasculitis	Arnheim, 2013	4vHPV	RR	14	1.55 (0.83; 2.88)	1.11 (0.86; 1.42)

	Miranda, 2017	4vHPV	HR	66	1.04 (0.79; 1.42)	
	Hviid, 2018	4vHPV	RR	11	1.01 (0.55; 1.85)	
	Frisch, 2018[£]	4vHPV	RR	2	2.05 (0.50; 8.38)	-
	Miranda, 2017	2vHPV	HR	3	1.00 (0.31; 3.15)	-
Neurological						
Bell's palsy	Arnheim, 2013	4vHPV	RR	41	1.02 (0.72; 1.43)	0.79 (0.46; 1.35)
	Hviid, 2018	4vHPV	RR	21	**0.59 (0.39; 0.92)**	
	Frisch, 2018[£]	4vHPV	RR	2	0.56 (0.14-2.25)	-
	Skufca, 2018	2vHPV	HR	26	1.19 (0.63; 2.24)	1.37 (0.83; 2.26)
	Liu, 2018	2vHPV	IRR	65	1.73 (0.77; 3.89)	
Epilepsy	Arnheim, 2013	4vHPV	RR	116	**0.66 (0.54; 0.80)**	0.81 (0.54; 1.24)
	Hviid, 2018	4vHPV	RR	84	1.01 (0.81; 1.24)	
	Frisch, 2018[£]	4vHPV	RR	8	0.51 (0.26; 1.03)	-
	Skufca, 2018	2vHPV	HR	104	**0.72 (0.54; 0.95)**	-
Guillain Barre Syndrome	Chao, 2012	4vHPV	NC	0	-	1.79 (0.65; 4.94)
	Grimaldi-Bensouda, 2014	4vHPV	NC	0	-	
	Miranda, 2017	4vHPV	HR	17	**3.81 (1.71; 8.49)**	
	Andrews, 2017	4vHPV	IRR	15	1.61 (0.39; 6.54)	
	Deceuninck, 2017	4vHPV	RR	52	0.81 (0.29; 2.26)	
	Hviid, 2018	4vHPV	NC	0	-	

	Grimaldi-Bensouda, 2017	4vHPV & 2vHPV	NC	0	-	-
	Andrews, 2017	2vHPV	IRR	86	0.84 (0.30; 2.34)	
	Miranda, 2017	2vHPV	HR	2	**8.08 (1.69; 38.61)**	2.89 (0.58; 14.40)
	Skufca, 2018	2vHPV	HR	6	5.31 (0.62; 45.39)	
Chronic Fatigue Syndrome/Myalgic encephalomyelitis	Feiring, 2017	4vHPV	HR	290	0.86 (0.69; 1.08)	-
Chronic Fatigue Syndrome/Myalgic encephalomyelitis	Donegan, 2013	2vHPV	RR	187	1.07 (0.57; 2.00)	
Chronic Fatigue Syndrome/Systemic exertion intolerance disease	Skufca, 2018	2vHPV	HR	154	**0.75 (0.59; 0.95)**	**0.77 (0.62; 0.97)**
Chronic Fatigue Syndrome	Schurink-van't Klooster, 2018	2vHPV	IRR	16	0.24 (0.03; 2.09)	
Malaise and fatigue	Skufca, 2018	2vHPV	HR	152	**0.76 (0.60; 0.96)**	-
Narcolepsy	Arnheim, 2013	4vHPV	RR	6	0.71 (0.29; 1.79)	1.08 (0.64; 1.84)
	Hviid, 2018	4vHPV	RR	10	1.34 (0.70; 2.57)	
	Frisch, 2018[£]	4vHPV	RR	3	**3.44 (1.08-11.0)**	-
Other paralytic syndromes	Skufca, 2018	2vHPV	HR	6	1.02 (0.29; 3.63)	-
Paralysis	Arnheim, 2013	4vHPV	RR	20	**0.56 (0.35; 0.90)**	**0.52 (0.35; 0.77)**
	Hviid, 2018	4vHPV	RR	7	**0.42 (0.20; 0.89)**	
	Frisch, 2018[£]	4vHPV	RR	2	0.70 (0.17; 2.80)	-
	Skufca, 2018	2vHPV	HR	14	0.86 (0.39; 1.89)	-

Ophthalmic						
Neuromyelitis optica	Chao, 2012	4vHPV	NC	0	-	-
Optic neuritis	Chao, 2012	4vHPV	RR	5	**1.45 (1.00; 2.91)**	1.20 (0.84; 1.71)
	Arnheim, 2013	4vHPV	RR	6	0.67 (0.27; 1.64)	
	Baxter, 2016	4vHPV	OR	5	4.60 (0.60; 40.3)	
	Sridhar, 2017	4vHPV	RR	80	1.10 (0.62; 1.96)	
	Liu, 2018	2vHPV	IRR	67	1.57 (0.74; 3.33)	
Uveitis	Chao, 2012	4vHPV	RR	7	0.67 (0.49; 1.02)	-
Other demyelinating diseases						
Acute Demyelinating Encephalomyelitis	Chao, 2012	4vHPV	NC	0	-	- -
	Langer-Gould, 2014	4vHPV	NC[$]	5	-	
	Baxter, 2016	4vHPV	OR	5	1.50 (0.10; 10.70)	
	Liu, 2018	2vHPV	IRR	21	1.14 (0.28; 4.65)	-
Central Nervous system demyelinating syndrome	Langer-Gould, 2014	4vHPV	OR	71	0.82 (0.39; 1.73)	1.02 (0.77; 1.33)
	Miranda, 2017	4vHPV	HR	78	1.05 (0.78; 1.40)	
	Miranda, 2017	2vHPV	HR	4	1.01 (0.37; 2.76)	-
Central demyelination and Multiple sclerosis	Grimaldi-Bensouda, 2014	4vHPV	OR	4	**0.30 (0.10; 0.90)**	-
	Grimaldi-Bensouda, 2017	4vHPV & 2vHPV	OR	7	**0.31 (0.13; 0.73)**	-
Connective tissue disorders	Grimaldi-Bensouda, 2014	4vHPV	OR	6	0.80 (0.30; 2.40)	-
	Grimaldi-Bensouda, 2017	4vHPV & 2vHPV	OR	14	0.84 (0.41; 1.73)	-

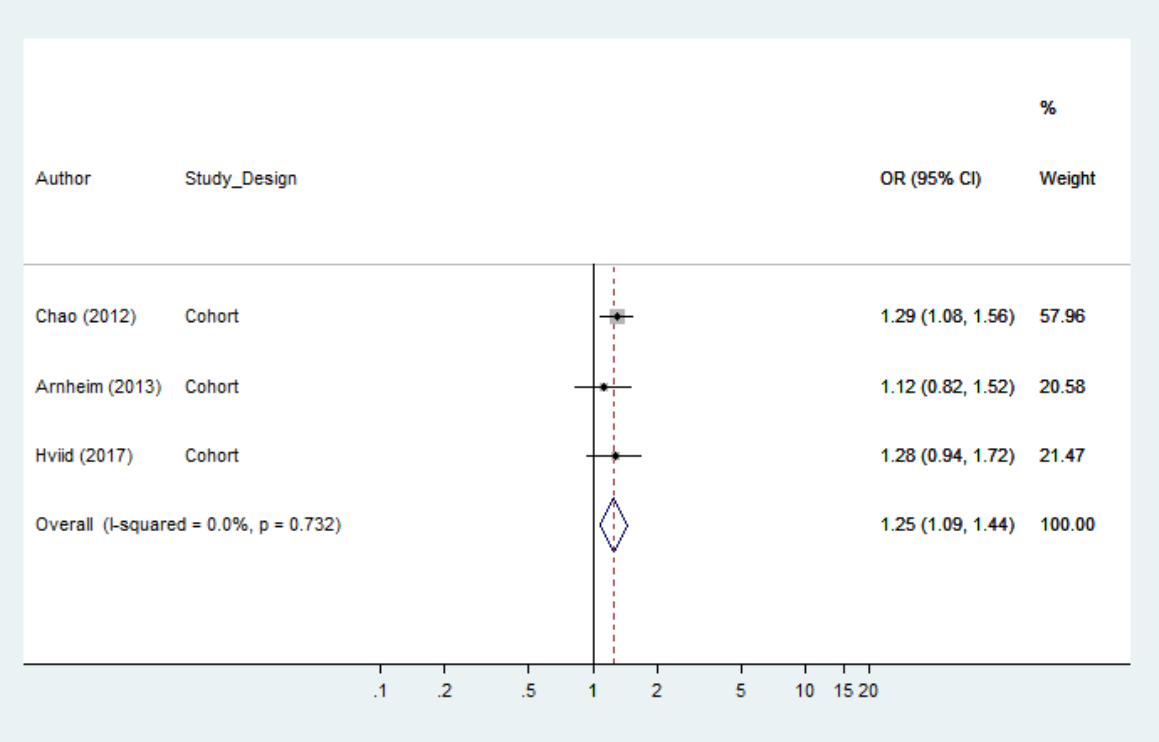
Myasthenia gravis	Hviid, 2018	4vHPV	RR	1	0.55 (0.07; 3.96)	-
Multiple sclerosis	Chao, 2012	4vHPV	RR	3	1.37 (0.74; 3.20)	
	Langer-Gould, 2014	4vHPV	OR	38	1.44 (0.56; 3.74)	0.96 (0.77; 1.21)
	Scheller, 2015	4vHPV	RR	73	0.90 (0.70; 1.15)	
Other demyelinating diseases	Scheller, 2015	4vHPV	RR	90	1.00 (0.80; 1.26)	-
Other demyelinating diseases of central nervous system	Chao, 2012	4vHPV	RR	1	0.71 (0.38; 2.13)	-
Other encephalitis	Hviid, 2018	4vHPV	RR	1	2.38 (0.31; 18.40)	-
Transverse myelitis	Baxter, 2016	4vHPV	OR	3	0.00 (0.00; 15.30)	-
Other disorders						
Acute rheumatic fever	Hviid, 2018	4vHPV	NC	0	-	-
Asthma	Skufca, 2018	2vHPV	HR	485	1.07 (0.93; 1.24)	-
Addison's disease	Hviid, 2018	4vHPV	RR	4	1.15 (0.42; 3.14)	-
Autism	Skufca, 2018	2vHPV	HR	88	0.86 (0.63; 1.18)	-
Autoimmune hepatitis	Liu, 2018	2vHPV	IRR	12	1.07 (0.09; 13.28)	-
Complex regional pain syndrome	Skufca, 2018	2vHPV	HR	5	0.34 (0.11; 1.05)	-
Clinically Isolated Syndrome	Langer-Gould, 2014	4vHPV	OR	28	0.26 (0.05; 1.32)	-
Polycystic ovaries	Skufca, 2018	2vHPV	HR	86	0.90 (0.65; 1.26)	-
Postural orthostatic tachycardia syndrome	Skufca, 2018	2vHPV	HR	18	0.99 (0.46; 2.11)	-
Raynaud's disease	Arnheim, 2013	4vHPV	RR	37	**1.67 (1.14; 2.44)**	**1.63 (1.21; 2.20)**

	Hviid, 2018	4vHPV	RR	17	1.56 (0.96; 2.56)	
	Skufca, 2018	2vHPV	HR	31	0.94 (0.54; 1.64)	-
Reiter's syndrome	Hviid, 2018	4vHPV	NC	0	-	-
Sarcoidosis	Hviid, 2018	4vHPV	RR	16	1.18 (0.72; 1.95)	-
Sjorgen syndrome	Miranda, 2017	4vHPV	HR	5	1.05 (0.33; 3.34)	1.34 (0.71; 2.51)
	Hviid, 2017	4vHPV	RR	7	1.48 (0.70; 3.15)	
	Miranda, 2017	2vHPV	NC	0	-	-
Venous Thrombocytopenia	Arnheim, 2013	4vHPV	RR	21	0.86 (0.55; 1.36)	0.80 (0.60; 1.07)
	Scheller, 2014	4vHPV	RR	29	0.77 (0.53; 1.11)	
	Frisch, 2018[£]	4vHPV	RR	4	0.88 (0.33; 2.35)	-
	Skufca, 2018	2vHPV	HR	7	1.16 (0.36; 3.75)	-
Wegener's granulomatosis	Hviid, 2018	4vHPV	RR	1	0.72 (0.10; 5.27)	-
Thyroid						
Hashimoto disease	Chao, 2012	4vHPV	RR	92	**1.29 (1.08; 1.56)**	**1.25 (1.09; 1.44)**
	Arnheim, 2013	4vHPV	RR	50	1.12 (0.82; 1.52)	
	Hviid, 2018	4vHPV	RR	45	1.28 (0.94; 1.72)	
	Skufca, 2018	2vHPV	HR	31	0.76 (0.45; 1.28)	0.88 (0.57; 1.36)
	Liu, 2018	2vHPV	IRR	NR	1.21 (0.55; 2.61)	
Grave's disease	Chao, 2012	4vHPV	RR	16	0.72 (0.50; 1.01)	0.88 (0.73; 1.07)
	Arnheim, 2013	4vHPV	RR	27	1.05 (0.69; 1.61)	

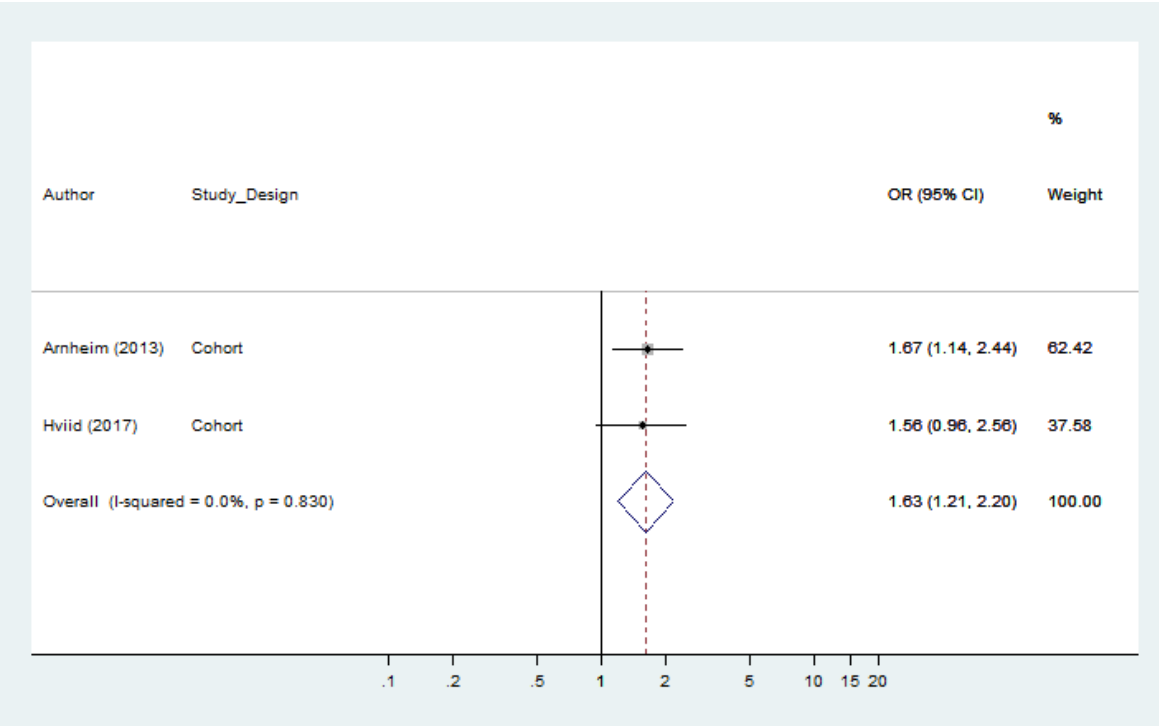
	Hviid, 2018	4vHPV	RR	53	0.93 (0.71; 1.22)	
	Skufca, 2018	2vHPV	HR	18	0.76 (0.39; 1.47)	1.12 (0.56; 2.24)
	Liu, 2018	2vHPV	IRR	NR	1.55 (0.92; 2.63)	
Autoimmune thyroiditis (Hashimoto+Grave's diseases combined)	Chao, 2012	4vHPV	RR	108	1.15 (0.97; 1.38)	1.10 (0.94; 1.27)
	Miranda, 2017	4vHPV	HR	77	0.97 (0.73; 1.29)	
	Willame, 2016	2vHPV	RR	15	**3.75 (1.25; 11.31)**	1.76 (0.65; 4.77)
	Miranda, 2017	2vHPV	HR	10	**2.43 (1.27; 4.66)**	
	Skufca, 2018	2vHPV	HR	36	0.75 (0.46; 1.22)	
	Grimaldi-Bensouda, 2017	4vHPV & 2vHPV	OR	6	**0.35 (0.13; 0.92)**	-
Hypothyroidism	Frisch, 2018[£]	4vHPV	RR	5	1.77 (0.73; 4.31)	-
	Hviid, 2018	4vHPV	RR	120	**0.65 (0.54; 0.78)**	-
	Skufca, 2018	2vHPV	HR	66	0.76 (0.53; 1.10)	-
Other hyperthyroidism	Arnheim, 2013	4vHPV	RR	23	0.99 (0.63; 1.55)	0.98 (0.79; 1.22)
	Hviid, 2018	4vHPV	RR	71	0.98 (0.77; 1.25)	
	Skufca, 2018	2vHPV	HR	34	0.97 (0.57; 1.65)	-

2vHPV = bivalent HPV vaccine; 4vHPV = quadrivalent HPV vaccine; RR = Relative Risk; OR = Odds ratio; HR = Hazard ratio.
NC = Not Computable. Not computable parameters correspond to 0 event reported in the original study.
*N = Number of events after HPV vaccination
**Pooled estimates were computed using fixed or random effect models in Stata v14.0.
[$] Not computable because of less than 10 events.
[£]Not included in pooled analysis because males were under assessment.
Bold estimates are statistically significant.

Figure S1: Overall ORs for Hashimoto disease (A) and Raynaud's disease (B) after 4vHPV vaccine.



A Hashimoto disease



B) Raynaud' disease.

Chapter 4: Safety evaluation of the bivalent HPV vaccine

4.1 Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom

Corinne Willame, Dominique Rosillon, Julia Zima, Maria-Genalin Angelo, Anke L. Stuurman, Hilde Vroling, Rachael Boggon, Eveline M. Bunge, Manel Pladevall-Vila, Laurence Baril

Human Vaccines & Immunotherapeutics. 2016 Nov;12(11):2862-2871. doi: 10.1080/21645515.2016.1199308.

Abstract

To assess the risk of autoimmune disease (AD) in 9-25 year-old women within 1 year after the first AS04-HPV-16/18 vaccine dose, a retrospective, observational database cohort study was conducted using CPRD GOLD. From CPRD GOLD 4 cohorts (65,000 subjects each) were retrieved: 1 exposed female cohort (received 1 AS04-HPV-16/18 vaccine dose between Sep2008–Aug2010) and 3 unexposed cohorts: historical female (Sep2005–Aug2007), concurrent male, and historical male. Co-primary endpoints were confirmed neuroinflammatory/ophthalmic AD and other AD, secondary endpoints were confirmed individual AD. Risk of new onset of AD was compared between cohorts (reference: historical cohort) using Poisson regression. The main analysis using confirmed cases showed no neuroinflammatory/ophthalmic AD cases in the female exposed cohort. Incidence rate ratio (IRR) (95% CI) of other AD was 1.41 (0.86 to 2.31) in female and 1.77 (0.94 to 3.35) in male cohorts when compared to the female and male historical cohort, respectively. Secondary endpoints were evaluated for diseases with >10 cases, which were Crohn's disease (IRR: 1.21 [0.37 to 3.95] for female and 4.22 [0.47 to 38.02] for male cohorts), autoimmune thyroiditis (IRR: 3.75 [1.25 to 11.31] for female and no confirmed cases for male cohorts) and type 1 diabetes (IRR: 0.30 [0.11 to 0.83] for female and 2.46 [1.08 to 5.60] for male cohorts). Analysis using confirmed and non-confirmed cases showed similar results, except for autoimmune thyroiditis in females, IRR: 1.45 (0.79 to 2.64). There was no evidence of an increased risk of AD in women aged 9 to 25 years after AS04-HPV-16/18 vaccination.

1. Introduction

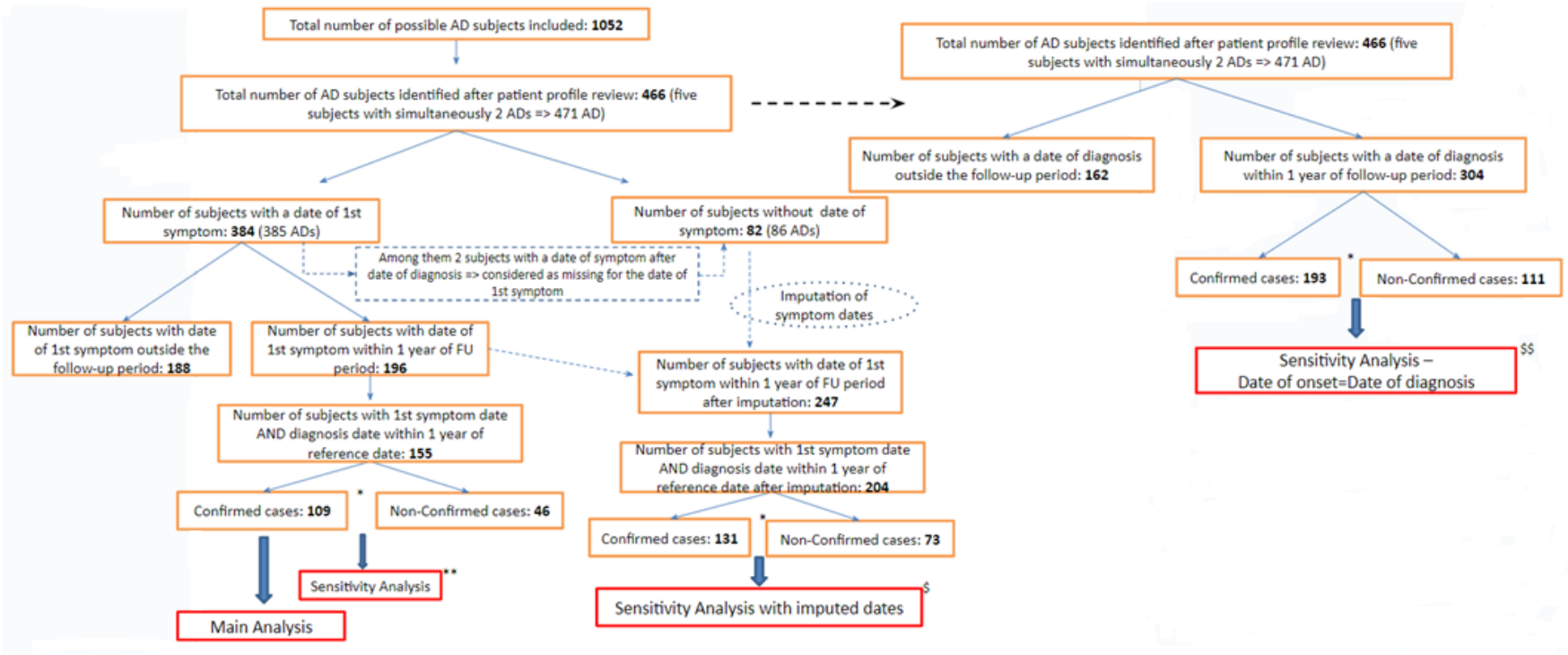
Human papillomavirus (HPV) is the main cause of cervical cancer [1], of which approximately 70% is caused by types 16 and 18 [2]. Cervarix™ (AS04-HPV-16/18 vaccine) is a GSK Vaccines' bivalent recombinant vaccine against HPV types 16 and 18. Efficacy and cross-protective efficacy of this AS04-HPV-16/18 vaccine against persistent infection, pre-cancerous lesions, and cervical cancers caused by oncogenic HPV was shown in the Papilloma Trial against Cancer In young Adults (PATRICIA) and, more recently in adult women from the Human Papilloma Virus: Vaccine Immunogenicity And Efficacy (VIVIANE) study [3-5]. Generally, pre-licensure clinical studies provide key vaccine safety data, but their power to detect rare events such as new onset of autoimmune diseases (AD) is limited by their sample size, since incidence rates of different AD vary roughly from 1 to 50 per 100,000 person-years [6]. The use of appropriate adjuvants can help to modulate optimally innate and adaptive immune responses following vaccination. However, the risk of developing an autoimmune response provoked by the adjuvant itself cannot be ruled out [7]. The Center for Biologics Evaluation and Research in the United States (US) requested GSK to conduct a post-licensure study to investigate the risk of AD among AS04-HPV-16/18 vaccine recipients. A pooled safety analysis of data from 57,580 adolescent and adult females aged 9 years and above, of whom 33,339 received at least one dose of AS04-HPV-16/18vaccine, showed that the rates of adverse events, medically significant conditions, serious adverse events, and potential immune mediated disorders were similar between HPV and control groups [8]. The aim of this observational cohort study using the Clinical Practice Research Datalink General Practice OnLine Database (CPRD GOLD) was to evaluate the risk of new onset of AD in women aged 9 to 25 years in the United Kingdom (UK) after administration of the AS04-HPV-16/18vaccine (exposed cohort) and in controls of the same age (unexposed cohorts).

2. Results

From a total of 168,662 HPV vaccinated female subjects in CPRD, 103,081 (61.12%) were eligible for the exposed cohort. The number of eligible subjects in the other cohorts was: 107,434 for the

unexposed historical female cohort, 142,772 for the concurrent male cohort and 92,337 for the historical male cohort. 65,000 Subjects were randomly selected from each of the cohorts, but 42 subjects were excluded because a de-enrolment date (death date or date of lost to follow-up) occurred before the study start date. Through the pre-defined algorithms 1,052 suspected AD cases were identified, of which 466 (44.3%) were identified as having confirmed or non-confirmed new onset AD after review of the individual subject profiles (Fig. 1).

Figure 1. Number of cases included in each analysis.



AD= Autoimmune Disease; FU= follow-up. Confirmation of cases was performed after subject profile review. The 46 non-confirmed cases were combined with the 109 confirmed cases in the sensitivity analysis for subjects with known first symptom dates. [$]Subjects for the imputed dates sensitivity analyses had either an imputed date of first symptom or a known date of first symptom. Sensitivity analyses for subjects with imputed/known first symptom dates were repeated using either confirmed cases only or confirmed and non-confirmed cases. [$$] Date of onset was assumed to be the same as date of disease diagnosis in this sensitivity analysis. Sensitivity analyses were repeated using either confirmed cases only or confirmed and non-confirmed cases.

Among them, the date of first symptom was known for 384 (82.4%) cases, of which 40.4% (n D 155) were eligible for the main analysis, because their first symptom date and date of disease diagnosis were within the one-year follow-up period. Out of these 155 AD cases, 109 (70.3%) were classified as confirmed cases and were included in the numerator in the main analysis (the 46 nonconfirmed cases were excluded from the numerator and their person-time was included in the denominator). The number of cases included during sensitivity analyses can be found in Figure 1. A total of 68 confirmed cases from the exposed cohort were included for the self-controlled case-series (SCCS) analysis. The overall population for the main analysis contained 259,876 subjects. Demographic and baseline characteristics of each cohort are depicted in Table 1.

Table 1. Demographic characteristics of the 4 cohorts.

		AS04-HPV-16/18 vaccine exposure N = 64,964		Unexposed historical female cohort N = 64,973		Unexposed concurrent male cohort N = 64,974		Unexposed historical male cohort N = 64,965	
Characteristics	Parameters or categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at study start date (years)	Mean (SD)	15.3 (2.1)	—	15.4 (2.1)	—	15.3 (2.1)	—	16.0 (2.0)	—
	Range	9.4–24.9	—	9.4–24.8	—	9.3–24.9	—	9.2–24.8	–
	9–13	20,654	31.8	19,783	30.4	21,252	32.7	13,361	20.6
	14–17	38,082	58.6	38,872	59.8	37,990	58.5	42,871	66.0
	18–21	6,199	9.5	6,291	9.7	5,708	8.8	8,689	13.4
	22–25	29	<0.1	27	<0.1	24	<0.1	44	<0.1
Region of GP practices	North England	36,818	56.7	34,646	53.3	35,906	55.3	33,247	51.2
	Midlands	8,396	12.9	8,556	13.2	8,423	13.0	8,724	13.4
	South England	19,648	30.2	21,733	33.4	20,616	31.7	22,971	35.4
	Ireland Scotland Wales	102	0.2	38	<0.1	29	<0.1	23	<0.1
Available HES linkage	Yes	38,656	59.5	36,148	55.6	37,832	58.2	37,616	57.9
Number of healthcare resources utilization the year prior to the study start date	Mean (SD)	8.8 (10.2)	—	7.0 (9.1)	—	6.0 (8.4)	—	5.3 (7.2)	—
	Range	0–243	—	0–157	—	0–254	—	0–132	—
	0 to 1	12,203	18.8	17,940	27.6	21,057	32.4	22,445	34.5
	2 to 4	15,746	24.2	17,056	26.3	17,448	26.9	18,262	28.1

	5 to 9	16,113	24.8	14,454	22.2	13,362	20.6	13,186	20.3
	≥ 10	20,902	32.2	15,523	23.9	13,107	20.2	11,072	17.0
Number of years of follow-up in CPRD GOLD at study start date	Mean (SD)10	9.4 (4.3)	—	7.6 (4.3)	—	9.1 (4.3)	—	7.8 (4.4)	—
	Range	1–21	—	1–19	—	1–21	—	1–19	—
	0 to 3	5,646	8.7	9,497	14.6	7,062	10.9	9,486	14.6
	3 to 6	9,638	14.8	16,923	26.0	10,054	15.5	16,510	25.4
	6 to 10	20,456	31.5	20,927	32.2	20,581	31.7	20,924	32.2
	≥ 10	29,224	45.0	17,626	27.1	27,277	42.0	18,045	27.8
Exposure to vaccines in the year prior to the study start date	Any vaccine	11,529	17.8	11,008	16.9	9,270	14.3	10,394	16.0
	Novel adjuvanted vaccine	311	0.5	0	0.0	325	0.5	0	0.0
	Live-attenuated vaccine	1,138	1.8	2,986	4.6	861	1.3	2,942	4.5
	Other vaccine	10,627	16.4	8,580	13.2	8,507	13.1	7,967	12.3
Exposure to vaccines in the follow-up period	Any vaccine	11,596	17.8	7,765	12.0	8,000	12.3	6,253	9.6
	Novel adjuvanted vaccine	1,679	2.6	0	0.0	1,559	2.4	0	0.0
	Live-attenuated vaccine	1,033	1.6	943	1.5	489	0.8	828	1.3
	Other vaccine	10,231	15.7	7,062	10.9	7,068	10.9	5,578	8.6

Note. HES = Hospital Episode Statistics; N = number of subjects; n/% = number/percentage of subjects in a given category; SD = standard deviation; Value = value of the considered parameter E.g. general practitioner consultations, prescriptions, and laboratory tests.

The female exposed cohort more frequently used healthcare, had more years of follow-up in CPRD GOLD at the study start date, and received more vaccines during the follow-up period than the historical female cohort. Similar differences existed between the 2 male cohorts, except that the male concurrent cohort received fewer vaccines in the year prior to the study start date than the male historical cohort.

Co-primary endpoints

In total, 3 confirmed cases of neuroinflammatory/ophthalmic AD and 106 confirmed cases of other AD were observed within the one year follow-up period (Table 2). There were no confirmed cases of neuroinflammatory/ophthalmic AD in the exposed female cohort, therefore the incidence rate ratio (IRR) could not be calculated. The corresponding age-adjusted IRR for male cohorts was 0.95 (95% confidence interval (CI): 0.06– 15.18). For the other AD, the age-adjusted IRRs were 1.41 (95% CI: 0.86–2.31) for the female cohorts and 1.77 (95% CI: 0.94– 3.35) for the male cohorts. Sensitivity analysis using confirmed and non-confirmed cases showed results similar to the main analysis (Table 2), as all the sensitivity analyses using the 2 other case definitions (Tables S1 and S2); models including more covariates (data not shown); and the SCCS analysis (Table S3).

Table 2. Incidence rate per 100,000 person-years and incidence rate ratios of co-primary endpoints.

		AS04-HPV-16/18 vaccine exposure (total PY = 64,705)		Unexposed historical female cohort (total PY = 64,841)		
Diseases		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	IRR* (95% CI) EXP/NNEXP
Neuroinflammatory/ ophthalmic AD	Confirmed cases	0	0.00 (0.00–5.70)	1	1.54 (0.04–8.59)	—
	All cases	4	6.18 (1.68–15.83)	7	10.80 (4.34–22.24)	0.57 (0.17–1.96)
Other AD	Confirmed cases	38	58.73 (51.56–80.61)	27	41.64 (27.44–60.58)	1.41 (0.86–2.31)
	All cases	51	78.82 (58.69–103.63)	41	63.23 (45.38–85.78)	1.25 (0.83–1.88)

		Unexposed concurrent male cohort (total PY = 64,859)		Unexposed historical male cohort (total PY = 64,868)		
Diseases		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	IRR* (95% CI) MALE/HIST

Co-primary endpoints						
Neuroinflammatory/ ophthalmic AD	Confirmed cases	1	1.54 (0.04–8.59)	1	1.54 (0.04–8.59)	0.95 (0.06–15.18)
	All cases	3	4.63 (0.95–13.52)	2	3.08 (0.37–11.14)	1.73 (0.29–10.47)
Other AD	Confirmed cases	26	40.09 (26.19–58.74)	15	23.12 (12.94–38.14)	1.77 (0.94–3.35)
	All cases	28	43.17 (28.69–62.39)	19	29.29 (17.64–45.74)	1.52 (0.85–2.73)

Note: AD = autoimmune disease; CI = confidence interval; EXP = AS04-HPV-16/18 vaccine; HIST = unexposed historical male cohort; IRR = incidence rate ratio; MALE = unexposed historical male cohort; n = number of subjects; NNEXP = unexposed historical cohort; PY = person-years

*Adjusted for age group (9–17 years, 18–25 years)

Individual diseases with >10 cases in female cohorts

Table 3 gives the number of cases per individual disease and the corresponding incidence rate in each of the 4 cohorts. There were 3 diseases for which more than 10 cases were found in the female cohorts, namely autoimmune thyroiditis, Crohn's disease, and type 1 diabetes. For autoimmune thyroiditis a significant increased risk was found in the female exposed cohort (IRR 3.75, 95% CI: 1.25–11.31) (Table 4). No IRR for males could be calculated as no confirmed cases were found in either male cohort. The IRR for Crohn's disease was 1.21 (95% CI: 0.37–3.95) for females and 4.22 (95% CI: 0.47–38.02) for males. For type 1 diabetes, the IRR was 0.50 (95%CI: 0.21–1.17) for females, while a significant increased risk was found in the concurrent male cohort (IRR 2.46, 95% CI: 1.08–5.60). A significant decreased risk of type 1 diabetes was found in the female exposed cohort, when adjusted for male effect (IRR 0.30, 95% CI: 0.11–0.83).

Sensitivity analysis using confirmed and non-confirmed cases showed similar results, except for autoimmune thyroiditis in females, for which a lower and non-significant IRR of 1.45 (95% CI: 0.79–2.64) was found (Table 4). No significant IRRs were found for females and males in any of the other sensitivity analyses (2 other case definitions: Tables S1 and S2, models using other covariates: data not shown), or in the SCSS analysis (Table S3).

Table 3. Incidence rate per 100,000 person-years of individual autoimmune diseases.

	AS04-HPV-16/18 vaccine exposure (total PY = 64,705)		Unexposed historical female cohort (total PY = 64,841)		Unexposed concurrent male cohort (total PY = 64,859)		Unexposed historical male cohort (total PY = 64,868)	
Diseases	n	IR per 100,000 PY	n	IR per 100,000 PY	n	IR per 100,000 PY	n	IR per 100,000 PY

Acute disseminated encephalomyelitis	Confirmed cases	0	0.00	0	0.00	0	0.00	0	0.00
	All cases	1	1.55	0	0.00	0	0.00	0	0.00
Autoimmune thyroiditis	Confirmed cases	15	23.18	4	6.17	0	0.00	0	0.00
	All cases	26	40.18	18	27.76	2	3.08	3	4.63
Autoimmune uveitis	Confirmed cases	0	0.00	0	0.00	0	0.00	0	0.00
	All cases	2	3.09	5	7.71	2	3.08	1	1.54
Crohn's disease	Confirmed cases	6	9.27	5	7.71	4	6.17	1	1.54
	All cases	8	12.36	5	7.71	4	6.17	2	3.08
Guillain-Barre syndrome	Confirmed cases	0	0.00	0	0.00	1	1.54	1	1.54
	All cases	0	0.00	0	0.00	1	1.54	1	1.54
Idiopathic thrombo-cytopenic purpura	Confirmed cases	1	1.55	1	1.54	0	0.00	2	3.08
	All cases	1	1.55	1	1.54	0	0.00	2	3.08
Inflammatory bowel disease	Confirmed cases	0	0.00	0	0.00	0	0.00	1	1.54
	All cases	0	0.00	0	0.00	0	0.00	1	1.54
Juvenile rheumatoid arthritis	Confirmed cases	1	1.55	0	0.00	0	0.00	1	1.54
	All cases	1	1.55	0	0.00	0	0.00	1	1.54
Multiple sclerosis	Confirmed cases	0	0.00	1	1.54	0	0.00	0	0.00
	All cases	0	0.00	1	1.54	0	0.00	0	0.00
Optic neuritis	Confirmed cases	0	0.00	0	0.00	0	0.00	0	0.00
	All cases	1	1.55	1	1.54	0	0.00	0	0.00
Other AD	Confirmed cases	1	1.55	0	0.00	0	0.00	0	0.00
	All cases	1	1.55	0	0.00	0	0.00	0	0.00
Psoriatic arthritis	Confirmed cases	1	1.55	1	1.54	0	0.00	0	0.00
	All cases	1	1.55	1	1.54	0	0.00	0	0.00
Rheumatoid arthritis	Confirmed cases	1	1.55	0	0.00	0	0.00	0	0.00
	All cases	1	1.55	0	0.00	0	0.00	0	0.00
Type 1 diabetes mellitus	Confirmed cases	8	12.36	16	24.68	20	30.84	8	12.33
	All cases	8	12.36	16	24.68	20	30.84	8	12.33
Ulcerative colitis	Confirmed cases	4	6.18	0	0.00	2	3.08	2	3.08
	All cases	4	6.18	1	1.54	2	3.08	2	3.08

Note. N = number of subjects; PY = person-years; AD = autoimmune disease, includes acute disseminated encephalomyelitis and autoimmune peripheral neuropathies and plexopathies

Table 4. Incidence rate per 100,000 person-years and incidence rate ratios of individual autoimmune diseases with >10 cases in female cohorts.

		AS04-HPV-16/18 vaccine exposure (total PY = 64,705)		Unexposed female cohort (total PY = 64,841)		
Diseases		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	IRR* (95% CI) MALE/HIST
Autoimmune thyroiditis	Confirmed cases	15	23.18 (12.98;38.24)	4	6.17 (1.68; 15.80)	3.75 (1.25–11.31)
	All cases	26	40.18 (26.25;58.88)	18	27.76 (16.45;43.87)	1.45 (0.79–2.64)
Crohn's disease	Confirmed cases	6	9.27 (3.40;20.18)	5	7.71 (2.50;18.00)	1.21 (0.37–3.95)
	All cases	8	12.36 (5.34;24.26)	5	7.71 (2.50;18.00)	1.61 (0.53–4.91)
Type 1 diabetes mellitus	Confirmed cases	8	12.36 (5.34;24.36)	16	24.68 (14.10;40.07)	0.30 (0.11–0.83)**
	All cases	8	12.36 (5.34;24.36)	16	24.68 (14.10;40.07)	0.50 (0.21–1.17)

		Unexposed concurrent male cohort (total PY: 64,859)		Unexposed historical male cohort (total PY: 64,868)		
Diseases		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	IRR* (95% CI) MALE/HIST
Autoimmune thyroiditis	Confirmed cases	0	0.00 (0.00; 5.69)	0	0.00 (0.00; 5.69)	—
	All cases	2	3.08 (0.37;11.14)	3	4.63 (0.95;13.52)	0.76 (0.13–4.60)
Crohn's disease	Confirmed cases	4	6.17 (1.68;15.79)	1	1.54 (0.04;8.59)	4.22 (0.47–38.02)
	All cases	4	6.17 (1.68;15.79)	2	3.08 (0.37;11.14)	2.06 (0.38–11.34)
Type 1 diabetes mellitus	Confirmed cases	20	30.84 (18.84;47.62)	8	12.33 (5.32;24.30)	2.46 (1.08–5.60)
	All cases	20	30.84 (18.84;47.62)	8	12.33 (5.32;24.30)	2.46 (1.08–5.60)

Note. CI= confidence interval; EXP= AS04-HPV-16/18 vaccine exposure; HIST= unexposed historical male cohort; IRR= incidence rate ratio; MALE= unexposed concurrent male cohort; n= number of subjects; NNEXP= unexposed historical female cohort; PY= person-years
*Adjusted for age group (9–17 years, 18–25 years).
**The IRR for confirmed type 1 diabetes in the female cohorts was adjusted for the male effect, because a significant difference in incidence rates was observed between the 2 male cohorts

Post-hoc analyses for the autoimmune thyroiditis cases

The number of autoimmune thyroiditis cases appeared to decrease over time during the one-year follow-up period in all cohorts. This was also seen for the other AD. After additional medical record review, most of the 49 autoimmune thyroiditis cases were classified as hypothyroiditis (81.6%). Corresponding IRRs for autoimmune hypothyroiditis in the female cohorts were 3.00 (95% CI: 0.97–9.31) for confirmed cases and 1.47 (95% CI: 0.76–2.83) for confirmed and non-confirmed cases. No confirmed autoimmune hypothyroiditis cases were found in the male cohorts, but when considering

confirmed and non-confirmed cases the IRR was 1.90 (95% CI: 0.17–20.94). These results confirm the estimates in females for all autoimmune thyroiditis (hypothyroiditis and hyperthyroiditis combined). After exclusion of subjects from the Northern Ireland, Scotland, and Wales regions (as per post-hoc analysis), a nonsignificant IRR for confirmed autoimmune thyroiditis was found (IRR 2.50, 95% CI: 0.79–7.98).

3. Discussion

The main analysis based on confirmed cases showed no significant IRRs for any of the co-primary endpoints. However, among the most frequent AD for which symptom start dates are difficult to establish, the risk of autoimmune thyroiditis was increased, and the risk of type 1 diabetes was decreased in the female vaccinated cohort. Sensitivity analysis using all cases (i.e. confirmed and non-confirmed) showed similar results, except for autoimmune thyroiditis in which the IRR was not significant anymore. The findings on autoimmune thyroiditis and type 1 diabetes from the main analysis were not confirmed in sensitivity analyses using other case definitions, nor in the SCCS analysis. A publication by the UK Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the safety profile of AS04-HPV-16/18vaccine use in the UK from September 2008 to July 2012, when over 6 million doses of the vaccine had been given across the UK and identified no new safety concerns [9]. Randomized clinical studies did not show any increased risk of AD in the vaccinated group compared to controls [8,10,11]. A postlicensure safety surveillance of routine use of AS04-HPV-16/ 18vaccine did not find any pattern or trend for potential immune-mediated diseases after vaccination [12]. This current vaccine post-licensure study confirms the overall acceptable safety profile of AS04-HPV-16/18vaccine. Research by Chao, in which the Kaiser Permanente Database was used and AD cases were found using similar case identification and ascertainment methods, showed an increased risk of Grave's and Hashimoto diseases combined and a decreased risk of type 1 diabetes after 4 vHPV vaccination [13]. A study by Arnheim-Dahlstrom using healthcare registers from Denmark and Sweden, on the contrary, found an increased risk of type 1 diabetes after 4 vHPV vaccination [14]. However, both authors concluded that there was no clear evidence of a safety signal following

vaccination with 4vHPV, because no cluster of disease onset in relation to vaccination timing was found and no significant increased risk of most other conditions was found in vaccinated women. Moreover, in a follow-up review of the study by Chao, the authors concluded that many of the confirmed incident Grave's disease cases were actually prevalent cases [15]. A recent observational study carried out in a cohort of approximately 4 million women aged 10 to 44 years in Denmark did not find an increased risk of multiple sclerosis or other demyelinating diseases after 4 vHPV vaccination [16]. Additionally, other observational studies did not find any increased risk of AD in the 4 vHPV vaccinated group compared to an unvaccinated group [17-19]. The incidence of autoimmune thyroiditis in the vaccinated cohort was within the same range as the one in CPRD GOLD for the studied age group (incidence rates from the feasibility assessment for the period 2008–2010: age group [9–18] D 1.22 and 5.52/100,000 person-years respectively in males and females, age group [18–25] D 1.88 and 8.30/100,000 person-years respectively in males and females), indicating that although we found a significantly increased incidence in the exposed cohort, this was still within expected ranges. The increased incidence of autoimmune thyroiditis could be explained by a change in diagnostic methods over time. Our study had a number of limitations. First, CPRD GOLD is based on data from general practices (GP), while most autoimmune diseases are probably diagnosed in specialist settings. Not all GPs participating in CPRD GOLD consented to the linkage between CPRD GOLD primary care data and Hospital Episodes Statistics (HES) data (linkage was around 50% as of the first quarter of 2013). Consequently, the number of autoimmune diseases, the quality of the information, and the diagnostic certainty might be limited. In particular, the specific information related to the onset of clinical symptoms, and radiological, biological and genetic predisposition data associated with the etiologic diagnosis of AD may not have all been available in the CPRD GOLD database and associated resources. This is reflected in the low confirmation rate for some of the AD (i.e., autoimmune thyroiditis, autoimmune uveitis). Second, when the first symptom of an AD for a subject was known but the date of onset of the symptom was not known (i.e. there was no indication regarding the date on which the first symptom started), the date of first report of this symptom was used as date of first symptom. This is a limitation in the main

analysis and sensitivity analysis using both known and imputed dates of first symptom, because it is highly likely that in a subset of these subjects the symptom has started (much) earlier, possibly before the first dose of AS04-HPV-16/18vaccine. Third, analyses for the first co-primary endpoint (neuroinflammatory/ophthalmic AD) and most of the individual AD were not possible due to the small number of cases. Fourth, an additional limitation could be the risk of identifying false negative cases (lack of sensitivity). The case ascertainment procedure ensured a high specificity of the endpoint(s), but the team did not review the subject profiles of the non-cases (because unfeasible for 65,000 subjects per cohort), and this means that possible cases of ADs could have been missed. However, a high specificity was required to avoid a bias toward the null hypothesis whereas high sensitivity was not essential. Lack of sensitivity does not bias the risk estimate but could impact the precision resulting in a somewhat broader confidence interval. Fifth, the number of AD cases seemed to decrease over time during the one-year follow-up period in all 4 cohorts. This could potentially be explained by our study design: a diagnosis of AD was searched in the database through algorithms during the one-year period after the first AS04-HPV-16/18vaccine dose or equivalent study start date and then it was verified by medical review whether the onset of symptoms occurred during this period. It is plausible that cases of AD with onset of symptoms late during the one-year follow-up period were not detected because the diagnosis was reported later than one year after the study start date. However, we feel that only a few cases might have been missed as the onset of several AD is (sub)acute. Sixth, studies of rare events typically have low power and therefore only large risk increases can be detected. The present study shares this limitation. To overcome this, 2 composite co- primary endpoints were defined. The observed incidence of the co-primary endpoint ‘other autoimmune diseases’ was in alignment with the sample size calculation assumptions, but it was lower than expected for the neuroinflammatory diseases. However, the absence of confirmed neuroinflammatory disease cases in the exposed cohort was quite re-assuring. Lastly, multiple endpoint comparisons increase the overall type I error. However, no adjustment for type I error is also the most conservative approach for safety endpoints since it avoids masking possible signals. Despite these limitations, we still think this study

performed well. A major strength of this study was that it was based on a large population-based database that is likely to be representative of young women and men in the UK. The use of the CPRD GOLD database provided a unique opportunity to study the effect of AS04-HPV-16/18vaccine on the occurrence of AD as AS04-HPV-16/18vaccine was used during 3 years in a universal mass vaccination program for young women in the UK. New onset of AD was assessed by thorough subject data review, combining data from CPRD, HES and free text, and using several case ascertainment steps including expert review. This procedure provides a high specificity of the endpoints which is crucial to minimize the risk of bias to the null hypothesis. Attempts were made to minimize case ascertainment bias by blinding experts for HPV vaccine status during case review. In order to prevent inclusion of vaccinated subjects in an 'unexposed' cohort, the vaccinated exposed cohort was compared to a historical unexposed cohort before the start of the AS04-HPV-16/ 18 vaccine programs in the UK. In addition, 2 unexposed male cohorts were enrolled in order to assess a possible change over time in reporting AD in CPRD GOLD independent of AS04HPV-16/18vaccine introduction. Though incidence rates of autoimmune diseases differ across gender, the male cohorts were used as an internal control. Finally, for the exposed cohort, an additional SCCS analysis was performed in order to control for all fixed confounders not varying with time during the follow-up period. Age-stratified analyses were also performed and generated consistent results (not presented here).

4. Conclusion

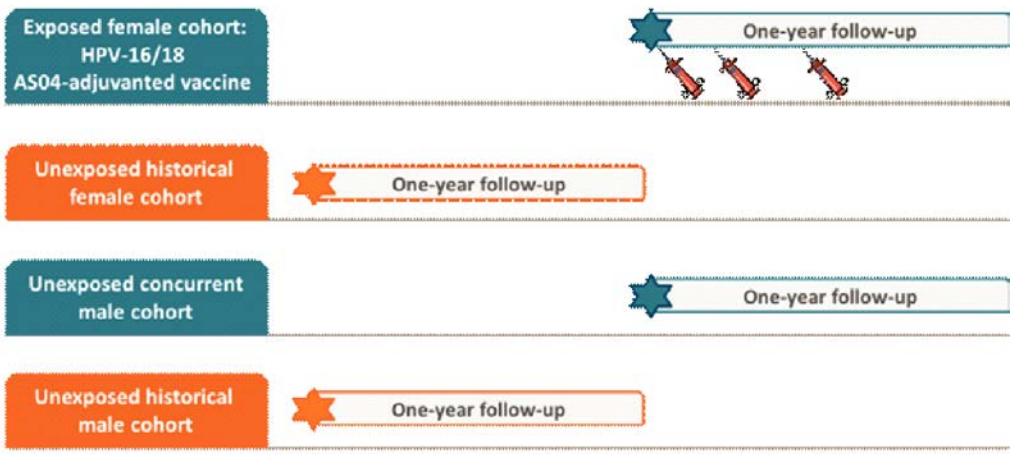
This observational study did not show evidence of an increased risk of AD following vaccination with AS04-HPV16/18 vaccine. No significant IRRs were found for the co-primary endpoints in the female cohorts. However, a significant increased risk of autoimmune thyroiditis (IRR: 3.75, 95% CI: 1.25–11.31) and a significant decreased risk of type 1 diabetes (after adjustment for male effect, IRRD0.30, 95% CI: 0.11– 0.83), was found in the female cohorts using confirmed cases only. Using all cases (i.e., confirmed and non-confirmed) showed similar results, except for autoimmune thyroiditis in which the IRR was not significant anymore. Sensitivity analyses using other case definitions and the SCCS analysis did not find any significant IRR between the exposed and unexposed female cohorts.

5. Materials and methods

Data source, population and setting

CPRD GOLD is one of the largest anonymised primary care databases, and captures longitudinal medical records including clinical events, laboratory results, drug prescriptions, referrals to specialists, and immunisation records from over 680 GPs in the UK [20]. Linkage between CPRD GOLD primary care data and HES data was available for approximately 50% of subjects as of the beginning of 2013 [21]. Complementary information to coded GP data can be obtained through the free text data captured in the practice management system from CPRD GOLD [20]. Free text data include notes or documents entered or scanned in by the GP, including letters from specialists in secondary or private care settings. A public immunization program targeting girls between 12– 13 years of age including a catch-up program for young women up to 18 years was undertaken in the UK during the academic year 2008/09. The phased catch-up program for females born 1 September 1991 to 31 August 1995 during the 2008/09 academic year was completed by the end of the 2009/10 academic year. The program was delivered largely through secondary schools [22-24]. In the UK public HPV immunization program (12–13-year-olds), HPV vaccination coverage for 2010/11 was 89.0%, 87.6% and 83.8% for the first, second and third dose respectively [25]. The bivalent vaccine was replaced in the program by the tetravalent vaccine Gardasil (4vHPV; Merck & Co) in September 2012. The study population included female and male subjects registered in CPRD GOLD for at least one year before the study start (Fig. 2).

Figure 2. Cohort design



Reference date between 1 SEPTEMBER 2005 and 31 AUGUST 2007: female and male subjects with ≥1 general practitioner consultation.

Reference date between 1 SEPTEMBER 2008 and 31 AUGUST 2010: female subjects vaccinated with a first dose of vaccine and male subjects with ≥1 general practitioner consultation. Not all female subjects who received one *Cervarix* vaccine completed all three planned *Cervarix* vaccinations.

Reference date between 1 September 2005 and 31 August 2007: female and male subjects with1 general practitioner consultation. Reference date between 1 September 2008 and 31 August 2010: female subjects vaccinated with afirst dose of AS04-HPV-16/18 vaccine and male subjects with1 general practitioner consultation. Not all female subjects who received one AS04-HPV-16/18 vaccine dose completed all 3 planned AS04-HPV-16/18 vaccine doses.

The female population was composed of subjects vaccinated with AS04-HPV-16/18 vaccine between the ages of 9 and 25 years and unexposed subjects of the same age identified from historical data. A historical unexposed cohort before the start of the Cervarix program in the UK was chosen in order to prevent inclusion of vaccinated subjects in an 'unexposed' cohort (because when no vaccination is reported in CPRD GOLD, it cannot be ruled out that the subject did receive the vaccine). The male population was composed of 9 to 25year-old subjects not vaccinated with AS04-HPV-16/18 vaccine, comprising both a concurrent and a historical male cohort. Comparison of the unexposed concurrent male cohort with the unexposed historical male cohort was used as an internal control for changes over time in the incidence of AD in CPRDGOLD. Women who received at least one dose of AS04HPV-16/18 vaccine administered according to local practice between 1 September 2008 and 31 August 2010 were eligible for the exposed group. Men with at least one GP consultation during the same period (concurrent male group), and women and men with at least one GP consultation between 1 September 2005 and 31 August 2007 (historical groups) were eligible for the unexposed groups. Subjects who received an unspecified HPV vaccine or 4 vHPV were excluded, as were unexposed subjects who received any dose of AS04-HPV16/18 vaccine at any time before the study period. Subjects with a diagnostic code of any AD during the year prior to the study start were also excluded.

The study protocol was approved by the Independent Scientific Advisory Committee for the MHRA database research. No patient informed consent was needed because patient information in CPRD GOLD is fully anonymised. The study is registered at www.clinicaltrials.gov (NCT01953822) and in the EU PAS Register (ENCEPP/SDPP/4584).

Study cohorts

Four cohorts were defined based on exposure to AS04-HPV16/18 vaccine and sex as recorded in the CPRD GOLD HPV16/18 vaccine (exposed), 2) unexposed historical female cohort, 3) unexposed concurrent male cohort, 4) unexposed historical male cohort. Subjects in the 3 unexposed cohorts were preselected after applying a frequency matching for age and practice region to the subjects included in the vaccinated (exposed) cohort. A random selection was applied to the pre-selected unexposed subjects in order to include the targeted number of subjects in each unexposed cohort. The study start date for the exposed cohort was the date of the first dose of AS04-HPV-16/ 18 vaccine. The study start date for the unexposed cohorts was a random date selected among the study start dates of the matched exposed cohort (minus 3 years for the historical cohorts).

Outcome definition

The primary study outcome was the occurrence of new onset of 2 groups of confirmed AD during the period of one year following the study start date (follow-up period). These two co-primary composite endpoints have been defined as: 1) neuroinflammatory/ophthalmic diseases: multiple sclerosis, transverse myelitis, optic neuritis, Guillain-Barre syndrome, autoimmune uveitis, and other demyelinating diseases, or 2) other AD: systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, Still's disease, psoriatic arthritis, ankylosing spondylitis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anaemia, type 1 diabetes mellitus, autoimmune thyroiditis, Crohn's disease, ulcerative colitis, and autoimmune hepatitis.

Secondary outcomes included the occurrence of new onset of individual confirmed AD during the period of one year following the study start date (follow-up period).

The one-year follow-up period was chosen in agreement with the Food and Drug Administration (and the European Medicines Agency, and is supported by the article from Tavares et al on the optimal conduct of clinical trials of new vaccines investigating the risk of AD [26].

Data collection and case ascertainment

Subjects with suspected AD diagnoses were identified in CPRD GOLD and/or HES using pre-defined algorithms (the algorithm for Guillain-Barre syndrome is given in Tables S4 and S5 as an example, the

other algorithms are available upon request). The final study database consisted of data for these subjects automatically extracted from CPRD GOLD (Tables S6 and S7), HES, and additional data from free text review. Information extracted included clinical diagnosis, laboratory testing, drug prescription, and HES-linked data. Specific de-identified free text associated with possible first symptoms, laboratory tests, drug prescriptions, and diagnosis of AD was requested when necessary in order to classify each subject as a confirmed new onset AD case, a non-confirmed new onset AD case, or a non-case. If a date of diagnosis did not fall within the follow-up period, a subject could not qualify as a case in any of the analyses. All subject profiles and requested free text were reviewed by Pallas, Health Research and Consultancy B.V., the Netherlands.

A safety physician from GSK and an external physician from Research Triangle Institute (RTI) Health Solutions reviewed all subjects with a doubtful outcome. Final case ascertainment was adjudicated by 5 independent external experts in the fields of rheumatology, ophthalmology, neurology, and internal medicine who remained blinded with respect to the exposure status of the subjects throughout the ascertainment process. Each expert reviewed the subjects, which included subjects with a doubtful outcome after review by Pallas, the GSK safety physician, and the RTI physician, and a 10% random sample of the remaining subjects per AD, according to their specialty. Fifty subjects were reviewed by the experts as part of the random check. Agreement on the date of first symptom, type of AD, confirmation of AD, and date of diagnosis existed for all subjects with rheumatology and neurology diagnoses and for most of the subjects with ophthalmology and internal medicine diagnoses. For autoimmune uveitis, however, the expert decided to include an additional first symptom (i.e. conjunctivitis/episcleritis) that had not been used by Pallas, GSK, and RTI. For inflammatory bowel disease, Crohn's diseases, and ulcerative colitis, the expert suggested other criteria to determine the date of diagnosis and confirmation of the diagnosis. All uveitis, inflammatory bowel disease, Crohn's disease, and ulcerative colitis subjects were therefore reviewed again by Pallas applying the revised criteria. Furthermore, after review by the expert of the systemic lupus erythematosus subjects, the

expert proposed other criteria to determine the diagnosis and its confirmation. The expert reviewed all remaining subjects and applied these criteria.

6. Statistical analysis

Main analyses

The main analysis included all confirmed AD cases with a known date of first symptom within the follow-up period (i.e., the date of first symptom was set as the date of disease occurrence). A known date of first symptom was either the date (from the free text) that a symptom was said by the patient to have started, or, if this was not available, the date the first symptom was reported in CPRD. If the date of first symptom was within the one year follow-up period but the date of diagnosis was after this period then this subject was not included as a case. The incidence rates of AD during the one year followup period were calculated as the number of cases divided by the total person-time. The individual person-time was defined as the time between the study start date and the end of followup period (one year from study start date), subject's date of death, CPRD de-enrolment date, date of unspecified HPV vaccine or 4vHPV, or date of first symptom of AD, whichever occurred first. The comparison of the incidence rates of AD (co-primary endpoints and individual diseases with more than 10 cases in the female cohorts: these concerned Crohn's disease, autoimmune thyroiditis, and diabetes mellitus type 1) was done using a Poisson regression model, with number of events as dependent variable, exposure status as independent variable, and age as covariate, and the log of person-time as an offset. The IRR (females: exposed/historical, males: concurrent/historical) was derived as the exponential of the coefficient associated with the exposure status and its 95% Wald CI. A Poisson regression model adjusted for time effect was performed for the AD for which a statistically significant difference in incidence rates was observed between the 2 male cohorts. This model included the 4 cohorts and a specific contrast for estimating the difference between the 2 female cohorts adjusted for the difference between the 2 male cohorts.

Sensitivity analyses

The following sensitivity analyses were performed:

- Analyses of all cases (confirmed and non-confirmed) with known date of first symptom within the follow-up period;
- Analyses using cases with a known or imputed date of first symptom (confirmed cases only, and confirmed and nonconfirmed cases combined) within the follow-up period. In case of missing date of first symptom, a date was imputed using the disease-specific median number of days between the date of diagnosis and the known date of first symptom of all confirmed and non-confirmed cases. If the (imputed) date of first symptom was within the defined risk period but the date of diagnosis was after the risk period then this subject was not included as a case;
- Analyses where the date of diagnosis was set as the date of disease occurrence (confirmed cases only, and confirmed and non-confirmed cases combined);
- Analyses using, in addition to age, also region, other vaccination, and healthcare resource utilization during the year prior to the study start date as covariates.

Self-controlled case-series

A SCCS analysis for both co-primary endpoints and individual diseases was performed for the exposed female cohort. For the main SCCS, the risk period was one year after the first AS04-HPV-16/18 vaccine dose; a buffer period was defined as the 6 months after the end of the risk period and the control period was defined as one year after the end of the buffer period.

Potential pre-existing autoimmune conditions may influence vaccination status. For this reason, the control period did not include a pre-vaccine period. The relative incidence rate was calculated for the coprimary endpoints and individual diseases between risk and control periods as the ratio of the incidence rate in the risk period versus the incidence rate in the control period. Confirmed AD cases with a date of first symptom within these 30 months were included in the SCCS analysis. If the date of first symptom was within the defined risk period but the date of diagnosis was after the risk period then the case was excluded from the SCCS analysis. The same rule was applied for cases occurring in the control period because no diagnosis that occurred after the end of the control period was included

in the study. The reason for the use of this rule was to avoid a bias in the number of cases occurring in the risk period.

Post-hoc analyses

Post-hoc analyses included a descriptive analysis of time-to-onset of all confirmed autoimmune thyroiditis cases. Moreover, an additional subject profile review was performed for all confirmed and non-confirmed autoimmune thyroiditis cases with a known date of first symptom within the follow-up period in order to classify the cases as hypo- or hyperthyroiditis and to derive IRR's for these subtypes separately. Lastly, an analysis excluding subjects from Northern Ireland, Scotland, and Wales was performed, because a large proportion of confirmed autoimmune thyroiditis cases were observed in this region (10.2%), while this region represented less than 0.1% of the overall study population cohorts.

Sample size

For the cohort design, by hypothesizing that the incidence rates of neuro-inflammatory AD vary between 1 and 10/100,000 person-years and the incidence rates of other AD vary between 50 and 100/100,000 person-years, cohorts of 50,000 subjects each should allow the detection, with 80% power, of a relative risk between 18.7 and 3.7 and between 2.0 and 1.6 respectively for the neuro-inflammatory AD and other AD (our 2 co-primary endpoints). Because of risk of loss to follow-up and missing data, the sample size was increased by 30% for a total of 65,000 subjects in each cohort.

References

[1] Stanley M. Pathology and epidemiology of HPV infection in females. Gynecol Oncol 2010; 117:S5-10; PMID:20304221; http://dx.doi.org/ 10.1016/j.ygyno.2010.01.024

[2] de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, Tous S, Felix A, Bravo LE, Shin HR, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010; 11:1048-56; PMID:20952254; http://dx.doi.org/10.1016/S1470-2045(10)70230-8

[3] Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsague X, Skinner SR, Apter D, Naud P, Salmeron J, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012; 13:89-99; PMID:22075171; http://dx.doi.org/10.1016/S14702045(11)70286-8

[4] Skinner SR, Szarewski A, Romanowski B, GarlandSM, Lazcano-Ponce E, Salmeron J, Del Rosario-Raymundo MR, Verheijen RH, Quek SC, da Silva DP, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet 2014; 384:2213-27; PMID:25189358; http://dx.doi.org/10.1016/ S0140-6736(14)60920-X

[5] Wheeler CM, Castellsague X, Garland SM, Szarewski A, Paavonen J, Naud P, Salmeron J, Chow SN, Apter D, Kitchener H, et al. Crossprotective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, doubleblind PATRICIA trial. Lancet Oncol 2012; 13:100-10; PMID:22075170; http://dx.doi.org/10.1016/S1470-2045(11)70287-X

[6] Klein NP, Ray P, Carpenter D, Hansen J, Lewis E, Fireman B, Black S, Galindo C, Schmidt J, Baxter R. Rates of autoimmune diseases in Kaiser Permanente for use in vaccine adverse event safety studies. Vaccine 2010; 28:1062-8; PMID:19896453; http://dx.doi.org/ 10.1016/j.vaccine.2009.10.115

[7] Guimaraes LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. Pharmacol Res 2015; 100:190-209; PMID:26275795; http://dx.doi.org/10.1016/j.phrs.2015.08.003

[8] Angelo MG, David MP, Zima J, Baril L, Dubin G, Arellano F, Struyf F. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiol Drug Saf 2014; 23:466-79;

PMID:24644063; http://dx.doi.org/10.1002/pds.3554

[9] MHRA Public Assessment Report - Cervarix HPV vaccine: safety update at end of 4 years routine use in HPV immunisation programme. London: MHRA, 2012

[10] Descamps D, Hardt K, Spiessens B, Izurieta P, Verstraeten T, Breuer T, Dubin G. Safety of human papillomavirus (HPV)-16/18 AS04adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Hum Vaccin 2009; 5:332-40; PMID:19221517; http://dx.doi.org/10.4161/hv.5.5.7211

[11] Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, de Borba PC, Sanchez N, Zahaf T, Catteau G, Geeraerts B, Descamps D. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Hum Vaccin Immunother 2014; 10:2147-62; PMID:25424918; http://dx.doi.org/10.4161/hv.29532

[12] Angelo MG, Zima J, Tavares Da Silva F, Baril L, Arellano F. Postlicensure safety surveillance for human papillomavirus-16/18-AS04adjuvanted vaccine: more than 4 years of experience. Pharmacoepidemiol Drug Saf 2014; 23:456-65; PMID:24644078; http://dx.doi.org/ 10.1002/pds.3593

[13] Chao C, Klein NP, Velicer CM, Sy LS, Slezak JM, Takhar H, Ackerson B, Cheetham TC, Hansen J, Deosaransingh K, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012; 271:193-203; PMID:21973261; http://dx.doi.org/10.1111/j.1365-2796.2011.02467.x

[14] Arnheim-Dahlstrom L, Pasternak B, Svanstrom H, Sparen P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013; 347:f5906; PMID:24108159; http://dx.doi.org/ 10.1136/bmj.f5906

[15] Jacobsen SJ, Sy LS, Ackerson BK, Chao CR, Slezak JM, Cheetham TC, Takhar HS, Velicer CM, Hansen J, Klein NP. An unmasking phenomenon in an observational post-licensure safety study of adolescent girls and young women. Vaccine 2012; 30:4585-7; PMID:22580356; http://dx.doi.org/10.1016/j.vaccine.2012.04.103

[16] Scheller NM, Svanstrom H, Pasternak B, Arnheim-Dahlstrom L, Sundstrom K, Fink K, Hviid A. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015; 313:54-61; PMID:25562266; http:// dx.doi.org/10.1001/jama.2014.16946

[17] Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, Kulldorff M, Lewis E, Fireman B, Daley MF, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the vaccine

safety datalink. Vaccine 2011; 29:8279-84; PMID:21907257; http://dx.doi.org/ 10.1016/j.vaccine.2011.08.106

[18] Grimaldi-Bensouda L, Guillemot D, Godeau B, Benichou J, Lebrun-Frenay C, Papeix C, Labauge P, Berquin P, Penfornis A, Benhamou PY, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med 2014; 275:398-408; PMID:24206418; http://dx.doi. org/10.1111/joim.12155

[19] Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, Izurieta HS, Ball R, Miller N, Braun MM, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009; 302:750-7; PMID:19690307; http://dx.doi.org/ 10.1001/jama.2009.1201

[20] Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the general practice research database as an example of a UK primary care data resource. Ther Adv Drug Saf 2012; 3:89-99; PMID:25083228; http://dx.doi.org/10.1177/2042098611435911

[21] Thomas KH, Davies N, Metcalfe C, Windmeijer F, Martin RM, Gunnell D. Validation of suicide and self-harm records in the clinical practice research datalink. Br J Clin Pharmacol 2013; 76:145-57; PMID:23216533; http://dx.doi.org/10.1111/bcp.12059

[22] Crawford CaW J. Health Protection Agency survey of Primary Care Trust teenage vaccination programmes. Health Protection Agency 2009

[23] Sheridan AaW J. Annual HPV vaccine uptake in England: 2008/09: Routine programme for year 8 girls (12–13 years old) and catch-up campaign for year 13 girls (17–18 years old). Health Protection Agency Department of Health, 2009

[24] Sheridan AaW J. Annual HPV vaccine coverage in England in 2009/ 2010. Health Protection Agency Department of Health, 2010

[25] Annual HPV vaccine coverage in England in 2010/11. Health Protection Agency, 2012

[26] Tavares Da Silva F, De Keyser F, Lambert PH, Robinson WH, Westhovens R, Sindic C. Optimal approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines. Vaccine 2013; 31:1870-6; PMID:23391600; http://dx. doi.org/10.1016/j.vaccine.2013.01.042

Supplementary materials

Table S1: Incidence rate per 100,000 person-years and incidence rate ratios* of co-primary endpoints and individual diseases with >10 cases in female cohorts – sensitivity analysis with imputed date of first symptom

Diseases		AS04-HPV-16/18 vaccine exposure (total PY=64,730)		Unexposed historical female cohort (female total PY=64,844)		IRR* (95% CI) EXP/NNEXP
		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	
Co-primary endpoints						
Neuroinflammatory/ ophthalmic AD	Confirmed cases	0	0.00 (0.00; 5.70)	1	1.54 (0.04; 8.59)	1.00 (0.06; 16.08)
	All cases	5	7.72 (2.51; 18.03)	9	13.88 (6.35; 26.35)	0.56 (0.19; 1.66)
Other AD	Confirmed cases	42	64.89 (46.76;87.71)	33	50.89 (35.03;71.47)	1.27 (0.81; 2.01)
	All cases	60	92.69 (70.73; 119.31)	52	80.19 (59.89; 105.16)	1.16 (0.79; 1.67)
Individual diseases with >10 cases in female cohorts						
Autoimmune thyroiditis	Confirmed cases	16	24.72 (14.13; 40.14)	8	12.34 (5.33; 24.31)	2.00 (0.86; 4.67)
	All cases	32	49.44 (33.81; 69.79)	27	41.64 (27.44; 60.58)	1.19 (0.71; 1.98)
Crohn's disease	Confirmed cases	7	10.81 (4.35; 22.28)	5	7.71 (2.50; 17.99)	1.41 (0.45; 4.43)
	All cases	9	13.90 (6.36; 26.39)	5	7.71 (2.50; 17.99)	1.81 (0.61; 5.39)
Type 1 diabetes mellitus	Confirmed cases	10	15.45 (7.41; 28.41)	18	27.76 (16.45; 43.87)	0.56 (0.26; 1.21)
	All cases	10	15.45 (7.41; 28.41)	18	27.76 (16.45; 43.87)	0.56 (0.26; 1.21)

Diseases		Unexposed concurrent male cohort (total PY=64,865)		Unexposed historical male cohort (total PY=64,874)		IRR* (95% CI) MALE/HIST
		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	
Co-primary endpoints						
Neuroinflammatory/ ophthalmic AD	Confirmed cases	2	3.08 (0.37; 11.14)	1	1.54 (0.04; 8.59)	1.89 (0.17; 20.94)
	All cases	7	10.79 (4.34; 22.24)	4	6.17 (1.68; 15.79)	1.82 (0.53; 6.24)
Other AD	Confirmed cases	33	50.88 (35.02; 71.45)	19	29.29 (17.63; 45.74)	1.78 (1.01; 3.14)
	All cases	38	58.58 (41.46; 80.41)	29	44.70 (29.94;64.20)	1.35 (0.83; 2.19)

Individual diseases with >10 cases in female cohorts

Autoimmune thyroiditis	Confirmed cases	1	1.54 (0.04; 8.69)	0	0.00 (0.00; 5.69)	Not done
	All cases	5	7.71 (2.50; 17.99)	7	10.79 (4.34; 22.23)	0.73 (0.23; 2.31)
Crohn's disease	Confirmed cases	5	7.71 (2.50; 17.99)	1	1.54 (0.04; 8.59)	5.19 (0.60; 44.68)
	All cases	5	7.71 (2.50; 17.99)	2	3.08 (0.37; 11.14)	2.55 (0.49; 13.23)
Type 1 diabetes mellitus	Confirmed cases	23	35.46 (22.48; 53.21)	12	18.50 (9.56; 32.31)	1.89 (0.94; 3.82)
	All cases	23	35.46 (22.48; 53.21)	14	21.58 (11.80; 36.21)	1.65 (0.85; 3.20)

AD = autoimmune disease; CI = confidence interval; EXP = exposed female cohort; HIST = unexposed historical male cohort; IRR = incidence rate ratio; MALE = unexposed concurrent male cohort; n = number of subjects; NNEXP = unexposed historical female cohort; PY = person-years

* Adjusted for age group (9-17 years, 18-25 years)

Table S2: Incidence rate per 100,000 person-years and incidence rate ratios* of co-primary endpoints and individual diseases with >10 cases in female cohorts – sensitivity analysis with date of diagnosis as date of disease onset

		AS04-HPV-16/18 vaccine exposure (total PY=64,852)		Unexposed historical female cohort (total PY=64,893)		
Diseases		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	IRR* (95% CI) EXP/NNEXP
Co-primary endpoints						
Neuroinflammatory/ ophthalmic AD	Confirmed cases	1	1.54 (0.04; 8.59)	1	1.54 (0.04; 8.59)	1.00 (0.6; 16.10)
	All cases	6	9.25 (3.40; 20.14)	10	15.41 (7.39; 28.34)	0.60 (0.21; 1.65)
Other AD	Confirmed cases	58	89.44 (67.91; 115.62)	52	80.13 (59.85; 105.08)	1.12 (0.77; 1.62)
	All cases	87	134.15 (107.45; 165.48)	85	130.99 (104.63; 161.97)	1.024 (0.76; 1.38)
Individual diseases with >10 cases in female cohorts						
Autoimmune thyroiditis	Confirmed cases	23	35.47 (22.48; 53.22)	15	23.12 (12.94; 38.13)	1.53 (0.80; 2.94)
	All cases	48	74.01 (54.57; 98.13)	46	70.89 (51.90; 94.55)	1.04 (0.69; 1.56)
Crohn's disease	Confirmed cases	11	16.96 (8.47; 30.35)	9	13.87 (6.34; 26.33)	1.23 (0.51; 2.96)
	All cases	13	20.05 (10.67; 34.28)	9	13.87 (6.34; 26.33)	1.45 (0.62; 3.39)
Type 1 diabetes mellitus	Confirmed cases	11	16.96 (8.47; 30.35)	20	30.82 (18.83; 47.60)	0.55 (0.26; 1.15)
	All cases	11	16.96 (8.47; 30.35)	20	30.82 (18.83; 47.60)	0.55 (0.26; 1.15)

		Unexposed concurrent male cohort (total PY=64,897)		Unexposed historical male cohort (total PY=64,891)		
Diseases		n	IR per 100,000 PY (95% CI)	n	IR per 100,000 PY (95% CI)	IRR* (95% CI) MALE/HIST
Co-primary endpoints						
Neuroinflammatory/ ophthalmic AD	Confirmed cases	2	3.08 (0.37; 11.13)	1	1.54 (0.04; 8.59)	1.89 (0.17; 20.94)
	All cases	9	13.87 (6.34; 26.33)	3	4.62 (0.95; 13.51)	3.11 (0.84; 11.52)
Other AD	Confirmed cases	45	69.34 (50.58; 92.78)	33	50.85 (35.01; 71.42)	1.39 (0.88; 2.18)
	All cases	56	86.29 (65.18; 112.06)	48	73.97 (54.54; 98.07)	1.19 (0.81; 1.75)
Individual diseases with >10 cases in female cohorts						
	Confirmed cases	2	3.08 (0.37; 11.13)	0	0.00 (0.00; 5.69)	Not done

Autoimmune thyroiditis	All cases	10	15.41 (7.39; 28.34)	8	12.33 (5.32; 24.29)	1.25 (0.49; 3.18)
Crohn's disease	Confirmed cases	15	23.11 (12.94; 38.12)	8	12.33 (5.32; 24.29)	1.94 (0.82; 4.59)
	All cases	16	24.65 (14.09; 40.04)	10	15.41 (7.39; 28.34)	1.64 (0.74; 3.62)
Type 1 diabetes mellitus	Confirmed cases	23	35.44 (22.47; 53.18)	12	18.49 (9.56; 32.30)	1.89 (0.94; 3.82)
	All cases	23	35.44 (22.47; 53.18)	14	21.58 (11.80; 36.20)	1.65 (0.85; 3.20)

AD = autoimmune disease; CI = confidence interval; EXP = exposed female cohort; HIST = unexposed historical male cohort; IRR = incidence rate ratio; MALE = unexposed concurrent male cohort; n = number of subjects; NNEXP = unexposed historical female cohort; PY = person-years

* Adjusted for age group (9-17 years, 18-25 years)

Table S3: Relative incidence between risk and control periods for confirmed cases (self-controlled case-series analysis)

Diseases	Risk period (n)	Control period (n)	Relative incidence (95% CI)
Co-primary endpoints			
Neuroinflammatory/ophthalmic AD	0	2	0.00 (0.00-)
Other AD	38	28	1.36 (0.83-2.21)
Individual diseases with >10 cases in risk and control period			
Autoimmune thyroiditis	15	11	1.36 (0.63-2.97)
Type 1 diabetes mellitus	8	7	1.14 (0.41-3.15)

AD = autoimmune disease; CI = confidence interval; n = number of subjects;

Table S4: Algorithm for GBS case identification in CPRD and/or HES

Guillain Barré Syndrome	Guillain Barré Syndrome (GBS) cases will be identified where: – in *Clinical and Referral file*: a medcode for GBS is listed (see eTable 2) – in *HES (HES_diagnosis_epi file)*: an ICD10 diagnosis code for GBS is listed (see eTable 2) Eventdate should be between reference date and (reference date+365 days) for unexposed cohort and between reference date and (reference date+30months) for exposed cohort. Freetext related to GBS in the study period will be retrieved and the case will be sent for expert review. Additional information will be retrieved in order to complete the patient profile, the eventdate should be 1 year before the reference date or during the follow-up period: – in *Therapy file*: all prodcodes – in *Test file*: Nerve conduction studies (enttype=343) and cerebrospinal fluid examination (enttype=410)

Table S5: Medical codes and ICD-10 codes for Guillain Barre Syndrome:

Medcode (CPRD-GOLD Medical Code Events)	Read Code	Read Description	ICD-10 codes	Review
28294	F326100	Polyneuritis cranialis	G52.7	Possible
44512	F364.00	Idiopathic progressive polyneuropathy	G60.3	Possible
14884	F36y.00	Other idiopathic peripheral neuropathy	G60	Possible
1607	F370000	Guillain-Barre syndrome	G61.0	Y
24216	F370100	Postinfectious polyneuritis	G61.0	Possible
33841	F370200	Miller-Fisher syndrome	G61.0	Y
63555	F374z00	Polyneuropathy in disease NOS	G63	Possible
31551	F37X.00	Inflammatory polyneuropathy, unspecified	G61.9	Possible
69047	F37y000	Serum neuropathy	G61.1	Possible
96256	F37y100	Axonal sensorimotor neuropathy	G60	Y
15481	F37z.00	Toxic or inflammatory neuropathy NOS	G61.9	Possible
24226	F37z.11	Polyneuropathy unspecified	G62.9	Possible
55076	Fyu7.00	[X]Polyneuropathies & other disord of	G60/G64	Possible
97449	Fyu7000	[X]Other hereditary and idiopathic neuropathies	G60.8	Possible
97306	Fyu7200	[X]Other specified polyneuropathies	G62.8	Possible

Table S6: Variables directly extracted from CPRD GOLD

	Column name	Field name	Description	CPRD GOLD file
1	*Patient Identifier*	*patid*	Unique identifier given to a patient	patient
2	*Patient Gender*	*gender*	Patient's gender	patient
3	*Birth Month*	*mob*	Patient's month of birth (for those aged under 16)	patient
4	*Birth Year*	*yob*	Patient's year of birth	patient
5	*Practice Identifier*	*pracid*	Unique identifier given to a specific practice	practice
6	*Practice Region*	*region*	Practice region: Value to indicate where in the United Kingdom the practice is based	practice
7	*Death Date*	*deathdate*	Date of death of patient – derived using an algorithm	patient
8	*First Registration Date*	*frd*	First registration date: Date the patient first registered with the practice. If patient only has 'temporary' records, the date is the first encounter with the practice; if patient has 'permanent' records it is the date of the first 'permanent' record (excluding preceding temporary records)	patient
9	*Current Registration Date*	*crd*	Date the patient's current period of registration with the practice began (date of the first 'permanent' record after the latest transferred out period). If there are no 'transferred out periods', the date is equal to 'frd'	patient
10	*Registration Gaps*	*reggap*	Number of days missing in the patients registration details	patient
11	*Registration Status*	*regstat*	Registration status: Status of registration detailing gaps and temporary patients	patient
12	*Transfer Out Date*	*tod*	Date the patient transferred out of the practice	patient
13	*Transfer Out Reason*	*toreason*	Reason the patient transferred out of the practice. Includes 'Death' as an option	patient
14	*Up To Standard Date*	*uts*	Date at which the practice data is deemed to be of research quality. Derived using an algorithm that primarily looks at practice death recording and gaps in the data	practice
15	*Acceptable Patient Flag*	*accept*	Flag to indicate whether the patient has met certain quality standards: 1 = acceptable, 0 = unacceptable	practice
16	*Matching CPRD-HES*	*HES_e*	Flag (0,1) indicating whether patient is eligible for linkage to HES data	linkage_eligibility

[1] dd/mm/yyyy: Valid dates are in the format DD/MM/YYYY. Missing dates are NULL, and invalid dates are set to 01/01/2500.

[2] PAT_GAP: Number of days between patient's transferred out date and re-registration date for the patient's 'transferred out periods', regardless of whether the transfer was internal or not.

[3] PAT_STAT: Transferred out period is the time between a patient transferring out and re-registering at the same practice. If the patient has transferred out for a period of more than 1 day, and the transfer is not internal, this value is incremented. 0 means continuous registration, 1 means one 'transferred out period', 2 means two periods, etc. If the patient only has 'temporary' records then this value is set to 99.

Table S7: Variables derived from CPRD GOLD

	Column Name	Algorithms
17	*Date of Cervarix vaccination*	Search for the subject in *Immunisation file* where: – Immstype equals 67 (HPVCER) and status equals 1 – Retrieve the eventdates For the subjects with at least one recorded dose in *Immunisation file*: 1) Search for additional Cervarix vaccination in *Therapy file* where: – Cervarix prodcode = 36952 The vaccinations from *Therapy* file will be considered as additional Cervarix vaccination if the eventdate is not equal to eventdate (+/- 14 days) from *Immunisation file*. 2) Search for additional Cervarix vaccination in *Clinical file* (medcode=93489 93621 95554): - if the eventdate is equal to eventdate from *Immunisation or Therapy file* then vaccination is similar than the one from *Immunisation or Therapy file*. - if the eventdate is not equal to eventdate but in an interval of +/- 14 days from *Immunisation or Therapy file* then the vaccination is not an additional unspecified HPV vaccination – ntPV. the date is different, the dose is considered as an unspecified additional doses - if the eventdate is not equal to eventdate +/- 14 days from *Immunisation or Therapy file* then the vaccination is an additional unspecified HPV vaccination If the 1st dose of Cervarix is between 01Sep2008 and 31Dec2010, the subject will be included in the exposed cohort. The date of 1st dose of Cervarix vaccination is the study start date for exposed cohort. Eventdate of all of recorded Cervarix doses will be retrieved.
18	*Date of unspecified HPV or Gardasil vaccine*	This variable will retrieve a date of unspecified HPV OR Gardasil vaccination. Search for the subject in *Immunisation file* where: – Medcode in (93489, 93621, 95554) (HPV 1st, 2d, 3rd dose) AND immstype equals 58 or not specified – Retrieve the eventdates Search for additional unspecified HPV or Gardasil vaccine in *Therapy file* where: – prodcode = 32424 37955 /Gardasil prodcode =32147 The vaccinations from *Therapy file* will be considered as additional unspecified HPV or Gardasil vaccination if the eventdate is not equals to eventdate (+/- 14 days) from *Immunisation file*. Search for additional HPV vaccinations in *Clinical file* (medcode=93489 93621 95554): - if the eventdate is equal to eventdate from *Immunisation or Therapy file* then vaccination is similar than the one from *Immunisation or Therapy file*. - if the eventdate is not equal to eventdate but in an interval of +/- 14 days from *Immunisation or Therapy file* then the vaccination is not an additional unspecified HPV vaccination – ntPV. the date is different, the dose is considered as an unspecified additional doses. - if the eventdate is not equal to eventdate +/- 14 days from *Immunisation or Therapy file* then the vaccination is an additional unspecified HPV vaccination

	Column Name	Algorithms
19	*Date of any other vaccine*	This variable checks if a vaccine (other than HPV) was administered during the year before the study start date. Search for the subject in *Immunisation file and Therapy file* if a medcode (for vaccine) exist, retrieve eventdate, immstype and medcode and status=1 for *Immunisation file*. Search in *Therapy file* if a prodcode for vaccine exist, retrieve eventdate, drugsubstance, productname. Eventdate of vaccination should be between the study start date -365 and end of follow-up.
20	*Date of birth*	Date of birth will be derived from month of birth (mob) and year of birth (yob) in *Patient file*. If month of birth and year of birth are present, the date of birth will be read as "15mmyyyy". If month of year is not present, it will be read as "30JUNyyyy".
21	*CPRD Start Date*	From *Patient and Practice file*: If crd < Up to Standard Date then CPRD Start Date= Up to Standard Date (uts) If crd > Up To Standard Date then CPRD Start Date=Current registration Date (crd)
22	*Health care resource utilization*	The number of GP/primary care consultations during the year before the study start date will be retrieved from *Consultation file*.
23	*Date of autoimmune disease diagnosis*	The autoimmune diagnosis will be identified by applying the algorithm 24 from 42. If the same recorded medcode has more than one event date, then the first event will be used as the first date of autoimmune diagnosis.
24-42	*Autoimmune disease name*	Each autoimmune disease will be retrieved from algorithms (available upon request)

4.2 Meta-analysis of the risk of autoimmune thyroiditis, Guillain-Barré syndrome, and inflammatory bowel disease following vaccination with AS04-adjuvanted human papillomavirus 16/18 vaccine

Dominique Rosillon, Corinne Willame, Fernanda Tavares Da Silva, Adrienne Guignard, Sophie Caterina, Sarah Welby, Frank Struyf

Pharmacoepidemiology and Drug Safety. 2020 Sep;29(9):1159-1167. doi: 10.1002/pds.5063.

Abstract

Purpose: To assess the risk of three autoimmune diseases - autoimmune thyroiditis (AIT), Guillain-Barré syndrome (GBS), and inflammatory bowel disease (IBD) - in females following AS04-HPV-16/18 vaccination.

Methods: This meta-analysis included data from 18 randomized controlled trials, one cluster-randomized trial, two large observational retrospective cohort studies, and one case-control study. Following vaccination, a risk window of 2 years was defined for AIT and IBD and 42 days for GBS. Odds ratios (ORs) were estimated using three methods: meta-analysis inverse-variance with continuity correction (primary analysis), pooled estimate, and beta-binomial regression.

Results: In all studies apart from the case-control study, 154 398 exposed and 1 504 322 non-exposed subjects were included, among whom there were 141 and 1972 cases of (autoimmune) thyroiditis; 2 and 2 cases of GBS; and 43 and 401 cases of IBD, respectively. In the case-control study, there were 97 cases of AIT and 13 of GBS; matched with 802 and 130 controls, respectively. The primary analysis OR estimates were 1.46 (95% confidence interval [CI] 1.22-1.76), 11.14 (2.00-61.92), and 1.11 (0.75-1.66) for (autoimmune) thyroiditis, GBS, and IBD, respectively.

Conclusions: This meta-analysis did not show an increased risk of IBD following vaccination with AS04-HPV-16/18. The 1.5-fold increased risk of (autoimmune) thyroiditis does not allow us to conclude about a causal association. For GBS, the very low number of cases and wide 95% CIs negate any firm conclusion.

1. INTRODUCTION

Three humanpapillomavirus (HPV) vaccines are currently available: AS04-adjuvanted HPV-16/18 (AS04-HPV-16/18) vaccine (Cervarix; GSK) [1]; quadrivalent HPV-6/11/16/18 (Gardasil; Merck Sharp & Dohme Limited) [2], and a nonavalent HPV vaccine (Gardasil 9; Merck Sharp & Dohme Limited) [3]. All three vaccines contain antigens for the high-risk types HPV-16 and HPV-18. AS04-HPV-16/18 also contains AS04 - an adjuvant system containing 3-O-desacyl-4'-monophosphoryl lipid A (50 µg MPL) adsorbed on aluminium hydroxide (500 µg Al^{3+}) [1] to boost the immune response [4]. The other two HPV vaccines contain amorphous aluminium hydroxyphosphate sulphate adjuvant [2,3].

For many years, there have been alleged concerns that vaccines, per se, may be linked with autoimmune diseases and, more recently, that immunostimulating adjuvants may cause/trigger autoimmune diseases [5-8].

During the development of AS04-HPV-16/18, clinical trial data [9-26] did not indicate an increased risk of autoimmune diseases. As part of its safety monitoring, two pooled analyses of AS04-HPV-16/18 clinical trials were undertaken [27,28], examining a wide range of autoimmune events. The second and most comprehensive included 33 339 exposed and 24 241 non-exposed subjects [28]. Neither showed an increased risk of autoimmune diseases following AS04-HPV-16/18 vaccination [27,28]. However, two post-licensure observational studies identified potential safety signals for autoimmune thyroiditis (AIT) and Guillain-Barré syndrome (GBS) after vaccination with AS04-HPV-16/18; and for GBS and inflammatory bowel disease (IBD) following vaccination with HPV-6/11/16/18 [29,30].

In order to test these signals, we performed a meta-analysis to estimate the risk of AIT, GBS, and IBD in females following vaccination with AS04-HPV-16/18.

2. METHODS

2.1 Study selection

This meta-analysis included data from randomized controlled trials (RCTs) and post-marketing observational studies that were identified in GSK internal repository of studies sponsored and

supported by the Company, and information from Regulatory Authorities. In a complementary, systematic literature review searching for all studies published till end 2015. Details of the search strategy, the database consulted and number of references found and selected are described in Data S1. No study additional to those included in the GSK internal repository was found. AS04-HPV-16/18 clinical trials had to be interventional RCTs with a non-HPV vaccine control group in female subjects aged ≥9 years. Extension studies beyond 2 years following first vaccination and ongoing studies on the data lock point date (17 November 2015) were excluded. Post-marketing observational studies that specifically assessed the association between AS04-HPV16/18 and autoimmune diseases in females were also included. The following studies were included:

- A cluster-randomized trial, in which communities of subjects received different vaccination schedules [31,32]. This study was included separately, due to its large sample size and different safety follow-up methodology (passive safety surveillance via national registries).
- Two large observational, retrospective cohort studies: a United Kingdom (UK) database cohort study [30] and a French longitudinal study based on national healthcare administrative databases [29,33,34].
- A French case-control study [35,36], in which subjects with various autoimmune diseases were matched with controls who met the same general inclusion/exclusion criteria.

2.2 Data sources and extraction

Subject-level data were extracted from all studies except the French cohort study [29,33,34] and the case-control study [35,36]. For these, as individual data were not available, we used aggregated data from publicly available reports. Of note, data from the 2015 report of the French cohort study [29] were originally used for the AIT analysis (study report available online [37]). However, in 2017, a complementary analysis of the risk of thyroiditis was released [33] that used a more appropriate methodology for identifying (autoimmune) thyroiditis cases: cases of thyroiditis among those who had previous indicators of thyroiditis were discarded; all cases of thyroiditis reported in both in- and out-patient settings were included; and dates of disease onset were more accurately identified. For AIT, the meta-analysis includes the results of the French cohort study released in 2017 [33]. However, since

the meta-analysis of AIT including the original results [29,34] was also performed according to the original statistical analysis plan, we present this analysis for reason of data integrity, in Data S3.

The following data were extracted for each study: numbers of subjects exposed and non-exposed to AS04-HPV-16/18; mean ages; countries of enrollment; length of follow-up; and numbers of cases of (autoimmune) thyroiditis, GBS, and IBD during the risk period (defined below).

2.3 Endpoint case definitions

Clinical definitions of AIT, GBS, and IBD events varied across studies, as detailed in Data S4. Briefly, the clinical studies [9-26] and the cluster randomized trial [31,32] used MedDRA terminology; while the two

cohort studies [29,30,33,34] used International Classification of Diseases, 10th Revision (ICD-10) codes. The complementary analysis of (autoimmune) thyroiditis in the French cohort study defined cases by the use of thyroid disorder drugs combined with either routine thyroid function tests and complementary examination of the thyroid, or hospital stays with ICD-10 codes for thyroiditis, or a "new full coverage for thyroiditis as a long-term illness" [33]. The UK cohort study [30] also used "Read codes" classification and only included cases that were confirmed by a medical review of the charts. The case-control study [35,36] identified cases of autoimmune disorders through a network of specialist centres at university and general hospitals across France.

In the French cohort study [29,33,34], autoimmune and nonautoimmune thyroiditis cases were included as these were not differentiated in the reports. Therefore, a sensitivity analysis of AIT was performed excluding the French cohort study data [33].

2.4 Risk periods

The post-vaccination risk periods were determined based on the onset of the disease (acute or insidious) and possible or known pathologic mechanisms [38]. Irrespective of the underlying mechanisms, it can be assumed that the development of autoimmunity generally requires several weeks - if a causal association between the event and vaccination existed - which is similar to the

classical timeframe of several weeks suggested for the onset of post-infectious autoimmune phenomena [38,39].

As the clinical courses of AIT and IBD are generally insidious, 2 years between vaccination and disease onset was selected. For trials with longer follow-up periods, only cases that occurred during the 2 years following first vaccination were included. For the French cohort study [29,33,34], only the total numbers of events and the mean follow-up periods were known. Further, events were reported in exposed subjects and nonexposed subjects, which included a combination of non-vaccinated subjects plus the pre-exposure periods of subjects who were subsequently vaccinated with AS04-HPV-16/18 or HPV-6/11/16/18. Events were therefore estimated as detailed in Data S5.

For GBS, a shorter risk period (42 days following each vaccination) was considered for the main analysis, based on its anticipated acute onset. This period is also recommended by the Brighton Collaboration GBS Working Group [40], based on epidemiological data collected after swine flu vaccination during 1976-1977 [41,42]. For the French cohort study [29,34], the time-to-onset of the two GBS cases reported among exposed individuals was unknown. We conservatively assumed that these occurred during the 42 days following a vaccination dose and estimated non-exposed cases as detailed in Data S5. A sensitivity analysis for GBS included cases that occurred during the 2 years following first vaccination.

2.5 Statistical methods

To harmonize results across studies, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the numbers of cases and total numbers of subjects for the combined clinical studies (Data S2); the cluster-randomized trial [31,32]; each of the two cohort studies (UK [30] and French [29,33,34]); and the case-control study [35,36].

Meta-analysis of rare events is challenging due to the inclusion of studies with no event in one or both arms ("single-zero" and "double-zero," respectively) [43,44]. Therefore, three meta-analysis methods to estimate ORs were used.

In the inverse-variance method (primary analysis), a continuity correction (please see Data S6) was applied to all studies to overcome the single- and double-zero issue. This method was chosen as the primary analysis because all studies could be included and study heterogeneity could be estimated. In the pooled estimate method, data from all the studies except the case-control study [35,36] were pooled and an overall estimate was computed [45]. The beta-binomial regression method can include single- and double-zero studies without using continuity correction. Two different beta-binomial models were analyzed, including, or not, the case-control study [35,36]. All statistical analyses were performed using SAS and StatXact-8.1 procedure for SAS.

3. RESULTS

3.1 Study population

In 21 studies (all apart from the case-control study [35,36]), 154 398 exposed (9.3%) and 1 504 322 non-exposed (90.7%) subjects were included (Table 1). This imbalance was due to the much larger nonexposed cohort in the French cohort study [29,34]. The population sizes varied widely between studies, with 19 studies accounting for 3.8% of subjects, and the two cohort studies adding 7.8% [30] and 88.4% [29,34]. Exposed subjects were older than non-exposed subjects (mean age 16.1 vs 13.7 years) due to the imbalance in the French cohort study [29,34].

Table 1 Cohort studies included in the meta-analysis

	Number of subjects			Mean age, y		
Study	Exposed	Non-exposed	Control(s)	Exposed	Non-exposed	Countries
Pooled individually randomized clinical trials[9-26] (n = 18)	21 455	20 613	Refer to Data S2	22.1	22.4	Various[a]
Cluster-randomized trial[b31,32]	12 400	8119	HBV	14.1	14.1	Finland
UK cohort study[b30]	64 998	64 994	None	15.3	15.4	UK
French cohort study[c29,34]	55 545	1 410 596	None	15.0	13.5	France
Total	154 398	1 504 322	-	16.1	13.7	Various[d]

Abbreviations: HBV, hepatitis B vaccine; UK, United Kingdom.
[a] Overall: Costa Rica (17.8%), Finland (11.4%), US (10.0%), The Philippines (7.6%), Thailand (5.6%), Brazil (5.5%), Mexico (5.4%), others (<5% each). [b] Only females were included.
[c] Subjects vaccinated with HPV-6/11/16/18 were excluded. For (autoimmune) thyroiditis, 53 372 exposed and 1 360 003 non-exposed subjects were considered following re-analysis.[33] [d] Overall: Exposed: UK (42.3%), France (36.0%), Finland (9.6%), others (<5% each); Control: France (93.8%), others (<5% each).

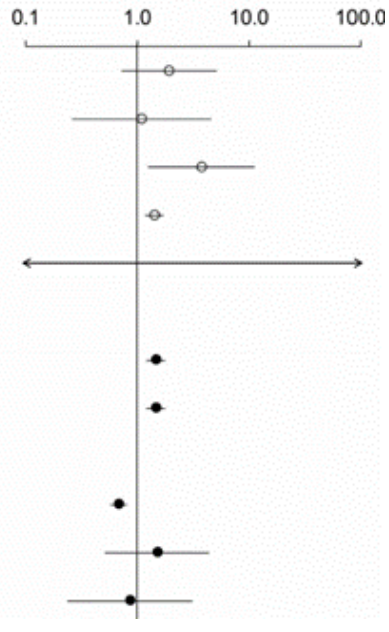
In the aggregated data study (case-control study) [35,36], 97 subjects with definite AIT were matched with 802 healthy controls. Only six subjects were exposed to AS04-HPV-16/18 vaccine, none of whom developed AIT (ie, all six were in the control group). Thirteen subjects with definite GBS were matched with 130 controls. None of these were vaccinated with AS04-HPV-16/18 during the preceding 42 days. IBD was not assessed in this study.

3.2 AIT

There were an estimated 140.6 cases of (autoimmune) thyroiditis among 152 225 exposed subjects (92/100 000) and 1971.5 cases among 1 453 729 non-exposed subjects (136/100 000). The OR using the inverse-variance method with continuity correction (primary method) was 1.46 (95% CI 1.22-1.76), the beta-binomial regression method without the case-control study [35,36] gave a similar OR estimate but had a broader CI, and the pooled OR estimate was 0.68 (95% CI 0.57-0.81) (Figure 1). Results using the original analysis of the French cohort study [29,34] are shown in Data S3 (primary method OR = 2.01 [95% CI 1.30-3.11]). The sensitivity analysis excluding the French cohort study [33] provided a primary method OR estimate of 2.15 (95% CI 1.12-4.14) (Data S7).

Figure 1 Risk of (autoimmune) thyroiditis during 2 years following the first dose of AS04-HPV-16/18.

	Exposed		Non-exposed		AIT (2 years)
	Events	Subjects	Events	Subjects	OR (95% CI)
Studies					
Pooled RCTs[9-26]	12	21,455	6	20,613	1.92 (0.72–5.12)
Cluster-randomized trial[31,32]	5	12,400	3	8,119	1.09 (0.26–4.57)
UK cohort study[30]	15	64,998	4	64,994	3.75 (1.24–11.30)
French cohort study[33]	108.6	53,372	1,958.5	1,360,003	1.41 (1.17–1.72)
Case–control study[35,36,*]	0	6	97.5	894	0.005 (0.00–1.49E+10)
Primary analysis: inverse-variance with continuity correction					
Fixed effect					**1.46 (1.22–1.76)**
Random effect	I^2 = 0.00%; P = 0.47				**1.46 (1.22–1.76)**
Secondary analyses					
Pooled estimate*	140.6	152,225	1,971.5	1,453,729	0.68 (0.57–0.81)
Beta-binomial regression (without case–control study[35,36])					1.50 (0.52–4.36)
Beta-binomial regression (with case–control study[35,36])					0.86 (0.24–3.10)



There were partial events for the French cohort study33due to the standardization of the follow-up time to 2 years; and for the case-control study35,36due to the continuity correction factor due to the "single-zero" cases in the exposed arm. AIT, autoimmune thyroiditis; AS04-HPV-

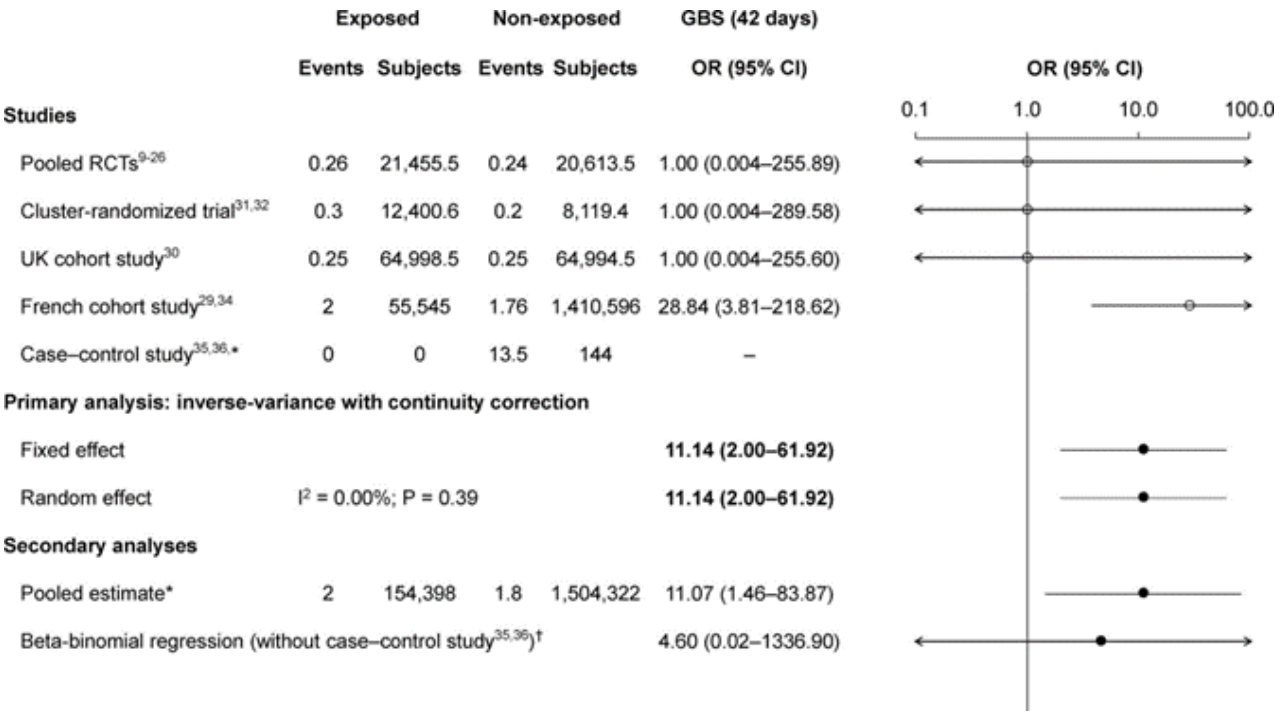
16/18, AS04-adjuvanted humanpapillomavirus-16/18 vaccine; CI, confidence interval; OR, odds ratio; RCTs, randomized controlled trials; UK, United Kingdom. *The case-control study was not included in the pooled estimate.

3.3 GBS

The only GBS cases were from the French cohort study [29,34], in which there were two cases of GBS in exposed subjects and 21 cases among non-exposed subjects (estimated to equate to 1.76 cases during an equivalent follow-up period in the non-vaccinated cohort).

The primary method OR was 11.14 (95% CI 2.00-61.92; Figure 2). The pooled estimate results were similar, while the beta-binomial regression method gave a lower estimate, although this was questionable because the low number of cases did not allow model convergence criteria to be met. When the risk period was increased to 2 years, the primary method OR was 3.83 (95% CI 1.08-13.57), with lower OR estimates using the other methods (Data S8).

Figure 2 Risk of GBS during 42 days following each dose of AS04-HPV-16/18.

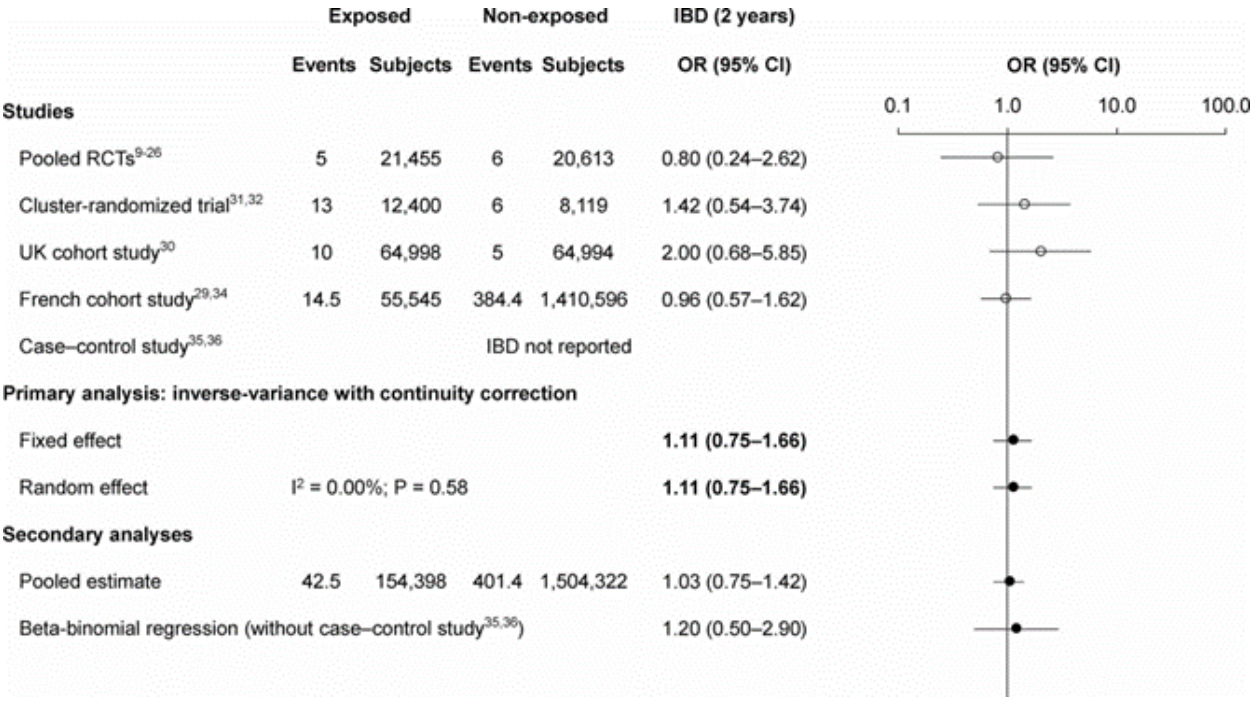


There are partial events for the non-exposed arm of the French cohort study[29,34] due to the standardization of the follow-up time to 42 days; and for the other studies due to the continuity correction factor due to the "single-zero" or "double-zero" cases. AS04-HPV-16/18, AS04-adjuvanted human papillomavirus-16/18 vaccine; CI, confidence interval; GBS, Guillain-Barré syndrome; OR, odds ratio; RCTs, randomized controlled trials; UK, United Kingdom. *The case-control study was not included in the pooled estimate. †The beta-binomial regression estimate is questionable because of convergence issue.

3.4 IBD

There were 42.5 cases of IBD among 154 398 exposed subjects (28/100 000) and 401.4 cases among 1 504 322 non-exposed subjects (27/100 000). The primary method OR was 1.11 (95% CI 0.75-1.66); the other methods gave similar estimates (Figure 3).

Figure 3 Risk of IBD during 2 years following the first dose of AS04-HPV-16/18.



There are partial events for the French cohort study29,34due to the standardization of the follow-up time to 2 years. AS04-HPV-16/18, AS04-adjuvanted human papillomavirus-16/18 vaccine; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; RCTs, randomized controlled trials; UK, United Kingdom.

4. DISCUSSION

This meta-analysis of AS04-HPV-16/18 studies was performed to study three autoimmune diseases (AIT, GBS, and IBD) that had been identified as safety signals in observational studies of AS04-HPV16/18 or HPV-6/11/16/18 vaccines [29,30]. The analysis included 18 RCTs [9-26], one cluster-randomized trial [31,32], two large observational, retrospective cohort studies [29,30,33,34], and one case-control study [35,36], which combined included approximately 150 000 exposed and 1 500 000 non-exposed subjects. Risk among females was assessed during pre-defined risk periods (2 years for AIT and IBD; 42 days for GBS).

The AIT primary analysis showed a slightly increased risk (OR = 1.46) of (autoimmune) thyroiditis following AS04-HPV-16/18 vaccination. This is likely a slight overestimation of risk given that this was

heavily influenced by the large French cohort study [33], for which we calculated an OR of 1.41 (95% CI 1.17-1.72) based on their crude data, but for which they reported an age-adjusted hazard ratio (HR) for (autoimmune) thyroiditis of 1.19 (95% CI 0.93-1.51). Despite this difference, both estimates are similar and <1.5 [46,47].

The other analysis methods showed ambiguous results for AIT due to differences in their weighting of data from different studies. The beta-binomial model estimate was similar to that from the primary analysis, but the pooled analysis estimate provided an OR of 0.68. This simple pooled estimate is biased because there was a much higher incidence of (autoimmune) thyroiditis in the French cohort study [33] than in the other studies (exposed: 203 vs 23-56/100 000; non-exposed: 144 vs 6-37/100 000) and the non-exposed cohort was much larger than the exposed cohort (1 360 003 vs 53 372) [33]. These differences in incidence probably reflect to differences in case definitions (Data S4), as the French cohort study [33] included all thyroiditis cases (ie, autoimmune and non-autoimmune), whereas the other studies specifically included AIT, and the French cohort study [33] included inpatient and outpatient cases. The French cohort study [33] therefore overcontributed to the incidence in the non-exposed cohort, resulting in a biased OR < 1. In additional to these limitations, most of the Hill's causal criteria for observational studies such consistency, specificity, coherence, analogy, experimental evidence, etc. were not met [48]. Similarly, the causality criteria on vaccine adverse events adopted by the Institute of Medicine [49] were also not encountered: the weight of epidemiological evidence is limited as well as and a plausible biological mechanism has not been identified [50]. Therefore, there is insufficient evidence to conclude a causal relationship between AS04-HPV-16/18 and AIT. Similar findings and conclusions have been published for HPV-6/11/16/18 [51].

The GBS results were driven by two cases among exposed individuals in the French cohort study [29,34], which were conservatively assumed to have occurred within 42 days following vaccination. The French cohort study [29] reported an adjusted HR of 8.14 (95% CI 1.70-38.92), while our OR estimate was much higher (28.84 [95% CI 3.91-218.62]), partly due to the different methodology and lack of age adjustment, but mainly because we conservatively assumed that both GBS cases occurred

with 42 days of vaccination. In our sensitivity analysis, when cases of GBS to 2 years were considered, our OR was much more in line with that reported in the French cohort study (3.83 [95% CI 1.08-13.57]) [29,34]. This was the only study that reported any GBS cases among AS04-HPV-16/18-vaccinated subjects. Given the low number of GBS cases (2/154398 exposed subjects) and the large CI, the risk of GBS following AS04-HPV-16/18 vaccination cannot be reliably quantified. Of note, a recent English study found no evidence of an increased risk of GBS during 3 months following vaccination (vs other periods) with AS04-HPV-16/18 (relative incidence 0.84; 95% CI 0.30-2.34) [52]. Further, no increased risk of GBS following vaccination with HPV-6/11/16/18 has been reported in other studies [51,53].

The IBD primary analysis did not show an increased risk following AS04-HPV-16/18 vaccination. This is in line with previous AS04-HPV16/18 pooled analyses [27,28]. In the current analysis, for every 100 000 subjects vaccinated vs not, IBD was reported for 28 vs 27. This is aligned with results from a 1-year database cohort study carried out prior to the introduction of HPV vaccines (2005) [54], in which 35 outpatient cases per 100 000 female adolescents were reported for presumed autoimmune "ulcerative colitis." These similarities support the lack of an increased risk of IBD with AS04-HPV-16/18.

Our results are also supported by a recent systematic review and meta-analysis that examined the risk of various autoimmune disorders after vaccination with any HPV vaccine [55]. They reported nonsignificant ORs between HPV vaccination and combined autoimmune disorders (1.00 [95% CI 0.95-1.06]), AIT (1.02 [0.91-1.14]), GBS (1.28 [0.65-2.52]), and IBD (1.05 [0.97-1.14]) [55]. They also examined various other autoimmune disorders and none had a significant association with HPV vaccination apart from a small increased risk of Hashimoto's thyroiditis (1.22 [1.09-1.36]) [55].

4.1 Strengths and limitations

This study highlights the potential value, as well as the limitations of, meta-analysis as a tool to investigate safety signals related to rare outcomes, which is challenging due to the inclusion of studies with no events in one or both arms [43,44]. The strength of the meta-analytical methods employed is that they allowed inclusion of all available information, regardless of the source or study design, resulting in a large sample size. However, as no quality of evidence assessment was performed prior

to the meta-analysis, the only factor contributing to the weight of each study was linked to the size of the population. The results of this meta-analysis were, therefore, driven by the two largest studies [29,30,34], which together contributed 78.1% of exposed and 98.1% of non-exposed subjects.

There was also heterogeneity between studies, in terms of study design, coding of medical events (Data S4), case ascertainment methods, outcome collection methods, outcome onset identification (eg, diagnosis date vs date of first clinical signs/symptoms), and subject ages. Despite these differences, heterogeneity - as assessed by the i^2 index (see Figures) - appeared to be very low, although the CIs were very broad, so the apparent lack of heterogeneity should be interpreted with caution.

Regarding study design, the AS04-HPV-16/18 exposed and nonexposed arms of the RCTs should have been balanced by randomization, but there could have been multiple unknown confounders between arms in the observational studies, which it is impossible to adjust for. Also, subjects in both arms could have received additional vaccines, with or without adjuvants, further complicating interpretation of the results. Another difference between the RCTs and observational cohort studies is the level of medical surveillance. In the RCTs, vaccinated and control subjects were followed up according to protocol-defined scheduled visits. However, in the two observational cohort studies [29,30,33,34], cases of autoimmune diseases were diagnosed in routine medical practice. By definition, the risk period in vaccinated subjects started at the time of the first dose, so vaccinated subjects in observational studies would have contact with a healthcare professional for subsequent dose(s), increasing the likelihood that an autoimmune disease would be diagnosed in the exposed vs non-exposed subjects. Such an “unmasking” effect has been reported in a post-licensure study of autoimmune diseases following HPV-6/11/16/18 vaccination [56].

The case-control study [35,36] had a very different design to the other studies, namely it identified girls with autoimmune diseases and matched them with age- and place of residence-matched controls. HPV vaccination status among these two groups was then ascertained. This study could capture events among a large cohort, but the number of subjects included in the study was quite small. It should also

be noted that around 1% and 14% of the "non-exposed" girls in the GBS and AIT analyses, respectively, received HPV-6/11/16/18.

Case definitions and ascertainment methods varied between studies. In the RCTs, all cases were fully medically validated, whereas in the French cohort study [29,33,34], there was no validation, and in the UK cohort study [30], there was an intermediate level of validation based on algorithms and patient medical data review. Exposure status validity also varied among studies. Exposure accuracy is close to 100% in clinical trials, but could be uncertain in observational studies. Exposure accuracy was improved in the UK cohort study [30] by including a historical (pre-vaccination implementation) non-exposed cohort. However, in the French cohort study [29,33,34], concomitant exposed and non-exposed cohorts could have reduced exposure accuracy.

Unfortunately, individual subject data (including time-to-event data) for the case-control study [35,36] and the French cohort study [29,33,34] were not available, which precluded adjustment for covariates. We had to calculate ORs rather than use their published HRs in order to have a common parameter for all studies. Also in the French cohort study [29,33,34], no distinction was made between AIT and non-autoimmune thyroiditis, limiting the clinical evaluation and interpretation of the findings regarding AIT. For the 42-day GBS analysis, the number of cases in the French cohort study control group had to be estimated from the overall data, assuming a constant incidence rate. It was assumed that early termination did not depend on exposure and, while this was a reasonable assumption for the other studies (even though subjects could withdraw at any time), this was not the case for the French cohort study. The switch from non-exposed to exposed status in the French cohort study [29,33,34] also resulted in a higher mean age for the exposed cohort.

Ideally, disease onset would be from the date of first symptoms, but this is not necessarily known, especially in retrospective database studies. Using diagnosis dates, some autoimmune cases that were diagnosed after vaccination may have had their first symptoms prior to vaccination. Conversely, some cases with first symptoms within 2 years or 42 days following vaccination might have been diagnosed after these windows and therefore not have been included.

Overall, our analysis illustrates that a meta-analysis can be powerful tool, but its strength is related to the quality of the input data.

5. CONCLUSIONS

This meta-analysis - including approximately 150 000 AS04-HPV16/18-exposed and 1 500 000 non-exposed subjects - did not indicate an increased risk of IBD. The results of the analysis showed a 1.5-fold increased risk of (autoimmune) thyroiditis, but based on existing epidemiological and mechanistic evidence, there is insufficient evidence to conclude a causal association with vaccination. No conclusion regarding the risk of GBS can be drawn as they were driven by two cases among exposed individuals, the times-to-onset of which were unknown. Although the GBS OR estimates were high, the number of cases was low and the 95% CIs were wide.

Considering the current results and ongoing surveillance of AS04-HPV-16/18 vaccination including other available post-marketing data and pooled analyses of clinical trial data [27,28], there is no evidence to confirm the hypothesis of an association between these autoimmune diseases and AS04-HPV-16/18 vaccination.

Given the overall safety data and the demonstrated high and sustained efficacy of AS04-HPV-16/18 against HPV-16/18 infection and cervical lesions [9-11,14,21,57-59], and the potential impact of high-risk HPV infection (ie, cervical lesions and cervical cancer), we conclude that that the results of the study does not modify the safety and benefit profile of the vaccine.

REFERENCES

1. European Medicines Agency. Cervarix. https://www.ema.europa.eu/en/medicines/human/EPAR/cervarix. Accessed January 10, 2019.
2. European Medicines Agency. Gardasil. https://www.ema.europa.eu/en/medicines/human/EPAR/gardasil. Accessed January 10, 2019.
3. European Medicines Agency. Gardasil 9. https://www.ema.europa.eu/en/medicines/human/EPAR/gardasil-9. Accessed January 10, 2019.
4. Garcon N, Chomez P, Van Mechelen M. GlaxoSmithKline adjuvant systems in vaccines: concepts, achievements and perspectives. Expert Rev Vaccines. 2007;6:723-739.
5. Perricone C, Colafrancesco S, Mazor RD, Soriano A, Agmon-Levin N, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: unveiling the pathogenic, clinical and diagnostic aspects. J Autoimmun. 2013;47:1-16.
6. Baker B, Eca Guimaraes L, Tomljenovic L, Agmon-Levin N, Shoenfeld Y. The safety of human papilloma virus-blockers and the risk of triggering autoimmune diseases. Expert Opin Drug Saf. 2015; 14:1387-1394.
7. Shoenfeld Y, Agmon-Levin N. 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. 2011;36:4-8.
8. Vera-Lastra O, Medina G, Cruz-Dominguez Mdel P, Jara LJ, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum. Expert Rev Clin Immunol. 2013;9:361-373.
9. Harper DM, Franco EL, Wheeler C, et al; GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet. 2004;364:1757-1765.
10. Harper DM, Franco EL, Wheeler CM, et al; HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet. 2006;367:1247-1255.
11. Paavonen J, Naud P, Salmeron J, et al; HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009;374:301-314.
12. Herrero R, Wacholder S, Rodriguez AC, et al; Costa Rica Vaccine Trial Group. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. Cancer Discov. 2011;1:408-419.

13. Medina DM, Valencia A, de Velasquez A, et al; HPV-013 Study Group. Safety and immunogenicity of the HPV-16/18 AS04adjuvanted vaccine: a randomized, controlled trial in adolescent girls. J Adolesc Health. 2010;46:414-421.
14. Skinner SR, Szarewski A, Romanowski B, et al; VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet. 2014;384:2213-2227.
15. Denny L, Hendricks B, Gordon C, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. Vaccine. 2013;31:5745-5753.
16. Sow PS, Watson-Jones D, Kiviat N, et al. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: a randomized trial in 10-25-year-old HIV-seronegative African girls and young women. J Infect Dis. 2013;207:1753-1763.
17. Leroux-Roels G, Haelterman E, Maes C, et al. Randomized trial of the immunogenicity and safety of the Hepatitis B vaccine given in an accelerated schedule coadministered with the human papillomavirus type 16/18 AS04-adjuvanted cervical cancer vaccine. Clin Vaccine Immunol. 2011;18:1510-1518.
18. Pedersen C, Breindahl M, Aggarwal N, et al. Randomized trial: immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. J Adolesc Health. 2012;50:38-46.
19. Schmeink CE, Bekkers RL, Josefsson A, et al. Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls. Vaccine. 2011;29:9276-9283.
20. Bhatla N, Suri V, Basu P, et al; Indian HPV Vaccine Study Group. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. J Obstet Gynaecol Res. 2010;36:123-132.
21. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 doubleblind, randomized controlled trial. Int J Gynecol Cancer. 2010;20: 847-855.
22. Kim YJ, Kim KT, Kim JH, et al. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10-14 years. J Korean Med Sci. 2010;25:1197-1204.
23. Ngan HY, Cheung AN, Tam KF, et al. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. Hong Kong Med J. 2010; 16:171-179.

24. Lim BK, Ng KY, Omar J, et al. Immunogenicity and safety of the AS04-adjuvanted human papillomavirus-16/18 cervical cancer vaccine in Malaysian women aged 18-35 years: a randomized controlled trial. Med J Malaysia. 2014;69:2-8.
25. Zhu F, Li J, Hu Y, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years. Hum Vaccin Immunother. 2014;10:1795-1806.
26. Kim SC, Song YS, Kim YT, et al. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15-25 years old healthy Korean women. J Gynecol Oncol. 2011;22:67-75.
27. Verstraeten T, Descamps D, David MP, et al. Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines. Vaccine. 2008;26:6630-6638.
28. Angelo MG, David MP, Zima J, et al. Pooled analysis of large and longterm safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiol Drug Saf. 2014;23: 466-479.
29. Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Vaccination contre les infections à HPV et risque de maladies auto-immunes : une étude Cnamts/ANSM rassurante - Point d'information. http://ansm.sante.fr/S-informer/Points-d-information-Points-dinformation/Vaccination-contre-les-infections-a-HPV-et-risque-de-mal adies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-inf ormation. Accessed August 26, 2016.
30. Willame C, Rosillon D, Zima J, et al. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus16/18 AS04-adjuvanted vaccine in the United Kingdom. Hum Vaccin Immunother. 2016;12:2862-2871.
31. Lehtinen M, Apter D, Baussano I, et al. Characteristics of a clusterrandomized phase IV human papillomavirus vaccination effectiveness trial. Vaccine. 2015;33:1284-1290.
32. GSK. An observational cohort study to assess the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix in the United Kingdom. Study number 116239 (EPI-HPV-040 VS UK). https://www.gsk-studyregister.com/study/ 4685. Accessed October 25, 2016.
33. Collin C, Miranda S, Zureik M, Dray-Spira R. HPV vaccines and the risk of thyroiditis in girls. Complementary analyses of the French cohort based on data from SNIIRAM of the ANSM in collaboration with CNAMTS; 2018.
34. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: a large cohort study of over 2 million young girls in France. Vaccine. 2017;35:4761-4768.

35. Grimaldi-Bensouda L, Rossignol M, Kone-Paut I, et al; PGRx-AD Study Group. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: six years of case-referent surveillance. J Autoimmun. 2017;79:84-90.
36. Grimaldi-Bensouda L, Aubrun E, Abenhaim L. Analysis of Cervarix® & Autoimmune Disorders Using the PGRx Information System. Data on File; 2015.
37. GSK. Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré syndrome, and inflammatory bowel disease following vaccination with Cervarix. https://www.gsk-studyregister.com/study/ 5822. Accessed February 7, 2019.
38. Tavares Da Silva F, De Keyser F, Lambert PH, Robinson WH, Westhovens R, Sindic C. Optimal approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines. Vaccine. 2013;31:1870-1876.
39. Allos BM. Association between campylobacter infection and GuillainBarré syndrome. J Infect Dis. 1997;176(Suppl 2):S125-S128.
40. Sejvar JJ, Kohl KS, Gidudu J, et al; Brighton Collaboration GBS Working Group. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29:599-612.
41. Langmuir AD. Guillain-Barré syndrome: the swine influenza virus vaccine incident in the United States of America, 1976–77: preliminary communication. J R Soc Med. 1979;72:660-669.
42. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol. 1979;110:105-123.
43. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23:1351-1375.
44. Bradburn MJ, Deeks JJ, Berlin JA, Russell LA. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007;26:53-77.
45. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-188.
46. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019;567:305-307.
47. XXX 2019. It's time to talk about ditching statistical significance. Nature. 21 MARCH 2019; 567:283 doi: 10.1038/d41586-019-00874-8.
48. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295-300.
49. Committee to Review Adverse Effects of Vaccines; Institute of Medicine, In Stratton K, Ford A, Rusch E, Wright Clayton E (Eds.) Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: National Academies Press (US); 2011.

50. Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. Immunity. 2010;33:492-503.
51. Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med. 2012;271:193-203.
52. Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barre syndrome after human papilloma virus vaccine: a self-controlled caseseries study in England. Vaccine. 2017;35:1729-1732.
53. Grimaldi-Bensouda L, Guillemot D, Godeau B, et al; PGRx-AID Study Group. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med. 2014;275:398-408.
54. Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J. 2007;26:979-984.
55. Jiang HY, Shi YD, Zhang X, et al. Human papillomavirus vaccination and the risk of autoimmune disorders: a systematic review and metaanalysis. Vaccine. 2019;37:3031-3039.
56. Jacobsen SJ, Sy LS, Ackerson BK, et al. An unmasking phenomenon in an observational post-licensure safety study of adolescent girls and young women. Vaccine. 2012;30:4585-4587.
57. Szarewski A, Poppe WA, Skinner SR, et al; HPV PATRICIA Study Group. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15-25 years with and without serological evidence of previous exposure to HPV-16/18. Int J Cancer. 2012;131:106-116.
58. De Carvalho N, Teixeira J, Roteli-Martins CM, et al. Sustained efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women. Vaccine. 2010;28:6247-6255.
59. Roteli-Martins CM, Naud P, De Borba P, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. Hum Vaccin Immunother. 2012;8:390-397.

Supplementary materials

Supporting information A. Supplementary systematic literature review – Final Report

Systematic literature review on Cervarix vaccination and autoimmune diseases

Final report

Rotterdam, January 7th, 2016

E.M. Bunge, PhD
J. Eeuwijk, MSc
F. van Kessel, MSc

Pallas health research and consultancy
www.pallashrc.com

A study commissioned by GlaxoSmithKline Vaccines

Summary

Background

Cervical cancer is the second leading cause of cancer-related death in women. Oncogenic human papillomavirus (HPV) plays a critical aetiological role in anogenital cancers[23].

Cervarix® is a bivalent vaccine, containing the virus-like particles (VLPs) of HPV16 and 18, the two types that cause 70% of cervical cancer worldwide, and even greater proportions of HPV-associated vulvar, vaginal, penile, anal, and oropharyngeal cancers[24]. The vaccine was first approved for use in 2007 and is currently licensed in at least 129 countries worldwide, including the US, Canada and European countries[25].

Recently, GSK has performed a study assessing the risk of autoimmune diseases (AID) in women aged 9-25 years within 1 year after the first dose of Cervarix vaccination (EPI-HPV-040 study). The results of the study did not show any evidence of increased risk for the two co-primary endpoints although an individual disease analysis showed an increased risk of autoimmune thyroiditis. In the meantime, the National French Agency of drugs safety (ANSM-Agence National de Sécurité du Médicament et de produits de santé) provided a report titled 'HPV vaccines and risk of AID: pharmaco-epidemiological study'. The results of this report show an increased risk of Guillain Barré Syndrome (GBS) and thyroiditis diseases after Cervarix vaccination.

GSK has planned to perform a meta-analysis including if possible the French's data. The meta-analysis will include GSK clinical trials and GSK pharmaco-epidemiological studies. However, to ensure that the meta-analysis will include any relevant studies, the MAH would like to check if additional studies assessing the risk of AID after Cervarix vaccination are made publicly available

Objectives

To identify in the literature potential studies assessing the risk of:

- Autoimmune thyroiditis
- Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD)
- Guillain Barré Syndrome (GBS)

following Cervarix vaccination.

Methods

The core of this review was a PubMed and Embase literature search. From the articles retrieved from PubMed and Embase, the relevant references were selected by a three-step selection procedure, based on: 1) screening of title and abstract, 2) screening of full text article, and 3) screening during data-extraction phase. During the second selection step, articles were critically appraised with the SIGN checklist. The search in PubMed and Embase yielded 519 unique hits.

An additional search was performed in Pubmed to check if articles were missed not mentioning autoimmune diseases (AID) in their title or abstract. This search yielded 485 hits.

Results

Studies were searched for any report on the occurrence of autoimmune thyroiditis, inflammatory bowel diseases, or Guillain Barré Syndrome in the follow-up period after Cervarix vaccination.

Three studies reported cases of one of these NOAD of interest after vaccination with Cervarix. The follow-up period ranged from twelve months to 36 months. In the first study, all participants received the HPV vaccine in various quantities and/or schedules. Ten subjects reported NOAD, consisting of thyroid disorders and one case each of diabetes mellitus, celiac disease and reactive arthritis. In the second study, no AID was reported in the HPV-16/18 vaccine group while in the control group one case of autoimmune thyroiditis was reported. In the third study, two cases of hypothyroidism were reported in the HPV-vaccine group and one case of hypothyroidism in the control group. All studies were funded or sponsored by GSK.

For the additional search on studies evaluating Cervarix but without mentioning AID in the abstract, no evidence tables were made as all relevant studies were funded or sponsored by GSK.

Eight studies were found in the NIH clinical trial database on bivalent HPV vaccine of which four studies were sponsored by GSK. All studies were still ongoing or recruiting.

Discussion

- Many studies reported number of SAE, NOCD or NOAD in general and did not specify AID.
- In some studies, the authors described only vaccine-related AID instead of giving an overview of all AID.
- Many studies were too small to detect rare AID, i.e. autoimmune thyroiditis, inflammatory bowel diseases or Guillain Barré Syndrome.

Contents

1. Background and objectives

1.1 Background

Cervical cancer is the second leading cause of cancer-related death in women. Oncogenic human papillomavirus (HPV) plays a critical aetiological role in anogenital cancers[23].

Cervarix® is a bivalent vaccine, containing the virus-like particles (VLPs) of HPV16 and 18, the two types that cause 70% of cervical cancer worldwide, and even greater proportions of HPV-associated vulvar, vaginal, penile, anal, and oropharyngeal cancers[24]. The vaccine was first

approved for use in 2007 and is currently licensed in at least 129 countries worldwide, including the United States (US), Canada and European countries[25].

Recently, GSK has performed a study assessing the risk of autoimmune diseases (AID) in women aged 9-25 years within 1 year after the first dose of Cervarix vaccination (EPI-HPV-040 study). The results of the study did not show any evidence of increased risk for the two co-primary endpoints (neuroinflammatory/ophthalmic diseases and other AID). An individual diseases analysis was performed for the following diseases: autoimmune thyroiditis, Crohn's disease and Type 1 diabetes mellitus. The results show an increased risk of autoimmune thyroiditis.

The EPI-HPV-040 study was a post-licensure commitment to the US Food and Drug Administration, a non-imposed post-authorisation safety study to the European Medicines Agency and a Post-Authorisation Measure. This study has been submitted to Committee for Medicinal Products for Human Use (CHMP) rapporteur for approval in June 2015.

In the meantime, the National French Agency of drugs safety (ANSM-Agence National de Sécurité du Médicament et de produits de santé) provided a report titled 'HPV vaccines and risk of AID: pharmaco-epidemiological study'. The results of this report show an increased risk of Guillain Barré Syndrome (GBS) and thyroiditis diseases after Cervarix vaccination.

The CHMP has requested to marketing authorisation holder (MAH) to explore the data of the French study (ANSM report). In the meantime, GSK has committed to CHMP to perform a meta-analysis including if possible the French's data. The meta-analysis will include GSK clinical trials and GSK pharmaco-epidemiological studies.

However, to ensure that the meta-analysis will include any relevant studies, the MAH would like to check if additional studies assessing the risk of AID after Cervarix vaccination are made publicly available

1.2 Research objectives

To identify in the literature potential studies assessing the risk of:

- Autoimmune thyroiditis
- Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD)
- Guillain Barré Syndrome

following Cervarix vaccination.

1.2 Geographical scope

The geographical scope was worldwide.

2. Methods

In order to meet the objectives as outlined in section 1.2, Pallas performed a systematic review of the literature. A systematic review is a method to collect, critically appraise, and summarize the best available evidence in a transparent and systematic way using generally accepted evidence-based principles.

Pallas finalized the search strategies, selected literature based on title and abstracts, critically appraised full-text articles based on checklists for Evidence Based Medicine, and summarized the evidence in consultation with GSK Vaccines. Results were documented in evidence tables and exclusion tables in order to ensure transparency and reproducibility of the results. The review steps are further outlined below.

2.1 Analysis international peer reviewed literature

The core of this review was a PubMed literature search, complemented with a search Embase.

2.1.1 Literature search

PubMed

In order to find relevant articles for the objective, Pallas made a search string consisting of:

1. Terms for disease
    a. Autoimmune thyroiditis
    b. Inflammatory bowel diseases, including ulcerative colitis and Crohn's disease
    c. Guillain Barré Syndrome
    d. Autoimmune disease in general
2. Terms for Cervarix vaccination

#1A: Autoimmune thyroiditis

"Thyroiditis, Autoimmune"[Mesh] OR autoimmune thyroiditis[tiab] OR auto-immune thyroiditis[tiab] OR "Hashimoto Disease"[Mesh] OR hashimot*[tiab] OR "struma lymphomatosa"[tiab] OR Autoimmune Thyroiditides[tiab] OR Lymphocytic Thyroiditis[tiab] OR Lymphomatous Thyroiditis[tiab] OR Lymphocytic Thyroiditides[tiab] OR Lymphomatous Thyroiditides[tiab]

#1B: Inflammatory bowel disease

"Crohn Disease"[Mesh] OR Crohn*[tiab] OR "Colitis,Ulcerative"[Mesh] OR ulcerative colitis[tiab] OR "Inflammatory bowel diseases"[Mesh] OR Inflammatory Bowel Disease[tiab] OR Colitis Gravis[tiab] OR Idiopathic Proctocolitis[tiab]

#1C: Guillain Barré Syndrome

"Guillain-Barre Syndrome"[Mesh] OR Guillain-Barre Syndrome*[tiab] OR "Miller Fisher Syndrome"[Mesh] OR miller fisher syndrome*[tiab] OR Acute Inflammatory Polyneuropathy[tiab] OR Guillain-Barré Syndrome[tiab] OR Acute Inflammatory Polyradiculoneuropathy[tiab] OR Landry-Guillain-Barre Syndrome[tiab] OR Landry Guillain Barre Syndrome[tiab] OR Acute Autoimmune Neuropathy[tiab] OR Acute Infectious Polyneuritis[tiab] OR Ophthalmoplegia, Ataxia and Areflexia Syndrome[tiab]

#1D: Autoimmune disease (general terms)

"Autoimmune Diseases"[Mesh] OR autoimmune[tiab] OR auto-immune[tiab]

#2. Cervarix vaccination

Cervarix[tw] OR "human papillomavirus vaccine, L1 type 16, 18"[Supplementary Concept] OR HPV L1 vaccine, bivalent 16,18[tiab] OR HPV-16/18 vaccine[tiab] OR human papillomavirus vaccine L1 16,18[tiab] OR HPV-16/18 AS04-adjuvanted vaccine[tiab] OR "Papillomavirus Vaccines"[Mesh] OR Human Papillomavirus Vaccine*[tiab] OR HPV Vaccine*[tiab]

Limits

No limits were applied.

Number of hits

The combination of these search strings, i.e. #1 (1A OR 1B OR 1C OR 1D) AND #2, yielded 112 hits (dd. November 18th 2015).

Embase

The Embase search was based on the same search strings as the PubMed search.

#1A: Autoimmune thyroiditis

'autoimmune thyroiditis'/exp OR ('autoimmune thyroiditis' OR 'auto-immune thyroiditis'):ti,ab OR 'Hashimoto disease'/exp OR (hashimot* OR 'struma lymphomatosa' OR 'Autoimmune Thyroiditides' OR 'Lymphocytic Thyroiditis' OR 'Lymphomatous Thyroiditis' OR 'Lymphocytic Thyroiditides' OR 'Lymphomatous Thyroiditides'):ti,ab

#1B: Inflammatory bowel disease

'Crohn disease'/exp OR Crohn*:ti,ab OR 'ulcerative colitis'/exp OR 'ulcerative colitis':ti,ab OR 'inflammatory bowel disease'/exp OR ('Inflammatory Bowel Disease' OR 'Colitis Gravis' OR 'Idiopathic Proctocolitis'):ti,ab

#1C: Guillain Barré Syndrome

'Guillain Barre syndrome'/exp OR ('Guillain-Barre Syndrome' OR 'Guillain-Barré Syndrome' OR 'miller fisher syndrome' OR 'Acute Inflammatory Polyneuropathy' OR 'Acute Inflammatory Polyradiculoneuropathy' OR 'Landry Guillain Barre Syndrome' OR 'Acute Autoimmune Neuropathy' OR 'Acute Infectious Polyneuritis' OR 'Ophthalmoplegia, Ataxia and Areflexia Syndrome'):ti,ab

#1D: Autoimmune disease (general terms)

'autoimmune disease'/exp OR (autoimmune OR auto-immune):ti,ab

#2 Influenza

'Cervarix'/exp OR ('human papillomavirus vaccine L1 type 16 18' OR 'HPV-16/18 vaccine' OR 'hpv-16/18 vaccine' OR 'HPV-16/18 AS04-adjuvanted vaccine'):ti,ab OR 'Wart virus vaccine'/exp OR ('Human Papillomavirus Vaccine' OR 'human papillomavirus vaccines'):ti,ab OR (hpv AND vaccine*:ti,ab)

Limits

No limits were applied.

Number of hits

The combination of these search strings, i.e. #1 (1A OR 1B OR 1C OR 1D) AND #2, yielded 488 hits (dd. November 18th 2015).

2.1.2 Additional search

An additional search was performed to check if articles were missed not mentioning autoimmune diseases in their title or abstract. References already included in the original search or hand search were excluded from the additional search.

PubMed

Cervarix vaccination

Cervarix[tw] OR "human papillomavirus vaccine, L1 type 16, 18"[Supplementary Concept] OR HPV L1 vaccine, bivalent 16,18[tiab] OR HPV-16/18 vaccine[tiab] OR human papillomavirus vaccine L1 16,18[tiab] OR HPV-16/18 AS04-adjuvanted vaccine[tiab] OR hpv bivalent vaccine[tiab]) OR 16 18 as04[tiab]Limits

Limits

No limits were applied.

Number of hits

The search yielded 485 hits (dd. December 3rd 2015).

2.13 Selection procedure

From the articles retrieved from PubMed and Embase, the relevant references were selected by a three-step selection procedure, based on:

1. Screening of title and abstract (first selection step): In this step, articles that seemed to contain relevant data for the objectives based on the title and abstract were selected for full-text screening, while articles that did not seem to contain relevant data were not selected. In case of doubt, the article was checked full-text in the second selection step.
   - Inclusion criteria:
     - Data relevant for the objectives.
   - Reasons for exclusion were:
     - Studies in boys;
     - Studies on Auto-inflammatory Syndrome induced by Adjuvants (ASIA);
     - Populations pre-existing AID;
     - Studies on Gardasil.

2. Screening of full article (second selection step): In this step the full text of the articles selected in step 1 were assessed. First it was determined whether the article answered one of the review questions. If this was the case, then the article was critically appraised using a standard set of criteria (see section 2.1.5). Reasons for exclusion in this stage were:

- A narrative review (e.g. no methods section that described the way the authors collected the literature);
- Non-pertinent publication type
- Gardasil or non-Cervarix 2vHPV vaccine (i.e. vaccine produced by a Chinese Pharmaceutical company);
- Phase I or phase II studies with small sample size and short follow-up period;
- Insufficient methodological quality;
- No quantitative data could be retrieved from the article.

3. Screening during data-extraction phase (third selection step): further scrutiny of the article during the data-extraction phase might lead to exclusion:
   - During the screening of full articles systematic reviews and meta-analysis were selected. The reference lists of these articles were checked on possibly missed relevant articles and thereafter excluded.
   - Systemic reviews and meta-analysis that were checked were:
     - Agorastos, T., et al., 2009
     - Angelo, M.G., et al., 2014
     - De Vincenzo, R.C., et al., 2014
     - Macartney, K.K., et al., 2013
     - Medeiros, L.R., et al., 2009
     - Pellegrino. P., et al., 2014
     - Stillo, M.P., et al., 2015

Recording of process

The process of selection and inclusion and exclusion of articles was registered in an Endnote library by one of the researchers. In this way, a clear overview of all selection steps was maintained at all phases and this assured reproducibility of the results.

Figure 1a gives a schematic overview of the selection procedure for the original objectives, including the number of articles found and retrieved from PubMed and Embase and the final number of articles included. Figure 1b gives a schematic overview of the selection procedure performed on the results of the additional search in PubMed (see 2.1.2).

Figure 1a. Selection procedure PubMed and Embase

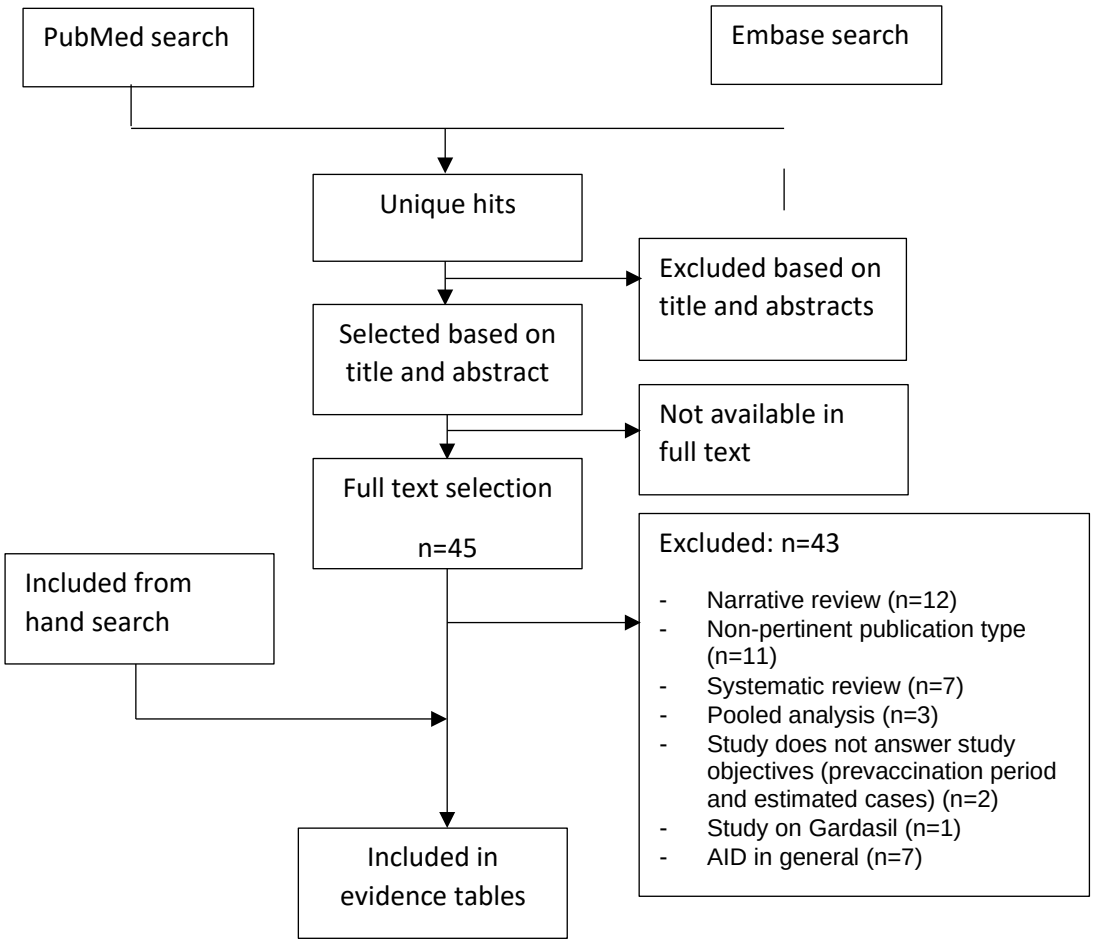
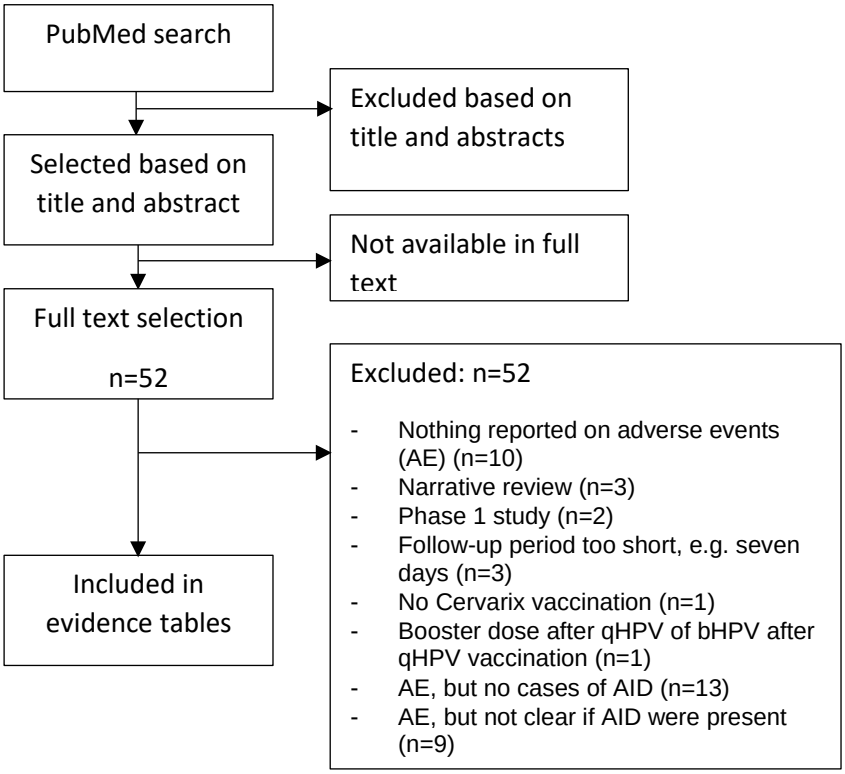

PubMed search
Embase search
Unique hits
Excluded based on title and abstracts
Selected based on title and abstract
Not available in full text
Full text selection
n=45
Included from hand search
Excluded: n=43
- Narrative review (n=12)
- Non-pertinent publication type (n=11)
- Systematic review (n=7)
- Pooled analysis (n=3)
- Study does not answer study objectives (prevaccination period and estimated cases) (n=2)
- Study on Gardasil (n=1)
- AID in general (n=7)
Included in evidence tables

Figure 1b. Selection procedure additional search in PubMed



2.1.4 Critical appraisal of the literature

The Pallas team critically appraised the methodological quality of the articles using the SIGN checklist (appendix I).

2.1.4 Data extraction

Relevant articles on the occurrence of autoimmune thyroiditis, IBD, or GBS in the follow-up period after Cervarix vaccination identified during the literature search in PubMed and Embase (see 2.1.1) were summarised using standardised data-extraction tables (evidence tables) in Word (appendix II).

In addition, a list is made of studies reporting the number of serious adverse events (SAE), new-onset chronic disease (NOCD) or new-onset autoimmune disease (NOAD), but without mentioning the exact number of the AIDs of interest in the treatment arms(appendix III). These articles are not summarized in evidence tables.

As agreed with GSK, for the additional search, no evidence tables were made as all relevant studies were funded or sponsored by GSK. Three lists were made (appendix IV):

- A list of studies presenting the number of SAE during the follow-up period , including the number of AID;

- A list of studies presenting the number of SAE during the follow-up period, but without further specifying which disease were found;
- A list of studies presenting the number of NOAD, but without further specifying the type of AID.

2.1.5 Quality control

The following quality control measures were put in place:

- The first 30% of titles and abstracts were screened in duplicate by two independent researchers from Pallas. The results were compared and discussed before the remaining references were assessed by one researcher. The differences between the two researchers were less than 5% with regard to the articles screened in duplicate.
- The first 10% of full text articles were critically appraised in duplicate by two independent researchers from Pallas. The results were compared and discussed early in the process. Any disagreements were adjudicated by a third researcher when necessary. The differences between the two researchers were less than 5% with regard to the articles screened in duplicate.
- Data extraction: the evidence tables were compiled by junior researchers and reviewed by the senior researcher of the project.

2.2 Grey and other literature search

The focus of this literature review was on peer-reviewed articles with sufficient quality, hence no grey literature search was performed. The National Institutes of Health (NIH) website 'www.clinicaltrials.gov' was checked (dd. January 4th 2016) for ongoing trials on Cervarix vaccination. In total, 243 trials were found in the database with a search for 'cervical cancer vaccine'. Studies with an unknown status were excluded.

In addition, the report entitled 'Vaccins anti-HPV et risque de maladies autoimmunes: étude pharmacoépidémiology by the Agence Nationale de sécurité du Médicament et des produits de santé' published in September 2015, was checked for relevant references.

3. Results

In total three articles were included in this review. In all three, thyroid disease was reported after Cervarix vaccination as SAE [26-28]. Inflammatory bowel disease or Guillain Barré Syndrome were not reported.

The results will be summarized in this chapter. More detailed results are presented in the evidence tables in Appendix II.

3.1 Cervarix vaccination and autoimmune disease

In three studies, new-onset autoimmune diseases were reported after vaccination with Cervarix. Two studies were multi-country studies[26,27]. One study was performed in Brazil [28]. The follow-up period ranged from twelve months to 36 months.

In the study of Romanowski et al., healthy girls and young women aged 9 to 25 years were randomized to one of the four HPV-vaccination groups. Group 1 received three doses of HPV-16/18 (20 µg/20 µg) vaccine at months 0, 1 and 6, group 2 received two doses of HPV-16/18 (20 µg/20 µg) vaccine at months 0 and 6, group 3 received two doses of HPV-16/18 (40 µg/40 µg) vaccine at months 0 and 6 and group 4 received two doses of HPV-16/18 (40 µg/40 µg) vaccine at months 0 and 2. In both group 1 and 2, 1.3% (three cases) reported NOAD while in both group 3 and 4, 0.8% (two cases) reported NOAD. NOADs consisted of thyroid disorders and one case each of diabetes mellitus, celiac disease and reactive arthritis. It was not stated in which groups the thyroid disorders were reported[27].

In another study, conducted in 57 centres in twelve different countries, healthy girls aged 10–14 years were randomized to receive HPV-16/18 vaccine in a 0-, 1-, 6-month schedule or a hepatitis A vaccine . One SAE in the control group was autoimmune thyroiditis. No autoimmune-diseases were reported in the HPV-16/18 vaccine group[26].

In the study of Naud et al., healthy women aged 15-25 years were recruited and randomized to receive HPV-16/18 vaccine or placebo. In the HPV-vaccine group, 0.9% (2 cases) reported hypothyroidism between 77 months to 114 months post initial vaccination while 0.5% (1 case) from the placebo group reported hypothyroidism between 77 months to 114 months post initial vaccination [28].

Table 1. Included studies with reported new-onset autoimmune disease

Ref Trialnr	**Country**	**Vaccine schedule**	**n**	**Follow-up**	**Outcome**
Romanowski, 2011 NCT00541970	Canada, Germany	1) 3-dose 20/20 M0,1,6 2) 2-dose 20/20 M0,6 3) 2-dose 40/40 M0,6 4) 2-dose 40/40 M0,2	960 1) n=239 2) n=240 3) n=241 4) n=240	24 months	Subjects with NOAD, % (n) 1) 1.3% (3) 2) 1.3% (3) 3) 0.8% (2) 4) 0.8% (2) Reported NOAD consisted of thyroid disorders and one case each of diabetes mellitus, celiac disease and reactive arthritis
Rivera Medina, 2010 NCT00196924	Australia, Colombia, the Czech Republic, France, Germany, Honduras, Korea,	1) HPV-16/18 vaccine: 20mg each of HPV-16 and HPV-18 L1 proteins in a 0-, 1-, 6-month schedule	2,067 1) n=1,035 2) n=1,032	12 months	Reported SAEs between months 7 and 12, n 1) 13 2) 10 One SAE in the control group was autoimmune thyroiditis.

	Norway, Panama, Spain, Sweden, Taiwan	2) HAV vaccine: 360 ELISA units inactivated HAV antigen			No AID were reported in the HPV-16/18 vaccine group
Naud, 2014 NCT00196924	Brazil	1) HPV-16/18 vaccine at 0, 1, and 6 mo 2) placebo ($Al[OH]_3$) at 0, 1, and 6 mo	437 1) n=224 2) n=213	36 months	Women reporting hypothyroidism between 77 mo and up to 113 mo post initial vaccination, % (95% CI); n 1) 0.9 (0.1-3.2); 2 2) 0.5 (0.0-2.6); 1
AID: autoimmune disease; $Al[OH]_3$: Aluminium hydroxide; CI: Confidence Interval; ELISA: enzyme-linked immunosorbent assay; HAV: hepatitis A virus; HPV: Human papillomavirus; mo: months; NOAD: new-onset autoimmune disease; SAE: serious adverse event					

All studies were sponsored or funded by GSK

3.2 Grey and other literature search

In total, 243 trials on cervical cancer vaccine were found in the NIH clinical trial database. Eight studies were found on a bivalent HPV vaccine and still ongoing or recruiting subjects.

One study is an extended follow-up (total of up to 10 years of follow-up) of young women in Costa Rica who received vaccination against HPV 16 and 18 and unvaccinated controls (NCT00867464). Women who were originally in the control arm were offered the HPV-16/18 vaccine at crossover and will also be invited for additional follow-up.

In four studies, subjects were followed after vaccination with Cervarix (NCT00779766, NCT01190176, NCT01190189, NCT01249365). These studies are sponsored by GSK. One study is active, but not recruiting. Three studies are still recruiting subjects.

The other three studies were from a Chinese pharmaceutical company (NCT01735006, NCT01356823, NCT02562508).

The report on autoimmune disease after HPV vaccine by the Agence Nationale de sécurité du Médicament et des produits de santé' did not yield any new references.

4. Discussion

4.1 Discussion of the results

Studies were searched for any report on the occurrence of autoimmune thyroiditis, inflammatory bowel diseases, or Guillain Barré Syndrome in the follow-up period after Cervarix vaccination.

Three studies reported cases of one of these NOAD of interest after vaccination with Cervarix. The follow-up period ranged from twelve months to 36 months. In the first study, all participants received the HPV vaccine in various quantities and/or schedules. Ten subjects reported NOAD, consisting of thyroid disorders and one case each of diabetes mellitus, celiac disease and reactive arthritis. In the second study, no AIDs were reported in the HPV-16/18

vaccine group while in the control group one case of autoimmune thyroiditis was reported. In the third study, two cases of hypothyroidism were reported in the HPV-vaccine group and one case of hypothyroidism in the control group. All studies were funded or sponsored by GSK.

For the additional search on studies evaluating Cervarix but without mentioning AID in the abstract, no evidence tables were made as all relevant studies were funded or sponsored by GSK

Eight studies were found in the NIH clinical trial database on bivalent HPV vaccine of which four studies were sponsored by GSK. All studies were still ongoing or recruiting.

4.2 Limitations of the studies

- Many studies reported number of SAE, NOCD or NOAD in general and did not specify AID.
- In some studies, the authors described only vaccine-related AID instead of giving an overview of all AID.
- Many studies were too small to detect rare AID, i.e. autoimmune thyroiditis, inflammatory bowel diseases or Guillain Barré Syndrome.

Abbreviations

AID	Autoimmune disease
Al[OH]3	Aluminium hydroxide
ASIA	Auto-inflammatory Syndrome induced by Adjuvants
CD	Crohn's disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
ELISA	Enzyme-linked immunosorbent assay
GBS	Guillain Barré Syndrome
HAV	Hepatitis A virus
HPV	Human papillomavirus
IBD	Inflammatory bowel diseases,
MAH	marketing authorisation holder
mg	Milligram
mo	Months
NIH	National Institutes of Health
NOAD	New-onset autoimmune disease
NOCD	New-onset chronic disease
SAE	Serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
UC	Ulcerative colitis
US	United States
VLP	Virus-like particles

References

1. Miltz A, Price H, Shahmanesh M, et al. Systematic review and meta-analysis of L1-VLP-based human papillomavirus vaccine efficacy against anogenital pre-cancer in women with evidence of prior HPV exposure. PLoS One 2014;**9**(3):e90348.
2. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;**30 Suppl 5**:F123-38.
3. Angelo MG, David MP, Zima J, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiology and drug safety 2014;**23**(5):466-79.
4. Rivera Medina DM, Valencia A, de Velasquez A, et al. Safety and Immunogenicity of the HPV-16/18 AS04-Adjuvanted Vaccine: A Randomized, Controlled Trial in Adolescent Girls. Journal of Adolescent Health 2010;**46**(5):414-21.
5. Romanowski B, Schwarz TF, Ferguson LM, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: Results from a randomized study. Human vaccines 2011;**7**(12):1374-86.
6. Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Human vaccines & immunotherapeutics 2014;**10**(8):2147-62.

APPENDIX I SIGN Checklists[1]

S I G N	**Methodology Checklist 2: Controlled Trials**		
Study identification (*Include author, title, year of publication, journal title, pages*)			
Guideline topic:		Key Question No:	Reviewer:
Before completing this checklist, consider: 1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+ 2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.			
Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):			
Section 1: Internal validity			
In a well conducted RCT study…		***3. Does this study do it?***	
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐	
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐	
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐	
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐	
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say ☐	
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐	

[1] SIGN: http://www.sign.ac.uk/methodology/checklists.html

1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

Section 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? Code as follows:	High quality (++) ☐ Acceptable (+) ☐ Low quality (-) ☐ Unacceptable – reject (0) ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

S I G N	**Methodology Checklist 3: Cohort studies**		
Study identification (*Include author, title, year of publication, journal title, pages*)			
Guideline topic:		Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question □ 2. Other reason □ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***3. Does this study do it?***	
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ Can't say ☐	No ☐
Selection of subjects			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes ☐ Can't say ☐	No ☐ Does not apply ☐
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes ☐	No ☐ Does not apply ☐
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes ☐ Can't say ☐	No ☐ Does not apply ☐
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.		
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes ☐ Can't say ☐	No ☐ Does not apply ☐

ASSESSMENT			
1.7	The outcomes are clearly defined.	Yes ☐ Can't say ☐	No ☐

1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes ☐ Can't say ☐	No ☐ Does not apply ☐
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes ☐ Can't say ☐	No ☐
1.10	The method of assessment of exposure is reliable.	Yes ☐ Can't say ☐	No ☐
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes ☐ Can't say ☐	No ☐ Does not apply ☐
1.12	Exposure level or prognostic factor is assessed more than once.	Yes ☐ Can't say	No ☐ Does not apply
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes ☐ Can't say ☐	No ☐
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes ☐	No ☐
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) ☐ Acceptable (+) ☐ Low quality (-) ☐ Unacceptable – reject (0) ☐	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes ☐	No ☐
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

SIGN	**Methodology Checklist 4: Case-control studies**

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a case-control study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question □ 2. Other reason □ (please specify):

Section 1: Internal validity

In an well conducted case control study:		***3. Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
Selection of subjects		
1.2	The cases and controls are taken from comparable populations.	Yes ☐ No ☐ Can't say ☐
1.3	The same exclusion criteria are used for both cases and controls.	Yes ☐ No ☐ Can't say ☐
1.4	What percentage of each group (cases and controls) participated in the study?	Cases: Controls:
1.5	Comparison is made between participants and non-participants to establish their similarities or differences.	Yes ☐ No ☐ Can't say ☐
1.6	Cases are clearly defined and differentiated from controls.	Yes ☐ No ☐ Can't say ☐
1.7	It is clearly established that controls are non-cases.	Yes ☐ No ☐ Can't say ☐
ASSESSMENT		

1.8	Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment.	Yes ☐ Can't say ☐	No ☐ Does not apply ☐
1.9	Exposure status is measured in a standard, valid and reliable way.	Yes ☐ Can't say ☐	No ☐
CONFOUNDING			
1.10	The main potential confounders are identified and taken into account in the design and analysis.	Yes ☐ Can't say ☐	No ☐
STATISTICAL ANALYSIS			
1.11	Confidence intervals are provided.	Yes ☐	No ☐
Section 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) ☐ Acceptable (+) ☐ Low quality (-) ☐ Unacceptable – reject (0) ☐	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes ☐	No ☐
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above..		

APPENDIX II Evidence tables

Reference **Country** **NCT registration number**	**Setting** **Study design** **Study period**	**Population** **Sample size** **Follow-up period**
Romanowski B., Human Vaccines, 2011 Canada, Germany NCT00541970	**Setting:** Twenty-one centers in Canada and Germany **Study design**: Phase I/II, partially-blind, controlled, randomized, age-stratified, parallel group trial **Study period**: October 2007 – May 2010	**Population**: Healthy girls and young women aged 9 to 25 years at the time of first vaccination **Exclusion criteria:** Autoimmune disease or immunodeficiency, more than 14d of immune-suppressants of immune-modifying drugs within 6 mo prior to the first vaccine dose, previously received HPV vaccine, AS04 adjuvant or 3-*O*-desacy-4'-monophosphoryl lipid A, pregnant or breast-feeding **Sample size**: Enrolled n=961, randomized and vaccinated n=960 of which n=845 had a follow-up of 24 months Participants were randomized to one of the four groups: -3-dose 20/20 M0,1,6: n=239 -2-dose 20/20 M0,6: n=240 -2-dose 40/40 M0,6: n=241 -2-dose 40/40 M0,2: n=240

Vaccine dose **Follow-up** **Outcome detection and definition**	**Results**	**Comments**
Vaccine dose: - Three doses of HPV-16/18 (20 µg/20 µg) vaccine at Months 0, 1 and 6 (i.e., the licensed vaccine formulation and schedule) (Group 20/20F M0,1,6) - Two doses of HPV-16/18 (20 µg/20 µg) vaccine at Months 0 and 6 (Group 20/20F M0,6) - Two doses of HPV-16/18 (40 µg/40 µg) vaccine at Months 0 and 6 (Group 40/40F M0,6) - Two doses of HPV-16/18 (40 µg/40 µg) vaccine at Months 0 and 2 (Group 40/40F M0,2) **Follow-up:** 24 months **Outcome detection and definition**: NOAD occurring through month 24 were documented. NOAD (potential autoimmune events, which excluded allergy-related events or isolated signs and symptoms) were identified by comparing all reported AEs with a pre-defined list of potential chronic diseases derived from the Medical Dictionary for Regulatory Activities	Subjects with new onset of autoimmune-disease, % (n) 3-dose 20/20 M0,1,6: 1.3% (3) 2-dose 20/20 M0,6: 1.3% (3) 2-dose 40/40 M0,6: 0.8% (2) 2-dose 40/40 M0,2: 0.8% (2) Reported new onset autoimmune diseases consisted of thyroid disorders and one case each of diabetes mellitus, celiac disease and reactive arthritis	- Not clear in which groups thyroid disorders occurred - Relatively small sample size - Trial was partially blinded within the 2-dose schedule group (observers were blinded to group assignment) and open in 3-dose schedule group - No main institute as 21 centres were involved - Limited information on documentation NOAD
AE: adverse events; HPV: human papillomavirus; M/mo: month; NOAD: new onset auto-immune disease		

Reference **Country** **NCT registration number**	**Setting** **Study design** **Study period**	**Population** **Sample size** **Follow-up period**
Rivera Medina D., Journal of adolescent health, 2010 Australia, Colombia, the Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden, Taiwan NCT00196924	**Setting:** Fifty-seven centers in Australia, Colombia, the Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden, Taiwan **Study design**: Phase III, observer-blind, multicenter, randomized, parallel group, controlled study **Study period**: June 2004 – August 2005	**Population**: Healthy girls aged 10–14 years **Exclusion criteria:** Immunodeficiency, history of allergic disease likely to be exacerbated by a vaccine component, known acute or chronic clinically significant neurologic, hepatic, or renal functional abnormality, history of chronic conditions requiring treatment, or acute disease at enrolment **Sample size**: Enrolled n=2,067, compliance with 3-dose schedule was 98.2% of which n=2,023 had a follow-up of 12 months Participants were randomized to one of the two groups: -HPV-16/18 vaccine: n=1,035 -Control vaccine (HAV vaccine): n=1,032

Vaccine dose **Follow-up** **Outcome detection and definition**	**Results**	**Comments**
Vaccine dose: - HPV-16/18 vaccine: 20mg each of HPV-16 and HPV-18 L1 proteins, self-assembled as virus like particles (VLP), adjuvanted with the Adjuvant System AS04 (comprising 500 mg of aluminum hydroxide and 50 mg of the immunostimulatory molecule, 3-O-desacyl-4' monophosphoryl lipid A) in a 0-, 1-, 6-month schedule - HAV vaccine: 360 ELISA units inactivated HAV antigen and 250 mg aluminum as aluminum hydroxide **Follow-up:** At months 0, 1, 2, 6, 7 with a telephone call at month 12 **Outcome detection and definition**: SAE, reported up to month 12	Between months 7 and 12, 13 girls and 10 girls reported SAEs in the HPV-16/18 vaccine and control groups, respectively. One SAE in the control group was autoimmune thyroiditis. No AID were reported in the HPV-16/18 vaccine group	- Limited information on documentation SAE - Not insight in the SAE reported up to month 7 - No main institute as 57 centres were involved - Small sample size - Concealment method unclear
AID: autoimmune disease; ELISA: enzyme-linked immunosorbent assay; HAV: hepatitis A virus; HPV: human papillomavirus; mg: milligram; SAE: serious adverse event.		

Reference **Country** **NCT registration number**	**Setting** **Study design** **Study period**	**Population** **Sample size** **Follow-up period**
Naud P., Human vaccines & immunotherapeutics, 2014 Brazil NCT00196924	**Setting:** Five hospital-based Brazilian centers **Study design**: Follow-up of an initial double-blind, randomized, multi-center vaccination study **Study period**: November 2007-2010	**Population**: Subset of women enrolled in HPV-001 and who participated in the follow-up study HPV-007 whose treatment allocation had remained blinded in both studies. For HPV-001, healthy women aged 15-25 y were recruited. Women were HPV-16 and HPV-18 seronegative by ELISA, HPV DNA-negative in the cervix by PCR for 14 oncogenic types (HPV-16,-18,-31,-33,-35,- 39,-45,-51,-52,-56,-58,-59,-66,-68),and had normal cervical cytology at baseline. Mean age at HPV-023 study entry was 26.5y (SD 3.1y) **Exclusion criteria:** NR **Sample size**: Enrolled in HPV-001 n=506, 448 continued into HPV-007, n=437 agreed to continue in HPV-023 of which n=431 completed the study Participants were randomized to one of the two groups: -HPV-16/18 vaccine: n=224 -Placebo ($Al[OH]_3$): n=213

Vaccine dose **Follow-up** **Outcome detection and definition**	**Results**	**Comments**
Vaccine dose: - 3 doses of HPV-16/18 vaccine at 0, 1, and 6 mo - 3 doses of placebo ($Al[OH]_3$) at 0, 1, and 6 mo **Follow-up:** Three years, with data collected from end of HPV-007 up to the final visit (month 36) in HPV-023. Mean follow-up time since first vaccination in HPV-001 was 107 months (8.9y, SD=0.4) **Outcome detection and definition**: NOCDs (e.g., NOADs, asthma, type I diabetes) were recorded	Number and percentage of women reporting NOAD between 77 mo and up to 113 mo post initial vaccination (36-mo follow-up), % (95% CI); n Vaccine (N=224) / Placebo (N=213) % (95% CI); n / % (95% CI); n NOAD in general: 1.8 (0.5-4.5); 4 / 0.5 (0.0-2.6); 1 - Hypothyroidism: 0.9 (0.1-3.2); 2 / 0.5 (0.0-2.6); 1	- Concealment method unclear - Unclear if subjects and investigators were kept blind about treatment allocation - Small sample size - No main institute mentioned

CI: confidence interval; DNA: deoxyribonucleic acid; ELISA: enzyme-linked immunosorbent assay; HPV: human papillomavirus; mo: month; NOAD: new onset autoimmune disease; NOCD: new onset chronic disease; NR: not reported; PCR polymerase chain reaction; SD: standard deviation; y: year.

APPENDIX III List of studies reporting number of NOAD, but with unclear number of the AID of interest (original search)

	ClinicalTrials.gov Identifier	Reference	Reported outcomes	GSK study[1]	Country	Follow-up period
1	Safety data from 11 Phase II/III trials	Descamps_ Hum Vaccin_ 2009	The overall percentage of women reporting NOADs was 0.3% (95% CI: 0.1, 0.9) in the HPV-16/18 vaccine group 10-14 yrs, 0.4% (95% CI:0.3-0.5) in the HPV-16/18 vaccine group15-24 yrs - "The most frequent NOADs were related to thyroid disease"	yes	30 countries in North and Latin America, Europe, Australia and Asia	-*
2	NCT00423046	Einstein_Hum Vaccin Immunother_ 2014	102 SAE, 66 subjects experienced NOCDs, 19 of these subjects reported NOCDs that were identified as NOADs. The most common NOCD/NOAD was hypothyroidism.	yes	US	48 mo
3	NCT00423046	Einstein_ Hum Vaccin Immunother_ 2014_2	20 NOAD, The most commonly identified NOCD and NOAD was hypothyroidism	yes	US	60 mo
4	NCT01462357	Leung_ Human Vaccines and Immunotherapeutic_ 2015	6 potential immune-mediated diseases. The reported pIMDs were reactive arthritis, juvenile idiopathic arthritis, erythema nodosum, alopecia areata, ulcerative colitis and celiac disease**	yes	France, Hong Kong, Singapore and Sweden	12 mo
5	NCT00689741 (NCT00518336/ NCT00120848)	Roteli-Martins_Hum Vaccin Immunother_2012	17 SAE, 7 NOCD, 2 NOAD, of which 1 case of hypothyroidism***	yes	(US, Canada) Brazil	8,4 y
6a	NCT00122681	Paavonen_Lancet_2007	57 NOAD, no mentioning of AID of interest	yes	14 countries in Asia Pacific, Europe, Latin America, and North America.	14,8 mo
6b	NCT00122681	Lehtinen_Lancet Oncol_2012	194 NOAD, no mentioning of AID of interest	Yes	14 countries in Asia Pacific, Europe, Latin America, and North America	48 mo

AID of interest: autoimmune thyroiditis, inflammatory bowel disease, or Guillain Barré Syndrome

1: study sponsored or funded by GSK; *pooled results from 11 trials, including safety results from 0-30 days post-vaccination, month 0-7, month 7-12 and post month 12. **Not clear in which treatment group *** Not clear of NOAD cases in vaccinated or placebo-group occured. "cases remain blinded with respect to treatment allocation as the study is still ongoing"

AID: autoimmune diease; mo: months; NOAD: new-onset autoimmune diease; NOCD: new-onset chronic disease; SAE: serious adverse event; y: years

APPENDIX IV List additional search

Number of serious adverse events reported, including the number of autoimmune disease cases

	ClinicalTrials.gov Identifier	Reference	Reported outcomes	GSK study[1]	Country	Follow-up period
1	NCT 00485732	Kim_J Gynecol Oncol_2011	3 SAE, 0 cases of AID*	Yes	Korean	7 mo
2	NCT00169494	Pedersen_J Adolesc Health_2007	8 SAE, 0 cases of AID*	Yes	Denmark, Estonia, Finland, Greece, The Netherlands, and Russia	7 mo
3	NCT00290277	Kim_J Korean Med Sci_2010	1 SAE, 0 cases of AID*	Yes	Korean	7 mo
4	NCT00306241	Ngan_Hong Kong Med J_2010	4 SAE, 0 cases of AID*	Yes	China/Hong Kong	7 mo
5	NCT00316693	Konno_Int J Gynecol Cancer_2009	16 SAE, 0 cases of AID*	Yes	Japan	7 mo
6	NCT00344032	Bhatla_J Obstet Gynaecol Res_2010	6 SAE, 0 cases of AID*	Yes	India	7 mo
7	NCT00345878	Lim_Med J Malaysia_2014	8 SAE, 0 cases of AID*	Yes	Malaysia	7 mo
8	NCT00426361	Garcia-Sicilia_J Adolesc Health_2010	12 SAE, 0 cases of AID*	Yes	France, Germany, and Spain	7-8 mo
9	NCT00578227	Pedersen-J Adolesc Health-2012	11 SAE, 0 cases of AID*	Yes	Canada, Denmark, Hungary, and Sweden	7 mo
10	NCT00689741; (initial study) (NCT00120848) NCT00518336; (current follow-up study)	De Carvalho_Vaccine_2010	9 SAE, 0 cases of AID*	Yes	Brazil	7.3 y
11	NCT00996125/ NCT01277042	Zhu-Hum Vaccin Immunother-2014	2 NOAD, 0 cases in HPV group	Yes	China	7 mo
12	NCT00128661	Hildesheim_Vaccine_2014	43 NOAD, of which: goiter (8 in HPV arm; 9 in control arm);), inflammatory bowel dis-ease (3 in HPV arm including 1 Crohn's disease; 2 in control arm) [other conditions (4 in HPV arm; 2 in control arm).] 15 death, Crohn's disease (1 in HPV arm)	Yes		4 y
13	No trial number	Brabin_Bmj_2008	No SAE	Yes	UK	Unclear

1: study sponsored or funded by GSK; 2: vaccine at 0, 1, and 6 months (although they mention only two doses) and a process for reporting serious adverse events; *AID of interest: autoimmune thyroiditis, inflammatory bowel disease, or Guillain Barré Syndrome ; AID: autoimmune disease; HPV: human papillomavirus; mo: months; NOAD: new-onset autoimmune disease; SAE: serious adverse event; y: years

Number of serious adverse events mentioned, but not clear if autoimmune disease were present

	ClinicalTrials.gov Identifier	Reference	Reported outcomes	GSK study [1]	Country	Follow-up period
1a	NCT00196924 (NCT00316706)	Schwarz_J Adolesc Health_2012	76 SAE, no description of AID*	Yes	Taiwan, Germany, Honduras, Panama, and Colombia	48 mo
1b	NCT00196924 (NCT00877877/ NCT00316706)	Schwarz_Pediatr Infect Dis J_2014	110 SAE, no description of AID*	Yes	Taiwan, Germany, Honduras, Panama and Colombia	72 mo
2a	NCT00196937 (105879/014)	Schwarz_Vaccine_2009	15 SAE, no description of AID*	Yes	Germany and Poland	24 mo
2b	NCT00196937 (105882)	Schwarz-Hum Vaccin-2011	29 SAE, of which 14 NOCD, no description of AID*	Yes	Germany and Poland	48 mo
2c	NCT00196937 (NCT00947115)	Schwarz-Bjog-2015	32 SAE, no description of AID*	Yes	Germany and Poland	72 mo
3a	NCT00316693	Konno_Int J Gynecol Cancer_2010 (interim analysis)	37 SAE, no description of AID*	Yes	Japan	13.6 mo
3b	NCT00316693	Konno_Int J Gynecol Cancer_2010	37 SAE, 11 NOCD, no description of AID*	Yes	Japan	24 mo
4	NCT00689741 Current study: NCT00546078	Moscicki_Vaccine_2012	No mentioning of SAE or NOCD (description in methods of safety assessment)	Yes	US, Canada, Brazil	7 days or 7 mo
5	No trial number	Khatun_Jpn J Clin Oncol_2012	Unclear description, no NOAD	No	Bangladesh	7 mo

*AID of interest: autoimmune thyroiditis, inflammatory bowel disease, or Guillain Barré Syndrome; 1: study sponsored or funded by GSK;

AID: autoimmune disease; mo: months; NOAD: new-onset autoimmune disease; SAE: serious adverse event; y: years

NOAD in general, disease not further specified

	ClinicalTrials.gov Identifier	Reference	Reported outcome	GSK study[1]	Country	Follow-up period
1	NCT00294047	Skinner_Lancet_2014	13 NOAD, not further specified	Yes	Australia, Canada, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Thailand, UK, and US	48 mo
2	NCT00337818	Petaja-Int J Cancer-2011	168 medically significant AEs, 23 NOCD, the most frequently reported NOCDs were asthma (5) and hypothyroidism (3)	yes	Denmark, Estonia and Finland	48 mo
3a	NCT00423046	Einstein_Hum Vaccin_2009	NOCD were observed in 14 women in the Cervarix™ group and 13 in the Gardasil ® group. The most frequent were depression, hypertension, and hypothyroidism. Four NOCD cases were considered to be NOAD.	Yes	US	7 mo
3b	NCT00423046	Einstein_Hum Vaccin_2011	NOAD in Cervarix group 1.1% (0.4-2.3) and HPV 6/11/16/18 group 1.8% (0.9-3.3), not further specified	Yes	US	24 mo
4	NCT00481767	Sow-J Infect Dis-2013	4 NOAD, 2 in vaccine group, not further specified	Yes	Senegal, Tanzania	12 mo
5a	NCT00541970	Romanowski_Hum Vaccin Immunother_2014	10 NOAD, not further specified	Yes	Canada, Germany	48 mo
5b	NCT00541970	Romanowski_Hum Vaccin Immunother_2015	11 NOAD, not further specified	Yes	Canada, Germany	60 mo
6	NCT00779766	Zhu-Int J Cancer-2014	4 NOAD, 2 in vaccine group, not further specified	Yes	China	15,3 mo
7	NCT00929526 (initial study: NCT00316693)	Konno_Hum Vaccin Immunother_2014	4 NOAD, 3 in vaccine group, not further specified	Yes	Japan	4 y
8	NCT00122681	Paavonen_Lancet_2009	155 NOAD, not further specified	Yes	14 countries in Asia Pacific, Europe, Latin America, and North America.	34,9 mo

1: study sponsored or funded by GSK

AID: autoimmune disease; HPV: human papillomavirus; mo: months; NOAD: new-onset autoimmune disease; SAE: serious adverse event; y: years

Supporting information B. RCTs included in the meta-analysis

Study[ref]	www.clinicaltrials.gov	Exposed, n	Control, n	Control	Age, years	Country
HPV-001[29] + follow-up: HPV-007†[30]	NCT00689741/ NCT00518336	560	553	Placebo‡	15–25	Canada, USA, Brazil
HPV-008[31]	NCT00122681	9328§	9337§	HAV	15–25	14
HPV-009[32]	NCT00128661	3729¶	3737¶	HAV	18–25	Costa Rica
HPV-013[33] + Extension M18 + Extention M24	NCT00196924/ NCT00316706/ NCT00877877	1035	1032	HAV	10–14	12
HPV-015[34]	NCT00294047	2881	2871	Placebo‡	26+	12
HPV-020[35]	NCT00586339	91	59	Placebo‡	18–25	South Africa
HPV-021[36]	NCT00481767	450	226	Placebo‡	10–25	Africa
HPV-026[37]	NCT00637195	76	76	HBV	20–25	Belgium
HPV-029[38]	NCT00578227	542	271	HAB	9–15	Canada, Denmark, Hungary, Sweden
HPV-030[39]	NCT00652938	494	247	HBV	9–15	The Netherlands, Sweden
HPV-031[40]	NCT00344032	176	178	Placebo‡	18–35	India
HPV-032[41]	NCT00316693	519	521	HAV	20–25	Japan
HPV-033[42]	NCT00290277	160	161	HAV	10–14	Korea
HPV-035[43]	NCT00306241	150	150	Placebo‡	18–35	China
HPV-036[44]	NCT00345878	135	136	Placebo‡	18–35	Malaysia
HPV-038[45]	NCT00485732	149	76	Placebo‡	15–25	Korea
HPV-058[46]	NCT00996125	374	376	Placebo‡	9–17	China
HPV-069[46]	NCT01277042	606	606	HBV	26–45	China
Total	–	21,455	20,613	–	–	–

HAB, combined hepatitis A and hepatitis B vaccine; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; RCT, randomized controlled trial; USA, United States of America; n, number of subjects.

†Limited to 2 years following the first dose.

‡$Al(OH)_3$.

§These numbers do not match those in the publications because we included an additional 21 patients who were excluded from the published analysis due to concerns about data integrity.

¶These numbers do not match those in the publications because two patients in the control group in the published analysis received an HPV dose so are included in the exposed cohort in this analysis.

References

1. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, Zahaf T, Innis B, Naud P, De Carvalho NS, Roteli-Martins CM, Teixeira J, Blatter MM, Korn AP, Quint W, Dubin G, GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine

in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364**: 1757-1765.

2. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G, HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006; **367**: 1247-1255.
3. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G, HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374**: 301-314.
4. Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer AR, Porras C, Schussler J, Jimenez S, Sherman ME, Quint W, Schiller JT, Lowy DR, Schiffman M, Hildesheim A, Costa Rica Vaccine Trial Group. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. *Cancer Discov* 2011; **1**: 408-419.
5. Medina DM, Valencia A, de Velasquez A, Huang LM, Prymula R, Garcia-Sicilia J, Rombo L, David MP, Descamps D, Hardt K, Dubin G, HPV Study Group. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls. *J Adolesc Health* 2010; **46**: 414-421.
6. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J, Del Rosario-Raymundo MR, Verheijen RH, Quek SC, da Silva DP, Kitchener H, Fong KL, Bouchard C, Money DM, Ilancheran A, Cruickshank ME, Levin MJ, Chatterjee A, Stapleton JT, Martens M, Quint W, David MP, Meric D, Hardt K, Descamps D, Geeraerts B, Struyf F, Dubin G, VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet* 2014; **384**: 2213-2227.
7. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, Durand C, Herve C, Descamps D. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. *Vaccine* 2013; **31**: 5745-5753.
8. Sow PS, Watson-Jones D, Kiviat N, Changalucha J, Mbaye KD, Brown J, Bousso K, Kavishe B, Andreasen A, Toure M, Kapiga S, Mayaud P, Hayes R, Lebacq M, Herazeh M, Thomas F,

Descamps D. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: a randomized trial in 10-25-year-old HIV-seronegative African girls and young women. *J Infect Dis* 2013; **207**: 1753-1763.

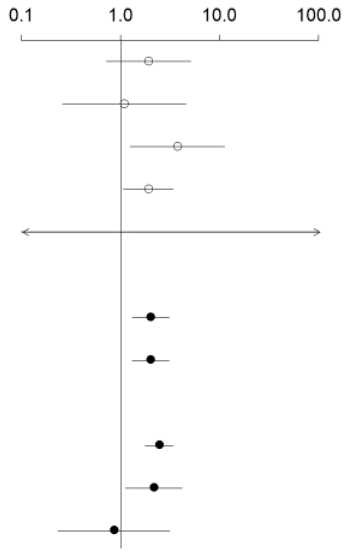
9. Leroux-Roels G, Haelterman E, Maes C, Levy J, De Boever F, Licini L, David MP, Dobbelaere K, Descamps D. Randomized trial of the immunogenicity and safety of the Hepatitis B vaccine given in an accelerated schedule coadministered with the human papillomavirus type 16/18 AS04-adjuvanted cervical cancer vaccine. *Clin Vaccine Immunol* 2011; **18**: 1510-1518.
10. Pedersen C, Breindahl M, Aggarwal N, Berglund J, Oroszlan G, Silfverdal SA, Szuts P, O'Mahony M, David MP, Dobbelaere K, Dubin G, Descamps D. Randomized trial: immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. *J Adolesc Health* 2012; **50**: 38-46.
11. Schmeink CE, Bekkers RL, Josefsson A, Richardus JH, Berndtsson Blom K, David MP, Dobbelaere K, Descamps D. Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls. *Vaccine* 2011; **29**: 9276-9283.
12. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, Descamps DJ, Bock HL, Indian HPV Vaccine Study Group. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. *J Obstet Gynaecol Res* 2010; **36**: 123-132.
13. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. *Int J Gynecol Cancer* 2010; **20**: 847-855.
14. Kim YJ, Kim KT, Kim JH, Cha SD, Kim JW, Bae DS, Nam JH, Ahn WS, Choi HS, Ng T, Bi D, Ok JJ, Descamps D, Bock HL. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10-14 years. *J Korean Med Sci* 2010; **25**: 1197-1204.
15. Ngan HY, Cheung AN, Tam KF, Chan KK, Tang HW, Bi D, Descamps D, Bock HL. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. *Hong Kong Med J* 2010; **16**: 171-179.
16. Lim BK, Ng KY, Omar J, Omar SZ, Gunapalaiah B, Teoh YL, Bock HL, Bi D. Immunogenicity and Safety of the AS04-adjuvanted Human Papillomavirus-16/18 Cervical Cancer Vaccine in Malaysian Women Aged 18-35 years: A Randomized Controlled Trial. *Med J Malaysia* 2014; **69**: 2-8.
17. Kim SC, Song YS, Kim YT, Kim YT, Ryu KS, Gunapalaiah B, Bi D, Bock HL, Park JS. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15-25 years old healthy Korean women. *J Gynecol Oncol* 2011; **22**: 67-75.
18. Zhu F, Li J, Hu Y, Zhang X, Yang X, Zhao H, Wang J, Yang J, Xia G, Dai Q, Tang H, Suryakiran P, Datta SK, Descamps D, Bi D, Struyf F. Immunogenicity and safety of the HPV-16/18 AS04-

adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years. *Hum Vaccin Immunother* 2014; **10**: 1795-1806.

Supporting information C.

Risk of AIT during 2 years following the first dose of AS04-HPV-16/18, using the original data from the French cohort study.[47,48] There are partial events for the French cohort study due to the standardization of the follow-up times to 2 years; and for the case–control study[49,50] due to the continuity correction factor due to the "single-zero" cases in the exposed arm. AIT, autoimmune thyroiditis; CI, confidence interval; OR, odds ratio; Randomized Controlled Trials; UK, United Kingdom.

	Exposed		Non-exposed		AIT (2 years)
	Events	Subjects	Events	Subjects	OR (95% CI)
Studies					
Pooled RCTs[5-22]	12	21,455	6	20,613	1.92 (0.72–5.12)
Cluster-randomized trial[23,24]	5	12,400	3	8119	1.09 (0.26–4.57)
UK cohort study[25]	15	64,998	4	64,994	3.75 (1.24–11.30)
French cohort study[1,2]	12.1	55,545	161.6	1,410,596	1.91 (1.06–3.42)
Case–control study[3,4,*]	0	9	106.5	974	0.004 (0.00–1.57E+10)
Primary analysis: inverse-variance with continuity correction					
Fixed effect					**2.01 (1.30–3.11)**
Random effect	I^2 = 0.00%; P = 0.71				**2.01 (1.30–3.11)**
Secondary analyses					
Pooled estimate*	44.1	154,398	174.6	1,504,322	2.46 (1.77–3.43)
Beta-binomial regression (without case–control study[3,4])					2.17 (1.12–4.21)
Beta-binomial regression (with case–control study[3,4])					0.86 (0.24–3.15)



*The case–control study was not included in the pooled estimate.

References

1. Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Vaccination contre les infections à HPV et risque de maladies auto-immunes : une étude Cnamts/ANSM rassurante - Point d'information. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information (accessed 26 August 2016).
2. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France. *Vaccine* 2017; **35**: 4761-4768.
3. Grimaldi-Bensouda L, Rossignol M, Kone-Paut I, Krivitzky A, Lebrun-Frenay C, Clet J, Brassat D, Papeix C, Nicolino M, Benhamou PY, Fain O, Costedoat-Chalumeau N, Courcoux MF, Viallard JF, Godeau B, Papo T, Vermersch P, Bourgault-Villada I, Breart G, Abenhaim L, PGRx-AD Study

Group. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *J Autoimmun* 2017; **79**: 84-90.

4. Grimaldi-Bensouda L, Aubrun E, Abenhaim L. ANALYSIS OF CERVARIX® & AUTOIMMUNE DISORDERS USING THE PGRx INFORMATION SYSTEM. Data on file. 2015.
5. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, Zahaf T, Innis B, Naud P, De Carvalho NS, Roteli-Martins CM, Teixeira J, Blatter MM, Korn AP, Quint W, Dubin G, GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364**: 1757-1765.
6. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G, HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006; **367**: 1247-1255.
7. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G, HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374**: 301-314.
8. Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer AR, Porras C, Schussler J, Jimenez S, Sherman ME, Quint W, Schiller JT, Lowy DR, Schiffman M, Hildesheim A, Costa Rica Vaccine Trial Group. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. *Cancer Discov* 2011; **1**: 408-419.
9. Medina DM, Valencia A, de Velasquez A, Huang LM, Prymula R, Garcia-Sicilia J, Rombo L, David MP, Descamps D, Hardt K, Dubin G, HPV Study Group. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls. *J Adolesc Health* 2010; **46**: 414-421.
10. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J, Del Rosario-Raymundo MR, Verheijen RH, Quek SC, da Silva DP, Kitchener H, Fong KL, Bouchard C, Money DM, Ilancheran A, Cruickshank ME, Levin MJ, Chatterjee A, Stapleton JT, Martens M, Quint W, David MP, Meric D, Hardt K, Descamps D, Geeraerts B, Struyf F, Dubin G, VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-

adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet* 2014; **384**: 2213-2227.

11. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, Durand C, Herve C, Descamps D. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. *Vaccine* 2013; **31**: 5745-5753.
12. Sow PS, Watson-Jones D, Kiviat N, Changalucha J, Mbaye KD, Brown J, Bousso K, Kavishe B, Andreasen A, Toure M, Kapiga S, Mayaud P, Hayes R, Lebacq M, Herazeh M, Thomas F, Descamps D. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: a randomized trial in 10-25-year-old HIV-seronegative African girls and young women. *J Infect Dis* 2013; **207**: 1753-1763.
13. Leroux-Roels G, Haelterman E, Maes C, Levy J, De Boever F, Licini L, David MP, Dobbelaere K, Descamps D. Randomized trial of the immunogenicity and safety of the Hepatitis B vaccine given in an accelerated schedule coadministered with the human papillomavirus type 16/18 AS04-adjuvanted cervical cancer vaccine. *Clin Vaccine Immunol* 2011; **18**: 1510-1518.
14. Pedersen C, Breindahl M, Aggarwal N, Berglund J, Oroszlan G, Silfverdal SA, Szuts P, O'Mahony M, David MP, Dobbelaere K, Dubin G, Descamps D. Randomized trial: immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. *J Adolesc Health* 2012; **50**: 38-46.
15. Schmeink CE, Bekkers RL, Josefsson A, Richardus JH, Berndtsson Blom K, David MP, Dobbelaere K, Descamps D. Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls. *Vaccine* 2011; **29**: 9276-9283.
16. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, Descamps DJ, Bock HL, Indian HPV Vaccine Study Group. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. *J Obstet Gynaecol Res* 2010; **36**: 123-132.
17. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. *Int J Gynecol Cancer* 2010; **20**: 847-855.
18. Kim YJ, Kim KT, Kim JH, Cha SD, Kim JW, Bae DS, Nam JH, Ahn WS, Choi HS, Ng T, Bi D, Ok JJ, Descamps D, Bock HL. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10-14 years. *J Korean Med Sci* 2010; **25**: 1197-1204.
19. Ngan HY, Cheung AN, Tam KF, Chan KK, Tang HW, Bi D, Descamps D, Bock HL. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. *Hong Kong Med J* 2010; **16**: 171-179.

20. Lim BK, Ng KY, Omar J, Omar SZ, Gunapalaiah B, Teoh YL, Bock HL, Bi D. Immunogenicity and Safety of the AS04-adjuvanted Human Papillomavirus-16/18 Cervical Cancer Vaccine in Malaysian Women Aged 18-35 years: A Randomized Controlled Trial. *Med J Malaysia* 2014; **69**: 2-8.

21. Kim SC, Song YS, Kim YT, Kim YT, Ryu KS, Gunapalaiah B, Bi D, Bock HL, Park JS. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15-25 years old healthy Korean women. *J Gynecol Oncol* 2011; **22**: 67-75.

22. Zhu F, Li J, Hu Y, Zhang X, Yang X, Zhao H, Wang J, Yang J, Xia G, Dai Q, Tang H, Suryakiran P, Datta SK, Descamps D, Bi D, Struyf F. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years. *Hum Vaccin Immunother* 2014; **10**: 1795-1806.

23. Lehtinen M, Apter D, Baussano I, Eriksson T, Natunen K, Paavonen J, Vanska S, Bi D, David MP, Datta S, Struyf F, Jenkins D, Pukkala E, Garnett G, Dubin G. Characteristics of a cluster-randomized phase IV human papillomavirus vaccination effectiveness trial. *Vaccine* 2015; **33**: 1284-1290.

24. GlaxoSmithKline Biologicals. An observational cohort study to assess the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix® in the United Kingdom. Study number 116239 (EPI-HPV-040 VS UK). https://gsk.sylogent.com/files/116239-Clinical-Study-Result-Summary.pdf (accessed 25 October 2016).

25. Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, Boggon R, Bunge EM, Pladevall-Vila M, Baril L. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Hum Vaccin Immunother* 2016; **12**: 2862-2871.

Supporting information D. Clinical definitions used in the studies

Event	Pooled clinical and cluster-randomized trial[51,52]	UK cohort study†[53]	French cohort study[47,48,54]	Case–control study[49,50]
	MedDRA Primary System Organ Class and Preferred Term	Read codes + ICD-10	ICD-10 codes	Study clinical definition
AIT	• Basedow's disease (10004161) • AIT (10049046)	Confirmed cases: • AIT • Basedow's disease • Graves' disease • Hashimoto's disease • De Quervain's thyroiditis • Riedel's thyroiditis (E05, E06.1, E06.3, E06.5)	Thyroiditis was defined by the use of specific drugs indicated for the treatment of thyroid disorders (≥2 dispensations within 6 months) plus ≥1 of: • Routine thyroid function tests (T3±T4±TSH) combined with complementary examination of the thyroid (imaging tests or autoantibody levels)‡,§ • Hospital stay with an ICD-10 code of thyroiditis¶ as the main diagnosis or a related diagnosis • A new full coverage for thyroiditis as a long-term illness.	AIT: definite case according to study definitions including Graves' disease and Hashimoto's disease††
GBS	GBS (10018767)	Confirmed cases of GBS† (G61.0, G60)	One of: • GBS (G61.0) • Occurrence of ALD30 (long-term diseases) for GBS • ≥1 hospitalization of ≥6 days with a principal diagnosis of stay or related diagnosis for GBS • ≥2 hospitalizations with a principal diagnosis of stay or related diagnosis for GBS	GBS definite case (level 1) according to the Brighton collaboration case definition:[55] requires clinical, electrophysiological, and CSF data consistent with the onset of GBS
IBD	• Colitis ulcerative (10009900) • Crohn's disease (10011401) • Proctitis ulcerative (10036783) • IBD (10021972) [not for HPV-040]	Confirmed cases of • Crohn's diseases (K50) • Ulcerative colitis (K51)	One of: • ALD30 (long-term disease) for IBD • ≥1 hospitalization with a principal diagnosis of stay or related diagnosis for IBD Plus: • 1 hospitalization for lower gastrointestinal endoscopy before or at the time of diagnosis (K50, K51)	Not assessed

AIT, autoimmune thyroiditis; CSF, cerebrospinal fluid; IBD, inflammatory bowel disease; ICD-10, **International Statistical Classification of Diseases and Related Health Problems**, 10th Revision; GBS, Guillain–Barré syndrome; MedDRA, Medical Dictionary for Regulatory Activity; PGRx, Pharmacoepidemiological General Research eXtension; TSH: thyroid-stimulating hormone; TPO, thyroperoxidase; UK, United Kingdom.

†In addition to the specific ICD-10 codes listed in the table, other codes were used to capture possible cases. Among these, only cases confirmed by a medical review were included.

‡Codes: 1206 (free triiodothyronine [FT3]); 1207 (free thyroxine [FT4]); 1208 thyroid-stimulating hormone (TSH) for diagnosis of thyroid dysfunction or thyroid function monitoring; 1209 (FT3 + FT4); 1210 (TSH + FT3); 1211 (TSH + FT4); 1212 (TSH + FT3 + FT4); 1483/4 (anti-thyroglobulin antibodies); 1485/6 (thyroid antimicrosomes antibodies); 1487 (thyroid peroxydase antibodies); 1488 (anti-TSH receptor antibodies).

§Medical procedures: KCHB001 (transcutaneous thyroid fine-needle aspiration cytology without ultrasound guidance); KCHJ001 (transcutaneous thyroid fine-needle aspiration cytology under ultrasound guidance); KCHJ002 (transcutaneous thyroid biopsy [several lesions] under ultrasound guidance); KCHJ003 (transcutaneous thyroid biopsy [one lesion] under ultrasound guidance); KCHJ004 (transcutaneous thyroid fine-needle aspiration cytology from several thyroid lesions under ultrasound guidance); KCQL001 (thyroid scintigraphy with iodine uptake measurement); KCQL002 (thyroid iodine uptake measurement); KCQL003 (thyroid scintigraphy); KCQM001 (thyroid ultrasound).

¶ICD-10 codes: E03.4 Atrophy of thyroid (acquired); E03.5 Myxedema coma; E03.8 Other specified hypothyroidism; E03.9 Hypothyroidism, unspecified; E04.0 Nontoxic diffuse goiter; E04.8 Other specified nontoxic goiter; E04.9 Nontoxic goiter, unspecified; E05.0 Thyrotoxicosis with diffuse goitre; E05.5 Thyroid crisis or storm; E05.8 Other thyrotoxicosis; E05.9 Thyrotoxicosis, unspecified; E06.0 Acute thyroiditis; E06.1 Subacute thyroiditis; E06.2 Chronic thyroiditis with transient thyrotoxicosis; E06.3 Autoimmune thyroiditis; E06.5 Other chronic thyroiditis; E06.9 Thyroiditis, unspecified.

††Definite case of AIT = hypothyroidism consistent with incident autoimmune thyroiditis AND antiperoxydase (anti-TPO) AND increased TSH >7 mU/L; Definite case of Graves' disease = Presence of exophthalmia or palsy or tachycardio or weight loss or weight gain AND anti-TSH-receptor AND decreased TSH.

References

1. Lehtinen M, Apter D, Baussano I, Eriksson T, Natunen K, Paavonen J, Vanska S, Bi D, David MP, Datta S, Struyf F, Jenkins D, Pukkala E, Garnett G, Dubin G. Characteristics of a cluster-randomized phase IV human papillomavirus vaccination effectiveness trial. *Vaccine* 2015; **33**: 1284-1290.
2. GlaxoSmithKline Biologicals. An observational cohort study to assess the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix® in the United Kingdom. Study number 116239 (EPI-HPV-040 VS UK). https://gsk.sylogent.com/files/116239-Clinical-Study-Result-Summary.pdf (accessed 25 October 2016).
3. Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, Boggon R, Bunge EM, Pladevall-Vila M, Baril L. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Hum Vaccin Immunother* 2016; **12**: 2862-2871.
4. Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Vaccination contre les infections à HPV et risque de maladies auto-immunes : une étude Cnamts/ANSM rassurante - Point d'information. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information (accessed 26 August 2016).

5. Collin C, Miranda S, Zureik M, Dray-Spira R. HPV vaccines and the risk of thyroiditis in girls. Complementary analyses of the French cohort based on data from SNIIRAM. 2018.
6. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France. *Vaccine* 2017; **35**: 4761-4768.
7. Grimaldi-Bensouda L, Rossignol M, Kone-Paut I, Krivitzky A, Lebrun-Frenay C, Clet J, Brassat D, Papeix C, Nicolino M, Benhamou PY, Fain O, Costedoat-Chalumeau N, Courcoux MF, Viallard JF, Godeau B, Papo T, Vermersch P, Bourgault-Villada I, Breart G, Abenhaim L, PGRx-AD Study Group. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *J Autoimmun* 2017; **79**: 84-90.
8. Grimaldi-Bensouda L, Aubrun E, Abenhaim L. ANALYSIS OF CERVARIX® & AUTOIMMUNE DISORDERS USING THE PGRx INFORMATION SYSTEM. Data on file. 2015.
9. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, Burwen DR, Cornblath DR, Cleerbout J, Edwards KM, Heininger U, Hughes R, Khuri-Bulos N, Korinthenberg R, Law BJ, Munro U, Maltezou HC, Nell P, Oleske J, Sparks R, Velentgas P, Vermeer P, Wiznitzer M, Brighton Collaboration GBS Working Group. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011; **29**: 599-612.

Supporting information E.

For the French cohort study,[47,48,54] only the total numbers of events and the mean follow-up periods were known. Further, events were reported in exposed and non-exposed subjects, which included a combination of non-vaccinated subjects plus the pre-exposure periods of subjects who were subsequently vaccinated with AS04-HPV-16/18 or HPV-6/11/16/18. The number of events occurring among only non-vaccinated subjects was estimated using the total number of events among non-vaccinated and pre-exposed subjects multiplied by the number of person-years of follow-up of the non-vaccinated subjects divided by the number of person-years of follow-up of the non-vaccinated cohort plus the pre-exposed person-years of the vaccinated cohort. As the mean follow-up period was longer for non-exposed versus exposed subjects, the numbers of cases for the 2-year analyses were calculated as N = events × 24 / follow-up (in months).

For GBS, a risk period of 42 days following each vaccination was considered for the main analysis. Given that 18% of the vaccinated cohort received 1 dose, 18% 2 doses, and 64% 3 doses, this gave a mean follow-up of 103 days per vaccinated individual. Among the non-exposed (non-vaccinated plus pre-vaccination) population, 21 GBS cases occurred (estimated 15.7 cases among non-vaccinated) during 30.2 months follow-up. The following calculation was used to estimate the number of GBS cases during the same time period: cases = 15.7 × 3.39 / 30.2 = 1.76.

References

1. Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Vaccination contre les infections à HPV et risque de maladies auto-immunes : une étude Cnamts/ANSM rassurante - Point d'information. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information (accessed 26 August 2016).
2. Collin C, Miranda S, Zureik M, Dray-Spira R. HPV vaccines and the risk of thyroiditis in girls. Complementary analyses of the French cohort based on data from SNIIRAM. 2018.
3. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France. *Vaccine* 2017; **35**: 4761-4768.

Supporting Information F.

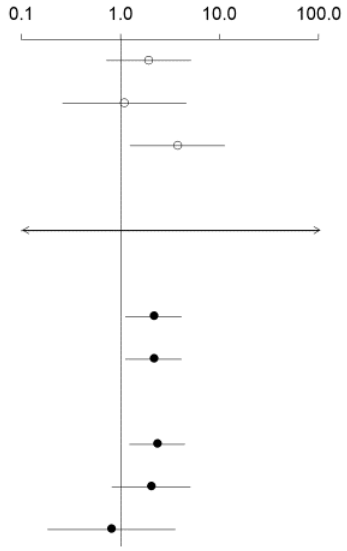
The continuity correction factor in the exposed arm, C_e, was computed as $C_e = 0.5\ N_e/N_T$ where N_e is the number of subjects in the exposed arm and N_T is the total number of subjects. The continuity correction factor in the non-exposed arm, C_{ne}, was similarly computed by substituting N_e by N_{ne}, the total number of subjects in the non-exposed arm. Both fixed- and random-effect models were used. The inverse-weighted variance method was used for the fixed-effect model. Heterogeneity among studies was tested using the Cochran *Q* test, the degree of heterogeneity by the I^2 index.[56] For the random-effect model, a component of inter-study variance was added in the overall variance.

Reference

1. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: *Q* statistic or I^2 index? *Psychol Methods* 2006; **11**: 193-206.

Supporting Information G. Risk of AIT during 2 years following the first dose of AS04-HPV-16/18, excluding the French cohort study.[47,48,54] There are partial events for the case–control study[49,50] due to the continuity correction factor due to the "single-zero" cases in the exposed arm. AIT, autoimmune thyroiditis; CI, confidence interval; OR, odds ratio; Randomized Controlled Trials; UK, United Kingdom.

	Exposed		Non-exposed		AIT (2 years)
	Events	Subjects	Events	Subjects	OR (95% CI)
Studies					
Pooled RCTs[6-23]	12	21,455	6	20,613	1.92 (0.72–5.12)
Cluster-randomized trial[24,25]	5	12,400	3	8119	1.09 (0.26–4.57)
UK cohort study[26]	15	64,998	4	64,994	3.75 (1.24–11.30)
French cohort study[1-3]			Excluded		
Case–control study[4,5,*]	0	6	97.5	894	0.005 (0.00–1.49E+10)
Primary analysis: inverse-variance with continuity correction					
Fixed effect					**2.15 (1.12–4.13)**
Random effect	I^2 = 0.00%; P = 0.56				**2.15 (1.12–4.13)**
Secondary analyses					
Pooled estimate*	32	98,853	13	93,726	2.33 (1.23–4.45)
Beta-binomial regression (without case–control study[4,5])					2.04 (0.82–5.07)
Beta-binomial regression (with case–control study[4,5])					0.81 (0.18–3.55)



*The case–control study was not included in the pooled estimate.

References

1. Collin C, Miranda S, Zureik M, Dray-Spira R. HPV vaccines and the risk of thyroiditis in girls. Complementary analyses of the French cohort based on data from SNIIRAM. 2018.
2. Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Vaccination contre les infections à HPV et risque de maladies auto-immunes : une étude Cnamts/ANSM rassurante - Point d'information. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information (accessed 26 August 2016).
3. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France. *Vaccine* 2017; **35**: 4761-4768.
4. Grimaldi-Bensouda L, Rossignol M, Kone-Paut I, Krivitzky A, Lebrun-Frenay C, Clet J, Brassat D, Papeix C, Nicolino M, Benhamou PY, Fain O, Costedoat-Chalumeau N, Courcoux MF, Viallard JF, Godeau B, Papo T, Vermersch P, Bourgault-Villada I, Breart G, Abenhaim L, PGRx-AD Study

Group. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *J Autoimmun* 2017; **79**: 84-90.

5. Grimaldi-Bensouda L, Aubrun E, Abenhaim L. ANALYSIS OF CERVARIX® & AUTOIMMUNE DISORDERS USING THE PGRx INFORMATION SYSTEM. Data on file. 2015.
6. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, Zahaf T, Innis B, Naud P, De Carvalho NS, Roteli-Martins CM, Teixeira J, Blatter MM, Korn AP, Quint W, Dubin G, GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364**: 1757-1765.
7. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G, HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006; **367**: 1247-1255.
8. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G, HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374**: 301-314.
9. Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer AR, Porras C, Schussler J, Jimenez S, Sherman ME, Quint W, Schiller JT, Lowy DR, Schiffman M, Hildesheim A, Costa Rica Vaccine Trial Group. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. *Cancer Discov* 2011; **1**: 408-419.
10. Medina DM, Valencia A, de Velasquez A, Huang LM, Prymula R, Garcia-Sicilia J, Rombo L, David MP, Descamps D, Hardt K, Dubin G, HPV Study Group. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls. *J Adolesc Health* 2010; **46**: 414-421.
11. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J, Del Rosario-Raymundo MR, Verheijen RH, Quek SC, da Silva DP, Kitchener H, Fong KL, Bouchard C, Money DM, Ilancheran A, Cruickshank ME, Levin MJ, Chatterjee A, Stapleton JT, Martens M, Quint W, David MP, Meric D, Hardt K, Descamps D, Geeraerts B, Struyf F, Dubin G, VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-

adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet* 2014; **384**: 2213-2227.

12. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, Durand C, Herve C, Descamps D. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. *Vaccine* 2013; **31**: 5745-5753.
13. Sow PS, Watson-Jones D, Kiviat N, Changalucha J, Mbaye KD, Brown J, Bousso K, Kavishe B, Andreasen A, Toure M, Kapiga S, Mayaud P, Hayes R, Lebacq M, Herazeh M, Thomas F, Descamps D. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: a randomized trial in 10-25-year-old HIV-seronegative African girls and young women. *J Infect Dis* 2013; **207**: 1753-1763.
14. Leroux-Roels G, Haelterman E, Maes C, Levy J, De Boever F, Licini L, David MP, Dobbelaere K, Descamps D. Randomized trial of the immunogenicity and safety of the Hepatitis B vaccine given in an accelerated schedule coadministered with the human papillomavirus type 16/18 AS04-adjuvanted cervical cancer vaccine. *Clin Vaccine Immunol* 2011; **18**: 1510-1518.
15. Pedersen C, Breindahl M, Aggarwal N, Berglund J, Oroszlan G, Silfverdal SA, Szuts P, O'Mahony M, David MP, Dobbelaere K, Dubin G, Descamps D. Randomized trial: immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. *J Adolesc Health* 2012; **50**: 38-46.
16. Schmeink CE, Bekkers RL, Josefsson A, Richardus JH, Berndtsson Blom K, David MP, Dobbelaere K, Descamps D. Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls. *Vaccine* 2011; **29**: 9276-9283.
17. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, Descamps DJ, Bock HL, Indian HPV Vaccine Study Group. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. *J Obstet Gynaecol Res* 2010; **36**: 123-132.
18. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. *Int J Gynecol Cancer* 2010; **20**: 847-855.
19. Kim YJ, Kim KT, Kim JH, Cha SD, Kim JW, Bae DS, Nam JH, Ahn WS, Choi HS, Ng T, Bi D, Ok JJ, Descamps D, Bock HL. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10-14 years. *J Korean Med Sci* 2010; **25**: 1197-1204.
20. Ngan HY, Cheung AN, Tam KF, Chan KK, Tang HW, Bi D, Descamps D, Bock HL. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. *Hong Kong Med J* 2010; **16**: 171-179.

21. Lim BK, Ng KY, Omar J, Omar SZ, Gunapalaiah B, Teoh YL, Bock HL, Bi D. Immunogenicity and Safety of the AS04-adjuvanted Human Papillomavirus-16/18 Cervical Cancer Vaccine in Malaysian Women Aged 18-35 years: A Randomized Controlled Trial. *Med J Malaysia* 2014; **69**: 2-8.

22. Kim SC, Song YS, Kim YT, Kim YT, Ryu KS, Gunapalaiah B, Bi D, Bock HL, Park JS. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15-25 years old healthy Korean women. *J Gynecol Oncol* 2011; **22**: 67-75.

23. Zhu F, Li J, Hu Y, Zhang X, Yang X, Zhao H, Wang J, Yang J, Xia G, Dai Q, Tang H, Suryakiran P, Datta SK, Descamps D, Bi D, Struyf F. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years. *Hum Vaccin Immunother* 2014; **10**: 1795-1806.

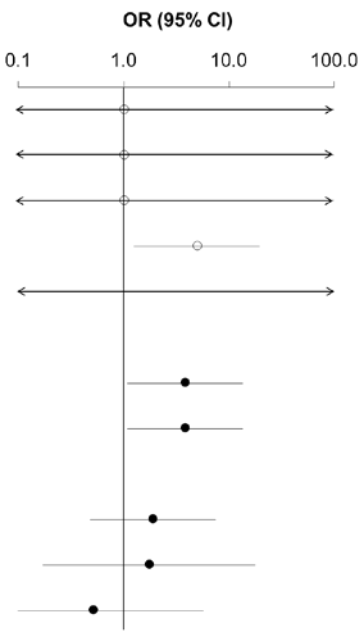
24. Lehtinen M, Apter D, Baussano I, Eriksson T, Natunen K, Paavonen J, Vanska S, Bi D, David MP, Datta S, Struyf F, Jenkins D, Pukkala E, Garnett G, Dubin G. Characteristics of a cluster-randomized phase IV human papillomavirus vaccination effectiveness trial. *Vaccine* 2015; **33**: 1284-1290.

25. GlaxoSmithKline Biologicals. An observational cohort study to assess the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix® in the United Kingdom. Study number 116239 (EPI-HPV-040 VS UK). https://gsk.sylogent.com/files/116239-Clinical-Study-Result-Summary.pdf (accessed 25 October 2016).

26. Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, Boggon R, Bunge EM, Pladevall-Vila M, Baril L. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Hum Vaccin Immunother* 2016; **12**: 2862-2871.

Supporting information H. Risk of GBS during ≤2 years following the first dose of AS04-HPV-16/18. CI, confidence interval; GBS, Guillain–Barré syndrome; OR, odds ratio; Randomized Controlled Trials; UK, United Kingdom

	Exposed		Non-exposed		GBS (2 years)
	Events	Subjects	Events	Subjects	OR (95% CI)
Studies					
Pooled RCTs[1-18]	0.3	21,455.5	0.2	20,613.5	1.00 (0.004–255.89)
Cluster-randomized trial[19,20]	0.3	12,400.6	0.2	8119.4	1.00 (0.004–289.58)
UK cohort study[21]	0.3	64,998.5	0.2	64,994.5	1.00 (0.004–255.60)
French cohort study[22,23]	2.4	55,545	12.5	1,410,596	4.93 (1.25–19.53)
Case–control study[24,25,*]	0	1	13.5	143	0.03 (0.00–8.84E+12)
Primary analysis: inverse-variance with continuity correction					
Fixed effect					**3.83 (1.08–13.57)**
Random effect	I^2 = 0.00%; P = 0.93				**3.83 (1.08–13.57)**
Secondary analyses					
Pooled estimate*	2.4	154,398	12.5	1,504,322	1.89 (0.48–7.49)
Beta-binomial regression (without case–control study[24,25])					1.74 (0.17–17.67)
Beta-binomial regression (with case–control study[24,25])					0.51 (0.05–5.77)



*The case–control study was not included in the pooled estimate.

References

1. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, Zahaf T, Innis B, Naud P, De Carvalho NS, Roteli-Martins CM, Teixeira J, Blatter MM, Korn AP, Quint W, Dubin G, GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364**: 1757-1765.
2. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G, HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006; **367**: 1247-1255.
3. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G, HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic

HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374**: 301-314.

4. Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer AR, Porras C, Schussler J, Jimenez S, Sherman ME, Quint W, Schiller JT, Lowy DR, Schiffman M, Hildesheim A, Costa Rica Vaccine Trial Group. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. *Cancer Discov* 2011; **1**: 408-419.
5. Medina DM, Valencia A, de Velasquez A, Huang LM, Prymula R, Garcia-Sicilia J, Rombo L, David MP, Descamps D, Hardt K, Dubin G, HPV Study Group. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls. *J Adolesc Health* 2010; **46**: 414-421.
6. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J, Del Rosario-Raymundo MR, Verheijen RH, Quek SC, da Silva DP, Kitchener H, Fong KL, Bouchard C, Money DM, Ilancheran A, Cruickshank ME, Levin MJ, Chatterjee A, Stapleton JT, Martens M, Quint W, David MP, Meric D, Hardt K, Descamps D, Geeraerts B, Struyf F, Dubin G, VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet* 2014; **384**: 2213-2227.
7. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, Durand C, Herve C, Descamps D. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. *Vaccine* 2013; **31**: 5745-5753.
8. Sow PS, Watson-Jones D, Kiviat N, Changalucha J, Mbaye KD, Brown J, Bousso K, Kavishe B, Andreasen A, Toure M, Kapiga S, Mayaud P, Hayes R, Lebacq M, Herazeh M, Thomas F, Descamps D. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: a randomized trial in 10-25-year-old HIV-seronegative African girls and young women. *J Infect Dis* 2013; **207**: 1753-1763.
9. Leroux-Roels G, Haelterman E, Maes C, Levy J, De Boever F, Licini L, David MP, Dobbelaere K, Descamps D. Randomized trial of the immunogenicity and safety of the Hepatitis B vaccine given in an accelerated schedule coadministered with the human papillomavirus type 16/18 AS04-adjuvanted cervical cancer vaccine. *Clin Vaccine Immunol* 2011; **18**: 1510-1518.
10. Pedersen C, Breindahl M, Aggarwal N, Berglund J, Oroszlan G, Silfverdal SA, Szuts P, O'Mahony M, David MP, Dobbelaere K, Dubin G, Descamps D. Randomized trial: immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. *J Adolesc Health* 2012; **50**: 38-46.

11. Schmeink CE, Bekkers RL, Josefsson A, Richardus JH, Berndtsson Blom K, David MP, Dobbelaere K, Descamps D. Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls. *Vaccine* 2011; **29**: 9276-9283.
12. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, Descamps DJ, Bock HL, Indian HPV Vaccine Study Group. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. *J Obstet Gynaecol Res* 2010; **36**: 123-132.
13. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. *Int J Gynecol Cancer* 2010; **20**: 847-855.
14. Kim YJ, Kim KT, Kim JH, Cha SD, Kim JW, Bae DS, Nam JH, Ahn WS, Choi HS, Ng T, Bi D, Ok JJ, Descamps D, Bock HL. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10-14 years. *J Korean Med Sci* 2010; **25**: 1197-1204.
15. Ngan HY, Cheung AN, Tam KF, Chan KK, Tang HW, Bi D, Descamps D, Bock HL. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. *Hong Kong Med J* 2010; **16**: 171-179.
16. Lim BK, Ng KY, Omar J, Omar SZ, Gunapalaiah B, Teoh YL, Bock HL, Bi D. Immunogenicity and Safety of the AS04-adjuvanted Human Papillomavirus-16/18 Cervical Cancer Vaccine in Malaysian Women Aged 18-35 years: A Randomized Controlled Trial. *Med J Malaysia* 2014; **69**: 2-8.
17. Kim SC, Song YS, Kim YT, Kim YT, Ryu KS, Gunapalaiah B, Bi D, Bock HL, Park JS. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15-25 years old healthy Korean women. *J Gynecol Oncol* 2011; **22**: 67-75.
18. Zhu F, Li J, Hu Y, Zhang X, Yang X, Zhao H, Wang J, Yang J, Xia G, Dai Q, Tang H, Suryakiran P, Datta SK, Descamps D, Bi D, Struyf F. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years. *Hum Vaccin Immunother* 2014; **10**: 1795-1806.
19. Lehtinen M, Apter D, Baussano I, Eriksson T, Natunen K, Paavonen J, Vanska S, Bi D, David MP, Datta S, Struyf F, Jenkins D, Pukkala E, Garnett G, Dubin G. Characteristics of a cluster-randomized phase IV human papillomavirus vaccination effectiveness trial. *Vaccine* 2015; **33**: 1284-1290.
20. GlaxoSmithKline Biologicals. An observational cohort study to assess the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix® in the United Kingdom. Study number 116239 (EPI-HPV-040 VS UK). https://gsk.sylogent.com/files/116239-Clinical-Study-Result-Summary.pdf (accessed 25 October 2016).

21. Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, Boggon R, Bunge EM, Pladevall-Vila M, Baril L. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Hum Vaccin Immunother* 2016; **12**: 2862-2871.

22. Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Vaccination contre les infections à HPV et risque de maladies auto-immunes : une étude Cnamts/ANSM rassurante - Point d'information. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information (accessed 26 August 2016).

23. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France. *Vaccine* 2017; **35**: 4761-4768.

24. Grimaldi-Bensouda L, Rossignol M, Kone-Paut I, Krivitzky A, Lebrun-Frenay C, Clet J, Brassat D, Papeix C, Nicolino M, Benhamou PY, Fain O, Costedoat-Chalumeau N, Courcoux MF, Viallard JF, Godeau B, Papo T, Vermersch P, Bourgault-Villada I, Breart G, Abenhaim L, PGRx-AD Study Group. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *J Autoimmun* 2017; **79**: 84-90.

25. Grimaldi-Bensouda L, Aubrun E, Abenhaim L. ANALYSIS OF CERVARIX® & AUTOIMMUNE DISORDERS USING THE PGRx INFORMATION SYSTEM. Data on file. 2015.

4.3 Risk of spontaneous abortion and other pregnancy outcomes in 15–25 year old women exposed to human papillomavirus-16/18AS04-adjuvanted vaccine in the United Kingdom

Laurence Baril, Dominique Rosillon, Corinne Willame, Maria Genalin Angelo, Julia Zima, Judith H. van den Bosch, Tjeerd Van Staa, Rachael Boggon, Eveline M. Bunge, Sonia Hernandez-Diaz, Christina D. Chambers

Vaccine. 2015 Nov 27;33(48):6884-91. doi: 10.1016/j.vaccine.2015.07.024.

Abstract

Background: We assessed the risk of spontaneous abortion (SA) after inadvertent exposure to HPV-16/18 vaccine during pregnancy using an observational cohort design.

Methods: The study population included women aged 15–25 years registered with the Clinical Practice Research Datalink General Practice OnLine Database in the United Kingdom (UK), who received at least one HPV-16/18-vaccine dose between 1st September 2008 and 30th June 2011. Exposed women had the first day of gestation between 30 days before and 45 days (90 days for the extended exposure period) after any HPV-16/18-vaccine dose. Non-exposed women had the first day of gestation 120 days–18 months after the last dose. SA defined as foetal loss between weeks 1 and 23 of gestation (UK definition).

Results: The frequency of SA was 11.6% (among 207 exposed) and 9.0% (632 non-exposed), women: hazard ratio (HR) adjusted for age at first day of gestation 1.30 (95% confidence interval: 0.79–2.12). Sensitivity analysis per number of doses administered (−30 to +45-day risk period) showed a HR for SA of 1.11 (0.64–1.91) for 18/178 women with one dose during the risk period versus 2.55 (1.09–5.93) in 6/29 women with two doses within a 4–5 weeks period. The proportion of pre-term/full-term/postterm deliveries, small/large for gestational age infants, and birth defects was not significantly different between exposed and non-exposed women. Results were consistent using a (United States) SA definition of foetal loss between weeks 1–19 and/or the extended risk period.

Conclusion: There was no evidence of an increased risk of SA and other adverse pregnancy outcomes in young women inadvertently HPV-16/18-vaccinated around gestation. Nevertheless, women who are pregnant or trying to become pregnant are advised to postpone vaccination until completion of pregnancy.

Cervarix and the risk of pregnancy outcomes

1. Introduction

Cervarix™ (Human papillomavirus [HPV]-16/18-vaccine, GSK vaccines) contains HPV-16 and HPV-18 virus-like particles formulated with the proprietary Adjuvant System, AS04. HPV-16/18-vaccine is indicated for girls and women from 9 years of age onwards, for the prevention of persistent infection, pre-cancerous lesions, and cervical and other genital cancers caused by oncogenic HPV.

Unintended exposure to HPV-16/18-vaccine prior to the onset of pregnancy or during pregnancy is possible in the population recommended for vaccination, and unplanned pregnancies and their outcomes were closely monitored in clinical trials. A pooled analysis of pre-licensure clinical trial data suggested a numerical imbalance in spontaneous abortion (SA) among young women 15–25 years of age when the first day of the last menstrual period (LMP) occurred between 30 days before and 45 days after (−30 to +45) any dose of HPV-16/18-vaccine (11.0%) versus controls who received hepatitis A vaccine (5.8%) [1]. The Center for Biologics Evaluation and Research in the United States (US) requested that GSK conduct a post-licensure analytic epidemiological study to investigate these findings further [2].

An independent analysis of two studies of HPV-16/18-vaccine concluded that an increased SA risk among pregnancies conceived within 3 months of vaccination could not be completely ruled out [3]. Post-licensure surveillance data indicate that pregnancy outcomes including SA in pregnant women who were inadvertently vaccinated with HPV-16/18-vaccine were in line with published literature in unvaccinated populations [4].

After a feasibility assessment (see web material), we assessed the risk of SA within a cohort of vaccinated women and compare pregnancies exposed around gestation to a non-exposed cohort of pregnancies using the Clinical Practice Research Datalink General Practice OnLine Database (CRPD GOLD) in the United Kingdom (UK). The HPV immunisation programme between the 2008 and 2010 school years, achieved a HPV-16/18-vaccine coverage of 89.0%, 87.6% and 83.8% for the first, second and third doses, respectively, by 2010/11 [5,6].

2.Methods

2.1. Data source, population and setting

CPRD GOLD is one of the largest anonymised primary care database, and captures longitudinal medical records including demographic and lifestyle parameters, clinical events, referrals to specialists and immunisation records from around 600 general practices [7]. Complementary information can be obtained through the free text data practice management system from CPRD GOLD [7]. Additionally, a mother–baby link allows linkage of medical records of women to those of offspring [8].

The study population included women aged 15–25 years registered in CPRD GOLD and with the first day of gestation available from the database between 1st September 2008 and 30th June 2011. Eligible women were to have received at least one dose of HPV-16/18-vaccine during the same period (see web material for CPRD GOLD HPV vaccination codes). Vaccinated women who received an unspecified HPV vaccine or Gardasil® (Merck & Co.) were excluded. Women in the non-exposed cohort who had a previous pregnancy included in the exposed cohort were also excluded.

If multiple pregnancy episodes occurred during the study period, only the first pregnancy in the database was considered for the analysis.

The study protocol was approved by the Independent Scientific

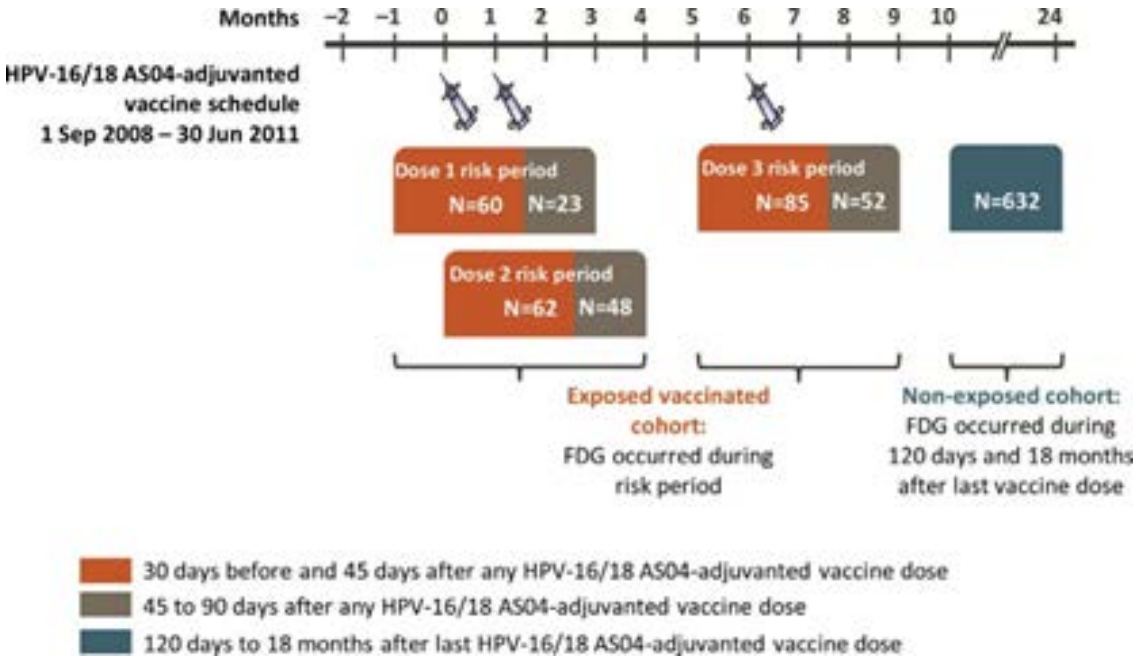
Advisory Committee for the Medicines and Healthcare Products Regulatory Agency database research [9]. No patient informed consent was needed because patient information in CPRD GOLD is fully anonymised. The study is registered at www.clinicaltrials.gov NCT01905462, EU PAS Register Number ENCEPP/SDPP/3310.

2.2. Study cohorts

Exposed and non-exposed cohorts were defined according to the first day of gestation, defined as the first day of LMP, or as the estimated date of delivery minus 280 days (equal to the median gestational age of 40 weeks), or as adjusted according to ultrasound dating, and exposure to HPV-16/18-vaccine as recorded in CPRD GOLD. Exposed women were those with first day of gestation between −30 and +45 days after any HPV-16/18-vaccine dose (an extended risk period −30 to +90 days after any HPV-16/18vaccine dose was also considered) (Fig. 1). Non-exposed women were protocol-defined as having

first day of gestation between 120 days to 18 months after the last HPV-16/18-vaccine dose, and had no further HPV-16/18-vaccine dose before the outcome (Fig. 1).

Figure 1 Number of subjects identified as exposed or non-exposed according to time of the first day of gestation in relation to HPV-16/18 vaccination. FDG = first day of gestation.



The analysis of SA excluded women who were not pregnant, or for whom the first day of gestation was outside the study period or not confirmed after medical record review. The analysis of other pregnancy outcomes, neonatal outcomes, and birth defects excluded women for whom the first day of gestation was not compatible with the confirmed outcome, or women whose pregnancy outcome was unknown.

2.3. Outcome definition

The primary study outcome was the occurrence of SA during weeks 1–23 of gestation (UK definition). Secondary outcomes included the occurrence of SA during weeks 1–19 of gestation (US definition) and the occurrence of other pregnancy outcomes: induced/therapeutic and other abortions, stillbirth (defined as intra-uterine death of foetus after 23 weeks gestation in the UK or after 19 weeks gestation in the US), birth defects, small (defined as ≤10th percentile for sex and age on birth weight or length) or large (≥90th percentile of normal weight or length) for gestational age at birth [10], pre/post-term delivery and infant death before age 12 weeks.

2.4. Data collection and case ascertainment

The final study database consisted of data extracted from CPRD GOLD (Supplementary Fig. 1). Pregnancy outcomes were identified using pre-defined algorithms (Supplementary Tables 1 and 2). Information extracted included demographic characteristics, obstetric history, lifestyle during pregnancy (smoking, alcohol consumption), medical conditions, vaccination records, and drug use during gestation. Specific de-identified free text associated with pregnancy endpoints, estimated date of delivery, ultrasound scan tests and birth details was requested for pregnancy endpoint confirmation. All subject profiles were reviewed by Pallas, Health Research and Consultancy B.V., the Netherlands.

A safety physician within GSK reviewed all pregnancy outcomes other than live, full-term deliveries of normal weight-for-gestation babies. Final case ascertainment was adjudicated by two independent external experts specialised in teratology who remained blinded with respect to the exposure status of the cases throughout the ascertainment process. Final ascertainment of cases of SA with a doubtful outcome, and all cases of therapeutic/other abortion, stillbirth, infant death and birth defect were reviewed by both experts. All other SA cases were reviewed by one expert, while the other expert reviewed a random sample of 10% of SA cases as a quality check (all decisions were in agreement with the classification made by Pallas). One expert reviewed all cases of unrealistically long pregnancy (more than 43 weeks gestation).

2.5. Statistical analysis

All statistical comparisons were made between the exposed and non-exposed cohorts. Demographic and baseline characteristics were compared using Fisher's exact test, Wilcoxon test or Cochran–Mantel–Haenszel test.

A Cox proportional hazards model that included the exposure status as a binary independent variable and the age at first day of gestation as a continuous covariate was used to estimate hazard ratios (HR) for SA. The dependent variable was the time between the first day of gestation and the event, or censoring (week 23 of gestation, date of induced/therapeutic abortion, date of maternal death, date of last available pregnancy data whichever occurred first). The aHR was derived as the exponential of

the coefficient associated with the exposure status and its 95% Wald confidence interval (95% CI) was estimated.

A planned sensitivity analysis used a Cox proportional hazards model, which in addition to age at first day of gestation, included the following covariates when they occurred in ≥5% of subjects: smoking, alcohol consumption, gestation start during the H1N1 pandemic season, general practice region, diabetes and high blood pressure during pregnancy, number of previous pregnancies, vaccination with another vaccine from −90 to +90 days gestation, and use of contra-indicated drugs during the first trimester of gestation. Another planned exploratory sensitivity analysis used Cox proportional hazards models to assess the risk of SA according to the number of doses received during the risk period (1 dose-, 2 dose-exposed subcohorts) compared to the non-exposed cohort. Additional (post hoc) analyses assessed the number of doses and time of vaccination (before or after first day of gestation); the dose received (1st, 2nd, or 3rd dose) in the pre-defined risk period; and excluding subjects receiving the third dose during the risk period.

We used criteria posed by the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS, see supplement) to interpret the results [11].

Logistic regression models were used to compare other pregnancy outcomes with occurrence of the outcome as a binary dependent variable, the exposure status as a binary independent variable and the age at first day of gestation as a continuous covariate. The odds ratio and its 95% CI were derived. It should be noted that these adverse events were secondary endpoints and the study was not powered to detect pre-defined risks for these endpoints. There was no previous safety signal for any other adverse pregnancy outcome.

2.6. Sample size

Based on a feasibility assessment which estimated the number of potential eligible subjects and assuming a proportion of SA of 11.5% of pregnancies and that 20% of subjects would have incomplete 23-week gestation data, the study had 98% power to detect a relative risk (HR) of 2.0 of SA between the exposed and non-exposed cohorts subjects if the first day of gestation was −30 to +45 days after

any dose of HPV-16/18-vaccine (two-sided log-rank test with type I error rate of 5%). The HR detectable with 80% power was 1.69.

3. Results

Of 161,849 HPV-vaccinated women in CPRD GOLD, 1046 (0.6%) met the inclusion criteria (see web material). Of these, 839 (962 for the extended risk period) were included in the primary analysis of SA: 207 (330) in the −30 to +45(+90) day exposed, and 632 in the non-exposed cohorts (Supplementary Fig. 1). The non-exposed cohort was approximately 6 months older than the exposed cohort ($p < 0.0001$), around 3 months younger at first vaccination dose ($p = 0.03$), had fewer pregnancy onsets during the H1N1 pandemic season (14.4% versus 36.2%, $p < 0.001$) and had fewer exposures to other vaccines within 3 months before first day of gestation (1.6% versus 4.8%, $p = 0.01$) (Table 1). The cohorts were similar in terms of general practice region, history of previous pregnancies and/or SA. Information about lifestyle and medical history, when available, indicated no differences between the cohorts (Table 1).

Table 1 Demographic characteristics of the exposed and non-exposed cohorts defined according to the first day of gestation (cohort for the analysis of spontaneous abortion, −30 to +45 day and −30 to +90 day risk periods).

Characteristic		Non-exposed, N = 632 n (%)	Exposed (−30 to +45 days), N = 207 n (%)	p-value	Exposed (−30 to +90 days), N = 330 n (%)	p-value
Age in years at first day of gestation	Mean (SD)	18.5 (1.18)	17.9 (1.13)	<0.0001	18.0 (1.18))	<0.0001
	Range	15.2–23.9	15.1–23.3	–	15.0–23.3	–
	9–15 year group	17 (2.7)	8 (3.9)	<0.0001	13 (3.9)	<0.0001
	16–18 year group	386 (61.1)	174 (84.1)	–	262 (79.4)	
	19–25 year group	229 (36.2)	25 (12.1)	–	55 (16.7)	
Age in years at first HPV-16/18 dose	Mean (SD)	17.30 (1.14)	17.54 (1.10)	0.027	17.6 (1.12)	<0.0001
	Range	14.23–23.47	14.58–23.23	–	14.3–23.2	
Region of residence	North England	137 (21.7)	37 (17.9)	0.71	56 (17.0)	0.35

	Midlands	96 (15.2)	33 (15.9)	–	57 (17.3)	
	South England	259 (41.0)	90 (43.5)	–	139 (42.1)	
	Ireland Scotland Wales	140 (22.2)	47 (22.7)	–	78 (23.6)	
Marital status	Single	105 (94.6)	37 (100)	0.01	55 (94.8)	0.02
	Married–Engaged-Co-habiting	6 (5.4)	0 (0.0)	–	3 (5.2)	
	Missing	521	170	–	272	
Number of previous pregnancies	0	164 (84.1)	78 (91.8)	0.33	116 (89.2)	0.46
	1	22 (11.3)	5 (5.9)	–	10 (7.7)	
	2	7 (3.6)	1 (1.2)	–	2 (1.5)	
	3+	2 (1.0)	1 (1.2)	–	2 (1.5)	
	Missing	437	122	–	200	
Number of previous abortions/stillbirths	0	181 (85.0)	84 (92.3)	0.15	127 (90.1)	0.27
	1	27 (12.7)	6 (6.6)	–	11 (7.8)	
	2	3 (1.4)	0 (0.0)	–	2 (1.4)	
	3+	2 (0.9)	1 (1.1)	–	1 (0.7)	
	Missing	419	116	–	189	
Smoking status during pregnancy	Smoker	45 (11.2)	20 (14.0)	0.37	31 (14.3)	0.30
	Missing	229	64	–	113	
Alcohol consumption during pregnancy	Yes	47 (29.0)	21 (32.3)	0.63	32 (30.5)	0.89
	Missing	470	142	–	225	
Diabetes during pregnancy	Yes/probable[a]	8 (15.4)	2 (10.0)	0.72	5 (17.2)	1.0
	Missing	580	187	–	301	
High blood pressure during pregnancy	Yes	37 (8.0)	15 (9.3)	0.62	21 (8.3)	0.89
	Missing	170	46	–	78	
First day of gestation during H1N1 pandemic	Before	3 (0.5)	50 (24.2)	<0.0001	65 (19.7)	<0.0001
	During	91 (14.4)	75 (36.2)		132 (40.0)	
	After	538 (85.1)	82 (39.6)		133 (40.3)	
Number of HPV-16/18-vaccine doses	1	83 (13.1)	32 (15.5)	0.14	49 (14.8)	0.07
	2	130 (20.6)	50 (24.2)	–	86 (26.1)	
	3	417 (66.0)	125 (60.4)	–	194 (58.8)	
	4	2 (0.3)	0 (0.0)	–	1 (0.3)	
Exposure to other vaccines	<3 mo before first day of gestation	10 (1.6)	10 (4.8)	0.015	24 (7.3)	<0.0001

Exposure to contraindicated drugs	Yes	215 (34.0)	74 (35.7)	0.67	119 (36.1)	0.57

N = number of subjects. p-value: Fisher exact test or Wilcoxon test, p-value for previous pregnancies, previous abortions and number of HPV vaccine doses are computed by Cochran–Mantel–Haenszel. n/% = number/percentage of subjects in a given category (unless otherwise specified). SD = Standard deviation. A diabetes in the Exposed and non-exposed -30 to +45 cohort: yes=7 cases and probable=3 cases. Diabetes in the exposed and non-exposed -30 to +90 cohort: yes=10 cases and probable=3 cases.

3.1. Pregnancy outcomes

3.1.1. Spontaneous abortion

Among 839 women in the primary analysis (Fig. 1), pregnancy outcome information was available in 87.0% (n = 730). SA occurred in 9.7% (n = 81): 11.6% (n = 24) in the exposed cohort and 9.0% (n = 57) in the non-exposed cohort. The mean gestational age at the time of SA was 78.4 days (range 48–142 days) in the exposed cohort and 73.7 days (range 34–134 days) in the non-exposed cohort.

The overall age-adjusted HR for SA in weeks 1–23 gestation in women with first day of gestation between −30 and +45 days after any HPV-16/18-vaccine dose was (1.30; 95% CI 0.79–2.12; p = 0.30) (Table 2, Fig. 2).

Table 2 Cox proportion hazard analysis of SA during the first 23 weeks of gestation – age adjusted, and for other covariates (cohort for the analysis of spontaneous abortion, −30 to +45 day risk period).

Category	N	n (%)	Adjusted HR (95% CI)	p-value
Primary analysis (age adjusted)				
Total	839	81 (9.7)	–	–
Exposed	207	24 (11.6)	1.30 (0.79; 2.12)	0.30
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	1.00 (0.82; 1.20)	0.96
Sensitivity analyses (adjusted for age and number of doses within the risk period)				
1 dose	178	18 (10.1)	1.11 (0.64; 1.91)	0.71
2 doses	29	6 (20.7)	2.55 (1.09; 5.93)	0.03
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	0.99 (0.82; 1.19)	0.91
Sensitivity analyses (adjusted for age and covariates)				
Exposed	207	24 (11.6)	1.34 (0.81; 2.24)	0.25
Non-exposed	632	57 (9.0)	1.00	–
Alcohol consumption during pregnancy	68	10 (14.7)	1.79 (0.78; 4.09)	0.17
Smoking during pregnancy	65	4 (6.2)	0.55 (0.20; 1.53)	0.25
High blood pressure during pregnancy	52	3 (5.8)	0.56 (0.18; 1.81)	0.33
Vaccination 3 months before or after first day of gestation	67	6 (9.0)	0.84 (0.36; 1.95)	0.69

Exposure to H1N1 pandemic	166	15 (9.0)	0.88 (0.49; 1.58)	0.67
Contraindicated drugs during pregnancy	289	29 (10.0)	1.06 (0.61; 1.84)	0.85
Region				
Midlands	129	13 (10.1)	0.83 (0.41; 1.70)	0.62
South England	349	32 (9.2)	0.83 (0.47; 1.46)	0.52
Ireland–Scotland–Wales	187	16 (8.6)	0.74 (0.38; 1.43)	0.37
North England	174	20 (11.5)	1.000	
Age at first day of gestation (continuous)	–	–	0.98 (0.81; 1.19)	0.86
Post hoc analyses (adjusted for age and covariates)				
1 or 2 dose exposure according to first day of gestation 1 dose before	102	10 (9.8)	1.09; (0.55; 2.15)	0.82
1 dose after	76	8 (10.5)	1.15; (0.54; 2.44)	0.71
2 doses before	6	1 (16.7)	1.78; (0.25; 12.87)	0.57
1 dose before and 1 after	23	5 (21.7)	2.80; (1.11; 7.06)	0.03
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	0.99 (0.82; 1.20)	0.95
Dose number (one dose)				
1st dose	52	5 (9.6)	1.10 (0.44; 2.80)	0.84
2nd dose	41	4 (9.8)	1.10 (0.39; 3.08)	0.86
3rd dose	85	9 (10.6)	1.14 (0.56; 2.32)	0.71
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	1.00 (0.82; 1.23)	0.97
Excluding women who received dose 3 only in the risk period				
1 dose	93	9 (9.7)	1.08 (0.52; 2.23)	0.83
2 doses	29	6 (20.7)	2.54 (1.09; 5.92)	0.03
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	0.99 (0.81; 1.20)	0.90

N = number of subjects in a given category. n/% = number of SAs. HR = hazard ratio with Wald 95% CI.

The HR adjusted for other covariates was similar to the main model (1.34, 95% CI: 0.81–2.24; p = 0.25). The model by number of doses received during the risk period showed that for subjects who received only 1 dose within the −45 to +30-day risk period (n = 18/178), there was no increase in SA risk (aHR 1.11, 95% CI 0.64–1.91; p = 0.71). For women who received two doses of HPV16/18-vaccine within the −45 to +30-day risk period (n = 6/29), the aHR was 2.55 (95% CI: 1.09–5.93, p = 0.03) (Table 2).

The findings for the extended −30 to +90-day risk period were consistent with the main analysis (Supplementary Table 3). The findings for the analysis defining SA as occurring between weeks 1 and 19 gestation were also consistent with the main analysis for both risk periods (Supplementary Table 4).

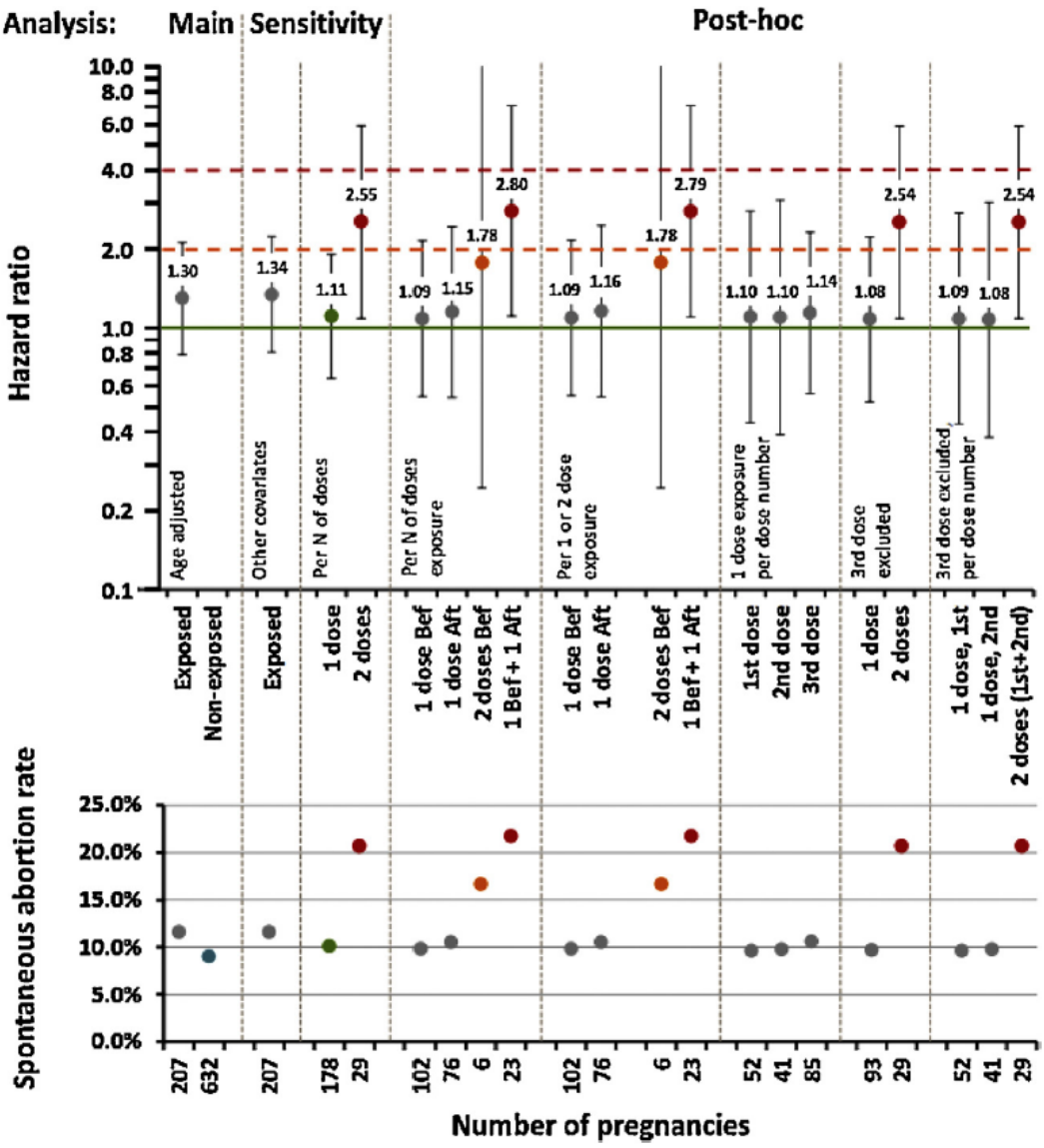
Additional analyses were conducted in order to explore the observed increased risk of SA in women who had received two doses of HPV-16/18 vaccine during the risk period. In women who received one HPV-16/18-vaccine dose during the −30 to +45-day risk period (n = 178), the Cox hazards proportional model did not show evidence of increased SA risk, regardless of dose number (first, second or third) or timing (before or after the first day of gestation) (Table 2 and Fig. 2).

For women who received two doses during the risk period (n = 29), the numbers were too small to explore different timings of exposure; for most women in whom one dose was administered before and one dose after the first day of gestation (n = 23 aHR 2.80, 95% CI: 1.11, 7.06; p = 0.03).

Considering the extended −30 to +90-day risk period, the highest frequency of SAs occurred when the time-interval between doses was 4–5 weeks (10/39, 26%) compared to an interval of longer than 5 weeks (1/20, 5%). The gestational age at SA was similar among the different cohorts and in subjects exposed to one or two doses within either risk period (data not shown).

Applying VAMPSS criteria, based on the HR and on the confidence intervals, the proposed interpretation of our study results are: “no evidence of risk” for the −30 to +45-day risk period and “evidence of relative safety” for the −30 to +90 risk period (for both the 1–23 and 1–19-week SA definitions) (Fig. 2). The difference between the two risk periods is mainly due to the width of the CI related to the number of subjects (207 versus 330) than a difference in the HR estimates (1.3/1.2). The results in a few women who received two doses during the risk period would be classified as showing “a positive association” whereas the results showed “evidence of relative safety” for one dose exposure (and similar results for the extended period).

Figure 2 Hazard ratios (HR) and spontaneous abortion (SA) rates for main, sensitivity and post-hoc analyses (-30/+45-day risk period) and interpreted using safety thresholds proposed by the Vaccines and Medications in Pregnancy Surveillance System [11].



The safety of any exposure cannot be considered absolute; estimates of safety reflect the degree of confidence that is consistent with an observation of no increased risk between a given exposure and outcome. Grey circle: no evidence of increased risk of SA in the exposed cohort (HR not statistically significant and 95% confidence interval [CI] upper limit of HR ≤4); Olive circle: evidence of relative safety in terms of the risk of SA in the exposed cohort (HR not statistically significant and 95% CI upper limit of HR ≤2); Red circle: statistically significant increased risk of SA in the exposed cohort (for subjects receiving 2 doses during the risk period a positive association was defined, but this finding was based on 29 subjects included in the sensitivity analysis); Orange circle: no statistically significant increased risk, but the 95% upper limit of the HR ≥4; Green circle: non-exposed cohort; N = number; Bef = vaccine dose administered before last menstrual period; Aft = vaccine dose administered after FGD; error bars represent 95% Wald CI.

3.1.2. Other pregnancy outcomes

There were seven stillbirths (0.8%), 1.4% (n = 3 at mean gestational age 185.7 days, range 162–204) in the exposed and 0.6% (n = 4, mean gestational age 180.3-days, range 162–190) in the non-exposed cohort. The proportion of pre-term, full-term and post-term deliveries appeared to be similar amongst the exposed and non-exposed cohorts (Table 3).

Table 3 Pregnancy outcomes in the exposed and non-exposed cohorts (cohort for the analysis of spontaneous abortion, −30 to +45 day and −30 to +90 day risk periods).

Outcome category	Exposed (−0 to +45), N = 207 n (%)	Exposed (−30 to +90), N = 330 n (%)	Non-exposed, N = 632 n (%)
Known confirmed outcome	182 (87.9)	227 (83.9)	548 (86.7)
Spontaneous abortion	24 (11.6)	34 (10.3)	57 (9.0)
Induced abortion	21 (10.1)	33 (10.0)	66 (10.4)
Therapeutic abortion	0 (0.0)	1 (0.3)	1 (0.2)
Other abortion	0 (0.0)	0 (0.0)	2 (0.3)
Stillbirth	3 (1.4)	3 (0.9)	4 (0.6)
Live births[a]	134 (73.6)	206 (74.4)	418 (76.3)
Pre-term delivery	6 (2.9)	16 (4.8)	27 (4.3)
Full-term delivery	109 (52.7)	167 (50.6)	349 (55.2)
Post-term delivery	19 (9.2)	23 (7.0)	42 (6.6)
At least one small for gestation	8 (6.0)	14 (6.8)	27 (6.5)
At least one large for gestation	1 (0.7)	4 (1.9)	14 (3.3)
Normal baby	64 (47.8)	88 (42.7)	186 (44.5)
Unknown for small/large for gestation	61 (45.5)	100 (48.5)	191 (45.7)
Unknown outcome	25 (12.1)	53 (16.1)	84 (13.3)

N = number of mothers. n/% = number/percentage of subjects in a given category. −30 to +45 day risk period.
[a] A total of five twin pregnancies resulted in three (full-term live births, one pre-term delivery and one stillbirth and one live pre-term birth from the same pregnancy). -30 to +90 day risk period: seven twin pregnancies among them one stillbirth and one pre-term live birth from the same pregnancy, four full-term pregnancies and two pre-terms pregnancies.

There were 557 babies born during the study period (51.4% male and 48.6% female). One minute Apgar scores were ≥8 in 89.7% and 91.3% of babies in each respective cohort.

Birth defects were confirmed in seven babies (5.9%, 7/136) from the exposed and 21 babies (6.0%, 21/421) from the non-exposed cohorts (Table 4). There were three neonatal deaths of which two were within 7 days of birth: one with an unspecified congenital abnormality and one with a thromboembolic disorder. The third death was due to sudden infant death syndrome 73 days after birth.

There was no evidence of a difference in the risk of other pregnancy outcomes between the exposed and unexposed populations for both risk periods (Supplementary Tables 5 and 6).

Table 4 Birth defects in the exposed and non-exposed cohorts (cohort for the analysis of other pregnancy outcomes −30 to +45 day and −30 to +90 day risk periods).

Characteristics	Categories	Exposed (−30 to +45), N = 136 n (%)	Exposed (−30 to +90), N = 210 n (%)	Non-exposed, N = 421 n (%)	Total, N = 557 n (%)
Birth defect	No	112 (94.1)	167 (94.9)	327 (93.4)	439 (93.6)
	Yes – confirmed	7 (5.9)	9 (5.1)	21 (6.0)	28 (6.0)
	Yes – unconfirmed[a]	0	0	2 (0.6)	2 (0.4)
	Missing	17	34	71	88
Classification[b]	At least one major birth defect	4 (57.1)	5 (55.6)	11 (52.4)	15 (53.6)
	At least one minor birth defect	3 (42.9)	4 (44.4)	10 (47.6)	13 (46.4)
	NA	0	0	2	2
	Missing	129	201	398	527

N = total number of babies. n/% = number/percentage of babies in a given category.
a The two unconfirmed birth defects were not classified (one congenital abnormality-not further specified and one undescended testicle).
b Major birth defects included: in the −30 to +45 day exposed cohort – positional talipes, diaphragmatic hernia, Trisomy 21, tetralogy of Fallot. Additionally in the −30 to +90 day exposed cohort – hypospadias. In the non-exposed cohort – microcephaly, developmental hip dysplasia, bilateral positional talipes, diaphragmatic hernia, oesophageal atresia, dislocation and subluxation of the hip, cystic kidney disease, cleft palate, cataract and lens abnormalities, peri-membranous ventricular septal defect, renal agenesis and dysgenesis, horseshoe kidney.

4. Discussion

We observed an SA rate during weeks 1–23 of gestation in UK women 15–25 years of age of 11.6% in the exposed cohort (first day of gestation within −30 to +45 days of HPV-16/18-vaccine administration) and 9.0% in the non-exposed cohort. We found no evidence of an increased risk of SA in women whose first day of gestation was within −30 to +45 (or −30 to +90) days of HPV-16/18vaccine administration, and there was no evidence of increased risk of any other adverse pregnancy outcome in exposed women. In a sensitivity analysis, we observed an increased risk of SA (n = 6) in the 29 women who received two HPV-16/18-vaccine doses in the risk period. Post hoc investigations suggested that the risk of SA increased in six women receiving two doses within a 4–5 weeks interval, where one dose was administered before and one dose after first day of gestation. The post hoc analyses confirmed no risk increase in subjects exposed to a single dose (HR close to 1) regardless of dose number or timing in relation to the first day of gestation.

The SA rates we observed are in range with the SA rate estimate from the feasibility assessment performed in CPRD GOLD on women aged between 11 and 50 years (11.6%), and with published rates for this and wider age ranges from the UK and developed countries [12–15]. The results are also consistent with an independent analysis on SA made by the National Cancer Institute in the United States [3], and with a later pooled analysis of HPV-16/18vaccine clinical trial data from 40 countries and including data from 10,476 pregnancies, in which the SA rate within the −30 to +45 day risk period was 12.9% in HPV-16/18 vaccinees and 10.1% in women who received control vaccines [16].

An additional analysis was conducted on a previously reported pooled clinical trial database [16], that included women aged 15–25 years (N = 9359 pregnancies) vaccinated with HPV-16/18-vaccine or a control vaccine. In women with a single dose of HPV-16/18 administered during the −30 to +45-day risk period (N = 326) the risk ratio (RR) was 1.54 (95% CI 0.95–2.54); compared to women exposed to a control vaccine during the same period (N = 338); the RR for two-dose exposure (N = 71) was 1.21 (95% CI 0.27–7.33) versus controls (N = 38) (GSK unpublished data).

This targeted safety study to assess the risk of SA has been conducted in a large population-based database that is likely to be representative of the general population of young women in the UK. The CPRD GOLD database has been used to undertake other research on pregnancy [17–19]. The assessment of SA rates in our study was feasible using a combination of data coded in the CPRD GOLD, including the mother–baby link [20], and information from free text. We were able to confirm study endpoints and pregnancy outcomes in the majority of women and made attempts to minimise case ascertainment bias by blinding experts during case review. By defining the non-exposed cohort as vaccinated women with a distant history of confirmed HPV-16/18 vaccination, we overcame the potential limitation related to incomplete vaccination records, increasing the specificity of the control group since it is unlikely that women would be vaccinated again after completing the three-dose HPV-16/18-vaccine schedule. Nevertheless, 13.1% and 20.6% of women had one or two recorded doses only (Table 1). So the risk that they were exposed to an unrecorded dose could not be totally excluded. This approach also decreased the risk of differing healthcare behaviours between exposed and

unvaccinated subjects, but led, as anticipated, to differences in terms of age at first day of gestation and exposure to the H1N1 pandemic (1st June 2009–28th February 2010 [21]). However, adjustment for these covariates and others corroborated the results of the main analysis. Sensitivity analyses adjusted for other possible risk factors, including missing data, yielded virtually the same results as the main analysis, suggesting that missing demographic data had no impact on the study results. Finally, early SA (before 9 weeks GA) may go unrecognised. These pregnancies were probably not documented in CRPD GOLD because women were not aware of their pregnancy. As they were not included in the denominator, the risk of underestimation of SA rate should be therefore limited. In conclusion, this study indicates that the rate of SA in HPV-16/18vaccinated young women is consistent with rates reported in the literature. The results show that in young women who are inadvertently vaccinated around gestation, there is no overall increase in SA or in other adverse pregnancy outcomes compared to women with similar characteristics from the same population who were not exposed. Nevertheless, women who are pregnant or trying to become pregnant, are advised to postpone vaccination until completion of pregnancy.

References

[1] Descamps D, Hardt K, Spiessens B, Izurieta P, Verstraeten T, Breuer T, Dubin G. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials Hum Vaccin 2009;5:332–40.

[2] , http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ ucm189804.htm (accessed 11.11.14) Approved Products – Postmarketing Requirement (PMR) Review Memo – Cervarix 2009. Center for Biologics Evaluation and Research; 2009.

[3] Wacholder S, Chen BE, Wilcox A, Macones G, Gonzalez P, Befano B, et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ 2010;340:c712.

[4] Angelo M, Zima J, Tavares F, Baril L, Arellano F. Post-licensure safety surveillance for human papillomavirus-16/18 AS04-adjuvanted vaccine: more than 4 years of experience. Pharmacoepidemiol Drug Saf 2014;23:456–65.

[5] Annual HPV vaccine coverage in England in 2010/2011. Department of Health; 2012. http://media.dh.gov.uk/network/211/files/2012/03/120319 HPV UptakeReport2010-11-revised acc.pdf [accessed 01.12.13].

[6] Annual HPV vaccine coverage in England in 2009/2010. GOV.UK; 2012. https:// www.gov.uk/government/publications/annual-hpv-vaccine-coverage-inengland-in-2009-2010 [accessed 01.12.13].

[7] Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf 2012;3:89–99.

[8] Wurst KE, Ephross SA, Loehr J, Clark DW, Guess HA. The utility of the general practice research database to examine selected congenital heart defects: a validation study. Pharmacoepidemiol Drug Saf 2007;16:867–77.

[9] ISAC (Independent Scientific Advisory Committee) for MHRA Database Research; 2014. http://www.cprd.com/ISAC/ [accessed 11.11.14].

[10] Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010;125:e214–24.

[11] Schatz M, Chambers CD, Jones KL, Louik C, Mitchell AA. Safety of influenza immunizations and treatment during pregnancy: the Vaccines and Medications in Pregnancy Surveillance System. Am J Obstet Gynecol 2011;204:S64–8.

[12]Ventura SJ, Abma JC, Mosher WD, Henshaw SK. Estimated pregnancy rates by outcome for the United States, 1990–2004. Natl Vital Stat Rep Cent Dis Control Prev Natl Cent Health Stat Natl Vital Stat Syst 2008;56(1–25):28.

[13]Seamark C. Design or accident? The natural history of teenage pregnancy. J R Soc Med 2001;94:282–5.

[14]Saraiya M, Berg CJ, Shulman H, Green CA, Atrash HK. Estimates of the annual number of clinically recognized pregnancies in the United States, 1981–1991. Am J Epidemiol 1999;149:1025–9.

[15]Devine S, West S, Andrews E, Tennis P, Hammad TA, Eaton S, et al. The identification of pregnancies within the general practice research database. Pharmacoepidemiol Drug Saf 2010;19:45–50.

[16]Angelo MG, David MP, Zima J, Baril L, Dubin G, Arellano F, Struyf F. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiol Drug Saf. 2014 May;23(5):466-79. doi: 10.1002/pds.3554. Epub 2014 Feb 20.

[17]Charlton RA, Weil JG, Cunnington MC, Ray S, de Vries CS. Comparing the General Practice Research Database and the UK Epilepsy and Pregnancy Register as tools for postmarketing teratogen surveillance: anticonvulsants and the risk of major congenital malformations. Drug Saf Int J Med Toxicol Drug Exp 2011;34:157–71.

[18]Charlton RA, Weil JG, Cunnington MC, de Vries CS. Identifying major congenital malformations in the UK General Practice Research Database (GPRD): a study reporting on the sensitivity and added value of photocopied medical records and free text in the GPRD. Drug Saf Int J Med Toxicol Drug Exp 2010;33:741–50.

[19]Charlton RA, Cunnington MC, de Vries CS, Weil JG. Data resources for investigating drug exposure during pregnancy and associated outcomes: the General Practice Research Database (GPRD) as an alternative to pregnancy registries. Drug Saf Int J Med Toxicol Drug Exp 2008;31:39–51.

[20]Hardy JR, Leaderer BP, Holford TR, Hall GC, Bracken MB. Safety of medications prescribed before and during early pregnancy in a cohort of 81,975 mothers from the UK General Practice Research Database. Pharmacoepidemiol Drug Saf 2006;15:555–64.

[21]Pebody RG, McLean E, Zhao H, Cleary P, Bracebridge S, Foster K, et al. Pandemic influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull 2010:15.

Supplementary materials

Feasibility assessment

A feasibility analysis of HPV vaccination records and pregnancy outcomes data in CPRD GOLD database was performed. Exploration of the CPRD GOLD database identified 148,731 vaccinated subjects and 83,686 aged between 15 and 25 years. A total of f 2440 out of 78,111 (3.1%) girls/women were identified who had received HPV-16/18-vaccination and had the first day of the last menstrual period in the study period.

Methods

CPRD GOLD HPV vaccination codes

Immunisation with HPV vaccine is coded in the CPRD GOLD with the following codes: 93489, 93621, and 95554 for the first, second and third dose, respectively.

Proposed Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) criteria to interpret risk.[11]

The safety of any exposure cannot be considered absolute; estimates of safety reflect the degree of confidence that is consistent with an observation of no increased risk between a given exposure and outcome. Power increases as more data are collected over time. For a null observation, increasing power leads to increasingly narrower confidence bounds and increasing assurance of relative safety. This is reflected in the following a priori criteria proposed by VAMPSS:

- When the 95% CI lower limit of the odds ratio/hazard ratio (OR/HR) is > 1.0, definition of this finding as a positive association.
- When the OR/HR that approximates 1.0 (or less) is observed with an upper 95% confidence bound of $\leq$ 4.0, this finding might be defined as “no evidence of risk”.
- When the OR/HR that approximates 1.0 (or less) is observed with an upper 95% confidence bound of $\leq$ 2.0, this finding might be defined as “evidence of relative safety”

Results

There were 161, 849 HPV-vaccinated women identified in CPRD GOLD. The subject disposition is as follows:

	n	%
Number of HPV vaccinated women in CPRD GOLD	161849	
Number of selected subjects		
Subjects with *Cervarix* vaccination reported	153334	94.7
Subject with at least one dose of *Cervarix* between 1 September 2008-30 June 2011	142291	87.9
Subjects with at least one pregnancy identifier (see Supplementary Tables 1 and 2)	9375	5.8
Subjects with first day of gestation between 1 September 2008-30 June 2011	1921	1.2
Subjects with age at first day of gestation between 15 – 25 years	1839	1.1
Start in CPRD GOLD for at least 12 months at first day of gestation	1424	0.9
Subject flagged as acceptable in CPRD GOLD	1424	0.9
Exposed cohort (2)	379	26.6
Non-Exposed cohort (2)	667	46.8
Excluded subjects (neither exposed nor non-exposed) (2)	378	26.5
Number of screened subjects	1046	

Supplementary Table 1: Variables directly extracted from CPRD-GOLD

	Column name	Field name	Description	CPRD-*GOLD* file	Codelist	Type of variable
1	***Patient Identifier***	***patid***	unique identifier given to a patient in CPRD-GOLD	Patient	-	Num8.
2	***Family Number***	***famnum***	Family ID number	Patient	-	Num8.
3	***Patient Gender***	***gender***	Patient's gender	Patient	Lookup SEX	Num3.
4	***Marital Status***	***marital***	Patient's current marital status	Patient	Lookup MAR	Num3.
5	***Birth Month***	***mob***	Patient's month of birth (for those aged under 16)	Patient	-	Num8.
6	***Birth Year***	***yob***	Patient's year of birth	Patient	-	Num8.
7	***Practice Identifier***	***pracid***	unique identifier given to a specific practice in CPRD-GOLD	Patient_practice	-	Num3.
8	***Region***	***region***	Practice region: Value to indicate where in the UK the practice is based	Practice	Lookup PRG	Num3.
9	***Death Date***	***deathdate***	Date of death of patient – derived using a CPRD-GOLD algorithm	Patient	dd/mm/yyyy[1]	Num8.
10	***First Registration Date***	***frd***	First registration date: Date the patient first registered with the practice. If patient only has 'temporary' records, the date is the first encounter with the practice; if patient has 'permanent' records it is the date of the first 'permanent' record (excluding preceding temporary records)	patient	dd/mm/yyyy[1]	Num8.
11	***Current Registration Date***	***crd***	Date the patient's current period of registration with the practice began (date of the first 'permanent' record after the latest transferred out period). If there are no 'transferred out periods', the date is equal to 'frd'	patient	dd/mm/yyyy[1]	Num8.
12	***Registration Gaps***	***reggap***	Number of days missing in the patients registration details	patient	PAT_GAP[2]	Num8.
13	***Registration Status***	***regstat***	Registration status: Status of registration detailing gaps and temporary patients	patient	PAT_STAT[3]	Num3.
14	***Up To Standard Date***	***uts***	Date at which the practice data is deemed to be of research quality. Derived using a CPRD GOLD algorithm that primarily looks at practice death recording and gaps in the data	practice	dd/mm/yyyy[1]	Num8.
15	***Acceptable Patient Flag***	***accept***	Flag to indicate whether the patient has met certain quality standards: 1 = acceptable, 0 = unacceptable	Practice	Boolean	Num3.

[1] **dd/mm/yyyy**: Valid dates are in the format DD/MM/YYYY. Missing dates are NULL, and invalid dates are set to 01/01/2500

[2] **PAT_GAP:** Number of days between patient's transferred out date and re-registration date for the patient's 'transferred out periods', regardless of whether the transfer was internal or not.

[3] **PAT_STAT:** Transferred out period is the time between a patient transferring out and re-registering at the same practice. If the patient has transferred out for a period of more than 1 day, and the transfer is not internal, this value is incremented. 0 means continuous registration, 1 means one 'transferred out period', 2 means two periods, etc. If the patient only has 'temporary' records then this value is set to 99.

Supplementary Table 2: Variables derived from CPRD GOLD

	Column name/ Variables name	Algorithm
16	***Outcome of spontaneous abortion***	Search for the subject in Clinical or Referral file where: - Medcode is any code listed in Annex 1 AND - Gestational age at event q 161 days (see section outcome definition) OR - Entity type in (114 126 77) Eventdate should be after First Day of gestation Additional information will be read in *Additional Clinical Details file* if variable adid not null Associated freetext will be reviewed for all adverse pregnancy outcomes before 161 days of gestation
17	***Outcome of induced/therapeutic abortion***	Search for the subject in *Clinical or Referral file* where: - Medcode is any code listed in Annex 2 AND - Gestational age at event q 161 days (see section outcome definition) Eventdate should be after First Day of gestation Additional information will be read in *Additional Clinical Details file* if variable adid not null Associated freetext will be reviewed for all adverse pregnancy outcomes before 161 days of gestation
18	***Outcome of other abortion***	Search for the subject in *Clinical or Referral file* where: - Medcode is any code listed see Annex 3 AND - Gestational age at event q 161 days (see section outcome definition) OR - Entity type in (77 114 126) Eventdate should be after First Day of gestation Additional information will be read in *Additional Clinical Details file* if variable adid not null Associated Freetext will be reviewed for all adverse pregnancy outcomes before 161 days of gestation
19	***Outcome of stillbirth***	Search for the subject in *Clinical or Referral file* where: - Medcode is any code listed in Annex 4 AND - Gestational age at event > 161 days (see section outcome definition) OR - Entity type in (114 126) Eventdate should be after First Day of gestation

	Column name/ Variables name	Algorithm
		Additional information will be read in *Additional Clinical Details file* if variable adid not null Associated freetext will be reviewed in case of inconsistency e.g. if another outcome is found.
20	***Outcome of preterm delivery***	Search for the subject in *Clinical or Referral file* where: - Medcode is any code listed in Annex 5 AND Gestational age at delivery < 259 days (see section outcome definition) Then the case is confirmed as preterm - Medcode is any code listed in Annex 5 but gestational age > 259 days Then freetext will be reviewed OR - Delivery date < 259 days but no medcode for preterm found in Annex 5 Then check codes listed Annex 8 OR - Entity type in 77 with adid not null. OR Search under baby identifier where Entity type=120 Eventdate should be after First Day of gestation Additional information will be read in *Additional Clinical Details file* if variable adid not null Associated freetext will be reviewed based on gestational age not lower than 259 days
21	***Outcome of post term delivery***	Search for the subject in *Clinical or Referral file* where: - Medcode is any code listed in Annex 6 AND gestational age at delivery > 294 days (see section outcome definition) Then the case is confirmed as post-term - Medcode is any code listed in Annex 6 but gestational age < 294 days Then freetext will be reviewed OR - Delivery date > 294 days but no medcode for post term found in Annex 6 Then check codes listed in Annex 8 OR - Entity type in 77 OR Search under baby identifier where Entity type=120, Eventdate should be after First Day of gestation Additional information will be read in *Additional Clinical Details file* if variable adid not null Associated freetext will be reviewed based on gestational age not greater than 294 days
22	***Outcome of full term delivery***	Search for the subject in Clinical or Referral file where: - Medcode is any code listed in Annex 7 AND gestational age at delivery between 259 and 294 days (see section outcome definition) Then the case is confirmed as full term - Medcode is any code listed in Annex 7 but gestational age not between 259 and 294 days Then freetext will be reviewed

	Column name/ Variables name	Algorithm
		OR - Delivery date > 294 days but no medcode for full term found in Annex 7 Then check codes listed in Annex 8 OR - Entity type in 77 OR Search under baby identifier where Entity type=120 Eventdate should be after First Day of gestation Additional information will be read in Additional Clinical Details file if variable adid not null Associated Freetext will be reviewed based on gestational age not between 259 and 294 days
23	***Small for gestational age at birth***	Variable will be derived from weigth or length and gestational age of baby (see section outcome definition) see variable Weight of baby and Length of baby. If the weight of baby at birth is strictly > or = to 3000 gr then the baby is not small for gestational age.
24	***Large for gestational age at birth***	Variable will be derived from weigth or length and gestational age of baby (see section outcome definition) see variable Weight of baby and Length of baby.
25	***Birth defect***	A birth defect will be identified by reviewing freetext associated with cases of therapeutic/induced abortion, other abortion and stillbirth. Eventdate should be after First Day of gestation. OR For live baby, birth defects will be detected under baby identifier up to 12 weeks of life: - In Clinical or Referral file appropriated medcode will be retrieved (see Annex 10) and/or Entity type in (24 31 32 35 36 41 63 69 74 75 76 79 80 84 85 115 133 150 285) Eventdate should be after Delivery Date up to (Delivery date +12 weeks). List of birth defect is based on MACDP Report, 2007 see Annex 10
26	***Alcohol consumption***	Search for the subject in Clinical and Referral file where: - Entity type (enttype) = 5 ('Alcohol-Lifestyle'); 7 ('Health Promotion – Alcohol') OR - Medcode in Annex 11 If variable adid not null, the corresponding data_field in Additional Clinical Details file will be read. Eventdate should be at any time. Alcohol consumption during pregnancy will be identified as confirmed or non-confirmed following data found.
27	***Smoking***	Search for the subject in Clinical and Referral file where: - Entity type (enttype) = 4 ('Smoking-Lifestyle'); 6 ('Health Promotion – Smoking') OR

	Column name/ Variables name	Algorithm
		- Medcode in Annex 12 If variable adid not null, the corresponding data_field in Additional Clinical Details file will be read. Eventdate should be at any time. Smoking during pregnancy will be identified as confirmed or non-confirmed following data found.
28	***Date of any other vaccination***	This variable checks if a vaccine (other than Cervarix) was administered from 3 months prior First day of gestation to (First day of Gestation + 90 days). Search for the subject in Immunisation file and in Clinical/Referral file if a medcode (for vaccine) exist, retrieve eventdate, immstype and medcode. Search in Therapy file if a prodcode for vaccine exist, retrieve eventdate, drugsubstance, productname. Subjects from Immunisation file have to have status=1 (vaccine given). Eventdate of vaccination should be between 3 months prior First day of gestation and (First day of Gestation + 90 days). All codes for vaccines are classified in three categories (see Annex 13 for cross tabulation of medcode/prodcode and names of vaccine): - Adjuvanted vaccine - Live attenuated vaccine - Other Two periods will be defined: Period 1: Eventdate within 3 months prior First Day of Gestation Period 2: Eventdate between First Day of Gestation and (First Day of Gestation +90 days) End of pregnancy corresponds to delivery date or date of any other outcome
29	***Drugs Contra-indicated during pregnancy***	Search for the subject in Therapy file if a prodcode is present between First day of gestation and (First day of Gestation + 90 days). If a prodcode is present, the following variables will be retrieved: Prodcode, Productname, Drugsubstance, Eventdate and Numdays. Eventdate should be between First day of gestation and (First day of Gestation + 90 days). A review of the therapy profil of the subject will be performed by a reviewer; each identified drug during pregnancy will be classified as non-contraindicated drugs, drugs to be used with caution and drugs to be avoided during pregnanc
30	***Diabetes as medical condition***	Search for the subject in Clinical or Referral file where: - Medcode is any code listed in Annex 14 OR - Entity type in (18 22 26 65 91 274 275): If variable adid not null, the corresponding data_field in Additional Clinical Details file will be read. Eventdate should be between First day of gestation and end of pregnancy.

	Column name/ Variables name	Algorithm
31	***High blood pressure as medical condition***	Search for the subject in Clinical or Referral file where: - Medcode is any code listed in Annex 15 OR - Entity type in (1 8 11 15 17 28) If variable adid not null, the corresponding data_field in Additional Clinical Details file will be read. High Blood Pressure is defined as Systolic > 140 or Diastolic > 90 Eventdate should be between First day of gestation and end of pregnancy.
32	***First day of LMP***	The First day of LMP will be extracted by priority order from: 1/ In Clinical file where Entity type (enttype) =129 ('Pregnancy date') and if adid not null, data2_field (=expected date of delivery, EDD) in Additional Clinical Details file will be read (recalculation following CPRD GOLD algorithm GEN_SDC) and ⇨ First day of LMP=EDD-283* *283 was replaced by 280 during the review of the pregnant women profiles by Pallas to fit the UK definition of the length of pregnancy (40 weeks) GEN_SDC: The date in dd/mm/yyyy format can be obtained as follows: 0 = An invalid/ missing date 2 = A date greater than 31/12/2014 3 = A date earlier than 01/01/1800 All other values = number of days between the date and the 31/12/2014 offset by 10. Example: A value of 4027 decodes to the date 01/01/2004. 4027 – 10 = 4017 days prior to the date 31/12/2014 is the date 01/01/2004 2/ LMP - In Clinical or Referral file where medcode equals to 6769 (=Last menstrual period -1st day), retrieve eventdate. The first day of LMP will be equal to eventdate if the sysdate is not equals to eventdate +/- 2 days. Otherwise for subjects having their sysdate equal to eventdate +/- 2 days, the first day of LMP will be retrieved from: 3/ EDD - In Clinical or Referral file where medcode equals to 8879 (=Estimated date of delivery) and First day of LMP=EDD-283* *283 was replaced by 280 during the review of the pregnant women profiles by Pallas to fit the UK definition of the length of pregnancy (40 weeks) In case of multiple pregnancies for the same subject, we will consider the first identified eligible pregnancy (first pregnancy closer to the Cervarix vaccination).
33	***First day of gestation***	First day of gestation could be the First day of LMP or an adjusted day based on ultrasound scan test. Ultrasound scan test will be retrieved by:

<table>
<tr><th></th><th>Column name/

Variables name</th><th>Algorithm</th></tr>
<tr><td></td><td></td><td>Ultrasound scan test

- In Test file where Entity type equals 284 (’Maternity ultrasound scan test’), data_field from 1 to 8 will be read. EDD directly extracted from data_field_8 (=expected date of delivery, applying of CPRD GOLD algorithm GEN_SDC) ⇨ First Day of Gestation= EDD-283* OR First Day of Gestation calculated from data_field_2/3 (=estimated size in weeks + Unit). The EDD data field will be also retrieved. *283 was replaced by 280 during the review of the pregnant women profiles by Pallas to fit the UK definition of the length of pregnancy (40 weeks)

The ultrasound scan test closer to 12 weeks (+/- 2 weeks) of First Day of LMP will be retrieved.

If ultrasound scan test at 12 weeks (+/- 2 weeks) of First Day of LMP is not available, the second closer ultrasound scan test to 12 weeks (+/- 2 weeks) of First Day of LMP will be retrieved.

- In Clinical or Referral file where medical code in (2029 12837 14083 14084 14085 16613 27056 39611) OR Entity type in (60 61 88 104 105 106 107 116 119 120 141). Specific medcodes to retrieve weeks of gestation in (13166 13167 29364 13169 26554 29627 13171 13170 29727 29610 26552 26553 29280)

Eventdate should be after First Day of LMP.

The First Day of Gestation will be adjusted only if there is a discrepancy between First Day of LMP and ultrasound-based First Day of Gestation. The adjustement of First Day of Gestation will follow:

<table>
<tr><th>Ultra-sound completed (Wk)</th><th>Ultrasound accuracy (days)</th><th>Subject-reported first day of gestation will be adjusted if discrepancy is greater than:</th></tr>
<tr><td>]0-14]</td><td>5 - 7</td><td>7 days compared to ultrasound-based LMP date</td></tr>
<tr><td>]14-26</td><td>10 - 14</td><td>14 days compared to ultrasound-based LMP date</td></tr>
<tr><td>>= 27</td><td>21</td><td>21 days compared to ultrasound-based LMP date</td></tr>
</table>

Associated free text will be reviewed for the ultrasound scan test performed to adjust for the first day of gestation when needed</td></tr>
<tr><td>34</td><td>Date of delivery</td><td>The delivery date will be derived from:

- In Clinical file where entity type = 114 (‘Pregnancy outcome’) and if adid not null, data_filed_1 (=Discharge date) in Additional Clinical Details file will be read (recalculation following CPRD GOLD algorithm GEN_SDC) OR
- In Clinical file where entity type = 126 (‘Maternity infant details’) and if adid not null, data_filed_1 (=Date of birth) in Additional Clinical Details file will be read OR
- In Clinical file where entity type in (69, 78, 93, 102, 119, 120, 141, 144, 150) and if adid not null, corresponding data_field in Additional Clinical Details file will be read

If no information available, the delivery date from CPRD GOLD MBL will be used or in Patient file mob/yob under baby identifier OR Entity type =115</td></tr>
</table>

	Column name/ Variables name	Algorithm
		Or if no MBL available, we will assign the EDD calculated from Ultrasound scan test or EDD reported or assign date reported for preterm, posterm or full term delivery. Eventdate should be after First Day of Gestation. Algorithm GEN_SDC see above
35	***Birth status***	The birth status will be derived from: - In Clinical file where entity type = 114 ('Pregnancy outcome') and if adid not null, data_field_2 (=Birth status) in Additional Clinical Details file will be read OR - In Clinical file where entity type = 126 ('Maternity infant details') and if adid not null, data_field_7 (=Outcome) in Additional Clinical Details file will be read OR - Entity type in 77 and if adid not null under data_field_2 OR - Entity type in (32 69 93 106 120 150). If variable adid not null, the corresponding data_field in Additional Clinical Details file will be read In Clinical file under Baby identifier: Entity type in (24, 31, 35, 36, 41, 63, 74, 75, 76, 85, 285, 112, 115, 120, 145). Corresponding data_field in Additional Clinical Details file will be read. The birth statut will also complete following the outcome. Eventdate should be after First Day of Gestation.
36	***Sex of baby***	The sex of baby will be derived where: - In Clinical file where entity type = 126 ('Maternity infant details') and if adid not null, data_field_2 (=Baby gender) in Additional Clinical Details file will be read OR - Medcode is listed in Annex 16 If CPRD GOLD MBL exists the gender under baby identifier in Patient file will also be retrieved. Eventdate should be after First Day of Gestation.
37	***Weight of baby***	The weight of baby will be derived where: - In Clinical file, Entity type = 126 ('Maternity infant details') and if adid not null, data_field_3 and data_field_4 (=Birth weight +Unit) in Additional Clinical Details file will be read OR - In Clinical or Referral file where medcode is listed in Annex 17 If baby identifier exist, weight could be also retrieved from Clinical or Referral file where: - Medcode is listed in Annex 17 OR - Entity type in (13) and if adid not null, data_field_1 (=weight baby in kg) in Additional Clinical Details file will be read Eventdate should be after First Day of Gestation.
38	***Length of baby***	The length of the baby will be retrieved under mother identifier or baby identifier from Clinical or Referral file where:

	Column name/ Variables name	Algorithm
		- Medcode is listed in Annex 18 OR - Entity type in (14) and if adid not null, data_field_1 (=height baby in meters) and data_field_2 (height centile) in Additional Clinical Details file will be read Eventdate should be after First Day of Gestation.
39	***Apgar score of baby***	The apgar score will be derived where: In Clinical file: - Entity type = 126 ('Maternity infant details') and if adid not null, data_field_5 and data_field_6 (=Apgar score at 1 min + Apgar score at 5 min) in Additional Clinical Details file will be read OR - Medcode is listed in Annex 19 If baby identifier exist, from Clinical or Referral file where: - Entity type = 112 ('CHS Apgar score at 1 minute) or 145 ('CHS Apgar score at 5 minutes) OR - Medcode is listed in Annex 19 Eventdate should be after First Day of Gestation.
40	***Baby identifier***	Link between mother and baby will be used from CPRD GOLD Mother-Baby-Link (babypatid)
41	***Date of Death of Baby***	The death of date of the baby will be derived from in Patient file (deathdate variable) OR Search under mother condition in Clinical or Referral file where: - Medcode is listed in Annex 20 Eventdate should be after First Day of Gestation.
42	***Number of previous pregnancies***	Search for the subject in Clinical or Referral file where: - Entity type = 77 ('Parity status') and if adid not null, data_field_1 (=Number of birth), and data_field_2 (=Number of miscarriage) in Additional Clinical Details file will be read. Eventdate date should be before First Day of Gestation OR - Medcode is listed in Annex 21. Eventdate should be at any time up to end of pregnancy.
43	***Woman's date of birth***	Date of birth of mother will be derived from month of birth (mob) and year of birth (yob) in Patient file. If month of birth and year of birth are present, the date of birth will be read as "15mmyyyy". If month of year is not present, it will be read as "30JUNyyyy". For borderline subjects: with a year of birth equal to 1983 or 1995 without computed month of birth (mob=0), the date of birth will be also read.
44	***Date of HPV Cervarix vaccination***	Search for the subject in Immunisation file where: - Medcode in (93489, 93621, 95554) (HPV 1st, 2d, 3rd dose) AND immstype equals 67 (HPVCER) AND status=1 - Retrieve the eventdates. Search for additional vaccinated subjects with HPV in Therapy file where: - Prodcode in (32424 32147 36952 37955) - Cervarix prodcode = 36952

	Column name/ **Variables name**	**Algorithm**
		- Gardasil prodocode=32147 Subjects retrieved from Therapy file will be considered as additional HPV vaccinated subjects if the eventdate is not equals to eventdate (+/- 14 days) from Immunisation file. If at least one dose of Cervarix is between 01Sep2008 and 30JUN2011, the subject will be included in the eligible population. The last dose can be first or second dose if no subsequent dose was administered. Unspecified HPV vaccine = from Immunisation file records with HPV codes but not HPVCER or from therapy file where prodcode in (32424 37955). The total number of administered Cervarix doses will be computed.
45	***CPRD-GOLD Start Date***	From Patient and Practice file: If crd < Up to Standard Date then CPRD-GOLD Start Date= Up to Standard Date If crd > Up To Standard Date then CPRD-GOLD Start Date=Current registration Date (crd)

Supplementary Table 3: Cox proportion hazard analysis of spontaneous abortions during the first 23 weeks of gestation - age adjusted, and for other covariates (Cohort for the analysis of spontaneous abortion, -30 to +90 day risk period)

Category	N	n (%)	Adjusted HR (95% CI)	P-value
Primary analysis (age adjusted)				
Total	962	91 (9.5)	-	-
Exposed	330	34 (10.3)	1.17 (0.76; 1.8)	0.49
Non-exposed	632	57 (9.0)	1.00	-
Age at first day of gestation [Continuous]	-	-	1.01 (0.85; 1.21)	0.88
Sensitivity analyses (adjusted for age and number of doses within the risk period)				
1 dose	271	23 (8.5)	0.95 (0.58; 1.56)	0.85
2 doses	59	11 (18.6)	2.26 (1.17; 4.35)	0.02
Non-exposed	632	57 (9.0)		-
Age at first day of gestation [Continuous]	-	-	1.02 (0.86; 1.22)	0.81
Sensitivity analyses (adjusted for age and covariate)				
Exposed	330	34 (10.3)	1.15 (0.73; 1.82)	0.54
Non-exposed	632	57 (9.0)	1.00	-
Alcohol consumption during pregnancy	79	10 (12.7)	1.93 (0.85; 4.38)	0.12
Smoking during pregnancy	76	4 (5.3)	0.46 (0.16; 1.26)	0.13
High blood pressure during pregnancy	58	3 (5.2)	0.53 (0.16; 1.68)	0.28
Vaccination 3 months before or after first day of gestation	85	8 (9.4)	0.91 (0.44; 1.90)	0.80
Exposure to H1N1 pandemic	223	23 (10.3)	1.15 (0.70; 1.89)	0.59
Contraindicated drugs during pregnancy	334	35 (10.5)	1.22 (0.72; 2.07)	0.46
Region				
Midlands	153	13 (8.5)	0.68 (0.34; 1.37)	0.28
South England	398	39 (9.8)	0.88 (0.52; 1.50)	0.65
Ireland-Scotland-Wales	218	17 (7.8)	0.65 (0.34; 1.24)	0.19
North England	193	22 (11.4)	1.00	-
Age at first day of gestation [Continuous]	-	-	0.99 (0.83; 1.19)	0.94
Post-hoc analyses (adjusted for age and covariate)				
1 or 2 dose exposure				
1 dose before first day of gestation	196	16 (8.2)	0.92 (0.53; 1.61)	0.78
1 dose after first day of gestation	75	7 (9.3)	1.04 (0.47; 2.29)	0.93
2 doses before first day of gestation	35	5 (14.3)	1.62 (0.64; 4.06)	0.31
1 dose before and 1 after the first day of gestation	24	6 (25.0)	3.38 (1.44; 7.93)	0.01
Non-exposed	632	57 (9.0)	1.00	-
Age at first day of gestation [Continuous]	-	-	1.03 (0.86; 1.23)	0.78
Dose number (One dose)				
1st dose	75	7 (9.3)	1.10 (0.49; 2.45)	0.81
2nd dose	61	4 (6.6)	0.77 (0.28; 2.15)	0.62
3rd dose	135	12 (8.9)	0.94 (0.51; 1.76)	0.86
Non-exposed	632	57 (9.0)	1.00	-
Age at first day of gestation [Continuous]	-	-	1.02 (0.84; 1.23)	0.88
Excluding women who received dose 3 only in the risk period				
1 dose	136	11 (8.1)	0.95 (0.49; 1.85)	0.89
2 doses	59	11 (18.6)	2.24 (1.16; 4.33)	0.02
Non-exposed	632	57 (9.0)	1.00	-
Age at first day of gestation [Continuous]	-	-	1.02 (0.84; 1.23)	0.87

N= number of subjects in a given category. n/% = number of SAs. HR = hazard ratio with 95% CI of Wald.

Supplementary Table 4: Cox proportion hazard analysis of SA during the first 19 weeks of gestation - age adjusted, and for other covariates (Cohort for the analysis of spontaneous abortion)

Category	N	n (%)	Adjusted HR (95% CI)	P-value
-30-+45 day risk period				
Primary analysis (age adjusted)				
Total	839	73 (8.7)	-	-
Exposed	207	20 (9.7)	1.15 (0.68; 1.96)	0.60
Non-exposed	632	53 (8.4)	1.00	-
Age at first day of gestation [Continuous]	-	-	0.98 (0.80; 1.20)	0.85
Sensitivity analyses (adjusted for age and number of doses within the risk period)				
1 dose	178	15 (8.4)	0.99 (0.55; 1.78)	0.96
2 doses	29	5 (17.2)	2.28 (0.91; 5.74)	0.08
Non-exposed	632	53 (8.4)	1.00	-
Age at first day of gestation [Continuous]	-	-	0.98 (0.80; 1.19)	0.80
Sensitivity analyses (adjusted for age and covariates)				
Exposed	207	20 (9.7)	1.19 (0.69; 2.05)	0.54
Non-exposed	632	53 (8.4)	1.00	-
Alcohol consumption during pregnancy	68	9 (13.2)	1.92 (0.80; 4.62)	0.15
Smoking during pregnancy	65	4 (6.2	0.62 (0.22; 1.75)	0.37
High blood pressure during pregnancy	52	3 (5.8)	0.62 (0.19; 1.98)	0.42
Vaccination 3 months before or after first day of gestation	67	5 (7.5)	0.80 (0.32; 2.01)	0.64
Exposure to H1N1 pandemic	166	13 (7.8)	0.84 (0.45; 1.55)	0.57
Contraindicated drugs during pregnancy	289	25 (8.7)	0.92 (0.52; 1.63)	0.76
Region				
Midlands	129	13 (10.1)	1.20 (0.55; 2.59)	0.65
South England	349	30 (8.6)	1.10 (0.58; 2.09)	0.77
Ireland-Scotland-Wales	187	16 (8.6)	1.06 (0.51; 2.18)	0.88
North England	174	14 (8.1)	1.00	-
Age at first day of gestation [Continuous]	-	-	0.97 (0.79; 1.19)	0.75
-30-+90 day risk period				
Primary analysis (age adjusted)				
Total	962	82 (8.5)		
Exposed	330	29 (8.8)	1.06 (0.67; 1.89)	0.80
Non-exposed	632	53 (8.4)	1.00	-
Age at first day of gestation [Continuous]	-	-	1.00 (0.83; 1.20)	0.99
Sensitivity analyses (adjusted for age and number of doses within the risk period)				
1 dose	271	19 (7.0)	0.84 (0.49; 1.43)	0.52
2 doses	59	10 (17.0)	2.19 (1.10; 4.35)	0.03
Non-exposed	632	53 (8.4)	1.00	-
Age at first day of gestation [Continuous]	-	-	1.01 (0.84; 1.21)	0.94
Sensitivity analyses (adjusted for age and covariate)				
Exposed	330	29 (8.8)	1.06 (0.65; 1.71)	0.84
Non-exposed	632	53 (8.4)	1.00	-
Alcohol consumption during pregnancy	79	9 11.4)	2.06 (0.86; 4.92)	0.11
Smoking during pregnancy	76	4 (5.3)	0.51 (0.18; 1.42)	0.20
High blood pressure during pregnancy	58	3 (5.2)	0.58 (0.18; 1.86)	0.36
Vaccination 3 months before or after first day of gestation	85	7 (8.2)	0.92 (0.42; 2.01)	0.83
Exposure to H1N1 pandemic	223	20 (9.0)	1.08 (0.64; 1.85)	0.77
Contraindicated drugs during pregnancy	334	30 (9.0)	1.06 (0.61; 1.82)	0.85
Region				
Midlands	153	13 (8.5)	0.94 (0.45; 2.00)	0.88
South England	398	36 (9.1)	1.11 (0.61; 2.01)	0.73
Ireland-Scotland-Wales	218	17 (7.8)	0.91 (0.46; 1.80)	0.78
North England	193	16 (8.3)	1.00	-
Age at first day of gestation [Continuous]	-	-	0.98 (0.81; 1.19)	0.85

N= number of subjects in a given category. n/% = number of SAs. HR = hazard ratio with Wald 95% CI.

Supplementary Table 5: Logistic regression: Pregnancy outcomes when the first day of the LMP was between 30 days before and 45 days after HPV-16/18 vaccination (Secondary analysis cohort, -30 to +45 days, age adjusted model)

Outcome	Exposed		Non-exposed		Adjusted OR	P-
	N	n (%)	N	n (%)	(95% CI)*	value
Live births	175	128 (73.1)	508	378 (74.4)	1.04 (0.70; 1.56)	0.84
Age at first day of gestation [Continuous]					1.20 (1.03; 1.38)	0.02
Pre-term delivery	128	6 (4.7)	378	24 (6.4)	0.76 (0.30; 1.94)	0.56
Age at first day of gestation [Continuous]					1.08 (0.78; 1.48)	0.65
Full-term delivery	128	103 (80.5)	378	314 (83.1)	0.87 (0.51; 1.47)	0.60
Age at first day of gestation [Continuous]					1.06 (0.87; 1.29)	0.56
Post-term delivery	128	19 (14.8)	378	40 (10.6)	1.37 (0.75; 2.50)	0.31
Age at first day of gestation [Continuous]					0.88 (0.70; 1.12)	0.30
Small for gestational age	73	8 (11.0)	225	27 (12.0)	0.81 (0.34; 1.95)	0.64
Age at first day of gestation [Continuous]					0.87 (0.63; 1.20)	0.40
Large for gestational age	73	1 (1.4)	225	14 (6.2)	0.26 (0.03; 2.06)	0.20
Age at first day of gestation [Continuous]					1.50 (0.95; 2.35)	0.08
Any birth defect	113	7 (6.2)	312	20 (6.4)	0.85 (0.34; 2.13)	0.73
Age at first day of gestation [Continuous]					0.83 (0.59; 1.15)	0.26
Major birth defect	113	4 (3.5)	312	10 (3.2)	1.00 (0.30; 3.37)	≥0.99
Age at first day of gestation [Continuous]					0.85 (0.54; 1.34)	0.48
Minor birth defect	113	3 (2.7)	312	10 (3.2)	0.72 (0.19; 2.76)	0.63
Age at first day of gestation [Continuous]					0.81 (0.51; 1.30)	0.38

OR = odds ratio

Supplementary Table 6: Logistic regression: Pregnancy outcomes when the first day of the LMP was between 30 days before and 45 days after HPV-16/18 vaccination (Secondary analysis cohort, -30 to +90 days, age adjusted model)

Outcome	Exposed		Non-exposed		Adjusted OR	P-
	N	n (%)	N	n (%)	(95% CI)*	value
Live births	263	193 (73.38)	508	378 (74.4)	1.03 (0.73; 1.46)	0.87
Age at first day of gestation [Continuous]					1.18 1.03; 1.35)	0.02
Pre-term delivery	193	15 (7.77)	378	24 (6.4)	1.36 (0.69; 2.71)	0.37
Age at first day of gestation [Continuous]					1.20 (0.91; 1.58)	0.20
Full-term delivery	193	155 (80.31)	378	314 (83.1)	0.83 (0.53; 1.31)	0.43
Age at first day of gestation [Continuous]					1.00 (0.84; 1.20)	0.98
Post-term delivery	193	23 (11.92)	378	40 (10.6)	1.07 (0.61; 1.88)	0.80
Age at first day of gestation [Continuous]					0.89 (0.71; 1.11)	0.29
Small for gestational age	106	14 (13.21)	225	27 (12.0)	1.03 (0.50; 2.11)	0.94
Age at first day of gestation [Continuous]					0.89 (0.67; 1.18)	0.41
Large for gestational age	106	4 (3.77)	225	14 (6.22)	0.74 (0.23; 2.35)	0.61
Age at first day of gestation [Continuous]					1.63 (1.11; 2.39)	0.01
Any birth defect	164	6 (5.49)	312	20 (6.41)	0.77 (0.34; 1.77)	0.54
Age at first day of gestation [Continuous]					0.84 (0.61; 1.16)	0.29
Major birth defect	164	5 (3.05)	312	10 (3.21)	0.89 (0.29; 2.71)	0.83
Age at first day of gestation [Continuous]					0.88 (0.57; 1.37)	0.58
Minor birth defect	164	4 (2.44)	312	10 (3.21)	0.67 (0.20; 2.24)	0.52
Age at first day of gestation [Continuous]					0.81 (0.52; 1.27)	0.36

OR = odds ratio

Chapter 5: Recommendations for implementation of vaccine safety studies

5.1 Importance of feasibility assessments before implementing non-interventional pharmacoepidemiologic studies of vaccines: lessons learned and recommendations for future studies

Corinne Willame, Laurence Baril, Judith van den Bosch, Germano Ferreira, Rachael Williams, Dominique Rosillon, Catherine Cohet

Pharmacoepidemiology and Drug Safety 2016; 25: 1397–1406.

ABSTRACT

Purpose: Investigational and marketed vaccines are increasingly evaluated, and manufacturers are required to put in place mechanisms to monitor long-term benefit–risk profiles. However, generating such evidence in real-world settings remains challenging, especially when rare adverse events are assessed. Planning of an appropriate study design is key to conducting a valid study. The aim of this paper is to illustrate how feasibility assessments support the generation of robust pharmacoepidemiological data.

Methods: Following an initiative launched by the International Society for Pharmacoepidemiology in May 2014, a working group including members of the private and public sectors, was formed to assess the value of conducting feasibility assessments as a necessary step before embarking on larger-scale post-licensure studies. Based on five real-life examples of feasibility assessments, lessons learned and recommendations were issued by the working group to support scientific reasoning and decision making when designing pharmacoepidemiologic vaccine studies.

Results: The working group developed a toolbox to provide a pragmatic approach to conducting feasibility assessments. The toolbox contains two main components: the scientific feasibility and the operational feasibility. Both components comprise a series of specific questions aimed at overcoming methodological and operational challenges.

Conclusions: A feasibility assessment should be formalized as a necessary step prior to the actual start of any pharmacoepidemiologic study. It should remain a technical evaluation and not a hypothesis testing. The feasibility assessment report may facilitate communication with regulatory agencies toward improving the quality of study protocols and supporting the endorsement of study objectives and methods addressing regulatory commitments.

1. INTRODUCTION

In pre-licensure studies, rare adverse effects of drugs and vaccines may go undetected. This safety concern drives regulatory authorities and public health agencies to put in place mechanisms to monitor the longer term and real-life safety and benefit of products as well as their added value for public health. Worldwide, the regulatory environment is ever-evolving, increasingly complex and stringent, requiring a high level of compliance and scientific expertise from pharmaceutical companies. Several guidance and directives related to requirements for post- marketing studies have been issued in Europe [1-3] and in the United States (US) [4,5]. Recently, some countries in other regions have also developed well-defined local pharmacovigilance regulations (e.g. India [6] or Brazil [7]). Organizations like the Clinical Practice Research Datalink General Practice OnLine Database [8] (CPRD GOLD) group have seen an increase in the number of database access requests to support the development of post-approval drug safety studies (68 protocols submitted to the Independent Scientific Advisory Committee in 2014, compared to 30 in 2011).

Since vaccines are generally administered to healthy populations, benefit–risk monitoring at the individual and community level are crucial. Entire birth cohorts of infants or children are targeted by a vast range of vaccines. For instance, approximately 85% of the vac- cines distributed by GSK are intended for the pediatric population (2014 unpublished GSK internal data). Also, in comparison to drugs used to treat existing dis- eases, vaccines are administered on a much larger scale in the population. Currently, around 72 million individuals worldwide have received the Human Papillomavirus (HPV) vaccine [9], and around 40% of people in the US are immunized with seasonal influenza vaccines each year [10]. These numbers raise the potential for very rare adverse events to be detected by surveillance.

Another specific feature of vaccines is that the immune response triggered by immunization can be expected to generate non-serious adverse reactions, such as fever or pain at injection site [11], in a not insignificant proportion of recipients and the level of acceptance of these and other side effects in, for example, healthy children is very low. Finally, the introduction of new technologies may raise some concerns: for example, novel adjuvanted vaccines have been raising questions related to their safety

profile and their theoretical capacity to cause autoimmune adverse reactions [12].

When vaccines are marketed, tolerance for any risk of serious adverse events (SAE) is extremely low. In addition, reliable risk estimates for very rare (incidence range: <1 to 10/100,000 person-years) safety out- comes cannot usually be provided by pre-licensure clinical studies. Pharmacoepidemiologic (PE) studies are often seen as the best option to deliver evidence of safety post-licensure [13]. It is challenging to design sufficiently robust PE studies to generate reliable evidence on rare safety outcomes in real-life settings. Depending on the specific research question, and for an acceptable level of evidence quality, careful attention must be given to the optimal study design and data source (e.g. field studies involving primary data collection vs. studies using large healthcare databases). In addition, because of constraints such as low vaccine uptake in certain regions/sub-populations, special populations with underlying conditions (e.g. pregnancy, comorbidities), governance and/or resource issues, prospective field studies cannot be implemented or deliver results rapidly. Retrospective studies using electronic medical records become a more time and cost-efficient alternative. On the other hand, because of their retrospective nature, such studies may have limitations related to exposure and/or outcome ascertainment. Regardless of the data source, the study design should consider the adequacy of the sample size (i.e. power), minimization/control of bias and confounding, accuracy of exposure information, and degree of specificity of the outcome assessment [13]. These aspects are challenged by ever-increasing expectations with respect to the quality of research voiced by the scientific community, the regulatory agencies, vaccine recommending bodies, and the public at large. Observational research in epidemiology/pharmacoepidemiology is supported by several guidelines such as, the Guidelines for Good Pharmacoepidemiological Practices (GPP) [14], the STROBE and RECORD recommendations [15,16], PRISMA statements [17], guidelines for good database selection [18], and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [3] (ENCePP) guidelines. In addition to these, the likelihood of success of a study can be optimized by essential pre-requisites such as a feasibility assessment or a pilot study [19].

Based on vaccine examples of feasibility assessments, the objectives of this paper are (i) to demonstrate

the value of conducting a formal feasibility assessment as a necessary step when planning and designing a safety and/or effectiveness study and (ii) to propose a toolbox and recommendations to support the scientific approach when assessing study feasibility.

2. METHODS

Working group

In May 2014, the International Society for Pharmacoepidemiology (ISPE) launched a call for manuscripts [20]. The requirement was to establish a working group with members from different horizons to develop a manuscript addressing the role and value of non-interventional pharmacoepidemiologic studies. This manuscript was prepared by seven volunteers from the private and public sectors and peer-reviewed by members of the ISPE Special Interest Group in Vaccines (VAXSIG).

Vaccine research studies—examples

Five post-licensure studies were used as the basis for collecting key elements on their respective feasibility assessments (Table 1). The studies were all post- licensure commitments fulfilling requirements from the Food and Drugs Administration (FDA) or European Medicine Agency (EMA). The need for a feasibility assessment was identified at an early stage of conceptualizing for each study. All studies were registered on www.clinicaltrials.gov and/or the ENCePP EU PAS (European post-authorization studies) register [3]. These studies were selected by the seven working group members who all had substantially contributed to at least one of the studies (Table 1).

Table 1. Description of selected post-licensure studies for which feasibility had been assessed.

Study #	Vaccine	Study objective	Study design/setting	Registered at clinicaltrials.gov	ENCePP E-Register number	Related publication
1	Cervarix™ HPV-16/18 vaccine	To assess the risk of spontaneous abortion after inadvertent exposure to HPV-16/18-vaccine during pregnancy	Observational cohort study in the CPRD database	NCT01905462	ENCePP id 3310	Baril *et al.*, 2015[22]
2	Cervarix™, HPV-16/18 vaccine	To assess the risk of autoimmune diseases in women aged 9–25 years within 1 year after the first vaccine dose	Observational cohort study in the CPRD database	NCT01953822	ENCePP id 4584	Submitted
3	Pandemrix™, H1N1 pandemic influenza vaccine	To assess the risk of solid organ transplant (SOT) rejection	Retrospective self-controlled case series in the CPRD database and HES	NCT01715792	ENCePP id7070	Cohet *et al.*, 2016[23]
4	Rotarix™, rotavirus vaccine	To assess the association between Rotarix™ and intussusception in infants in the context of the mass vaccination initiated in 2006 in Mexico	Prospective active surveillance study in hospital setting	NCT00595205	NA	Vélazquez *et al.*, 2012[24]
5	Mosquirix™, Malaria vaccine	To determine baseline rates of pre-defined diseases	Prospective cohort field study in health	NCT02374450	NA	NA

	and meningitis leading to hospitalization or death	care facilities

CPRD: Clinical Practice Research Datalink database, ENCePP: European Network for Centers for Pharmacoepidemiology and Pharmacovigilance; HES: Hos- pital Episodes Statistics; id: identifier; NA: not applicable; NCT: National Clinical Trial. Note: All studies were approved by the respective ethics committees/ ethical review boards.

Feasibility assessment output

Working group members provided details of the feasibility assessment for each example, including both information known *a priori* (i.e. before the start of the study) and new evidence specifically generated by the feasibility assessment. These data were grouped according to three main topics: population, exposure, and outcome. The output of this exercise is summarized in Table 2.

Table 2. Summary of feasibility assessment outputs

		Feasibility assessment outputs	
Study (exposure, outcome)	**Design criteria**	**What was known before the feasibility assessment?**	**What was found by conducting the feasibility assessment?**
Study #1 (HPV vaccine, spontaneous abortion)	Population and setting information	-Pivotal clinical trial data showed a potential risk.	-Deep understanding of the database (CPRD), for example benefit of using linked data sources.
		-Target population for the vaccine has a specific age indication.	-Identified need for partnership with specialized company and expert panel in teratology.
		-Previous field study negative or inconclusive.	
		-Lack of comprehensive information in using the selected database (CPRD).	
	Exposure	-Known vaccine coverage in the UK.	-Implementation of blinded procedure for exposure status during the case ascertainment.
		-Immunization programme through schools in the UK.	
	Outcome	-Data on background rates of spontaneous abortion published in the literature.	-Development of algorithms with high PPV for case finding
		-Studies related to pregnancy outcomes and using CPRD and free text were published.	-Need for a review of medical records and case ascertainment process with medical experts.
			-The database showed consistency in generating baseline data when comparing to literature.
Study #2 (HPV vaccine, autoimmune diseases)	Population and setting information	-Theoretical risk of autoimmune diseases with novel adjuvanted vaccine.	-Agreement with regulatory authorities reached on a pre-defined list of adverse events of special interest.
		-Target population for the vaccine has a specific age indication.	-Identified need for partnership with specialized company and experts in the medical area of interest.
		-Similar studies already published, for example study conducted by other vaccine manufacturer, availability of algorithms for case finding in database study.	
	Exposure	-Known vaccine coverage in the UK.	-Implementation of procedure blinded to exposure status for case ascertainment.
		-Immunization programme through schools in the UK.	

	Outcome	-Medical management of the outcome mainly in hospital/specialist settings.	-Systematic literature review conducted to reinforce background incidence data. -The database showed consistency in generating baseline data when comparing to literature. -Development of specific algorithms for case finding using HES. -Need for a review of medical records and case ascertainment process with an expert panel.
Study #3 (H1N1 pandemic influenza vaccine, solid organ transplant rejection)	Population and setting information	-A signal emerged from real-world use of the vaccine.	-Important proportion of missing data in the CPRD triggered need for collecting complementary information from GPs through questionnaire.
		-Target population for the vaccine is a high risk group.	However, lack of comprehensive information returned led to the use of HES as primary data source for case identification.
		-Previous feasibility assessment on field study inconclusive.	-Use of CPRD to extract covariates (risk factors) information
	Exposure	-H1N1 mass immunization through GPs in the UK. -Known brand-specific H1N1 vaccine coverage in the UK.	NA
	Outcome	-Clinical complexity of the outcome involving numerous risk factors.	-Development of specific algorithms for case finding, using HES as primary data source.
		-Medical management of the outcome mainly in hospital/specialist settings, questioning the appropriateness of using CPRD.	-Time since transplantation identified as risk factor for solid organ transplant rejection, thus included as covariate in analyses
Study #4 (Rotavirus vaccine, intussusception)	Population and setting information	-A signal emerged from the real-world use of a similar vaccine.	-Implementation of an active surveillance system.
		-Target population for the vaccine has a specific age indication.	
		-Availability of passive surveillance system for adverse events of special interest in Mexico.	
	Exposure	-Known vaccine coverage in Mexico.	NA
	Outcome	-Medical management of the outcome in hospital settings.	-Evaluation of the active surveillance system performed by an external company as part of a pilot study.

Study #5 (Malaria vaccine, autoimmune disease, KD, meningitis)	Population and setting information	-Theoretical risk of autoimmune diseases with novel adjuvanted vaccine.	-Comprehensive literature review conducted to reinforce background incidence data.
		-Pivotal clinical trial data showed a potential risk of meningitis.	-Positive scientific opinion by experts or health agency on the proposed study protocol.
		-Literature reviews show scarcity of background rates for adverse events in SSA.	-Identified need for partnership with specialized agency (HDSS).
		-No existing databases in SSA thus need for prospective data collection.	-Identified need for capacity building, for example know-how in pharmacovigilance systems, medical diagnosis, laboratory capacities.
	Exposure	NA	NA
	Outcome	-Multiple outcomes (AEs) of interest	-Support of an expert panel for case ascertainment.

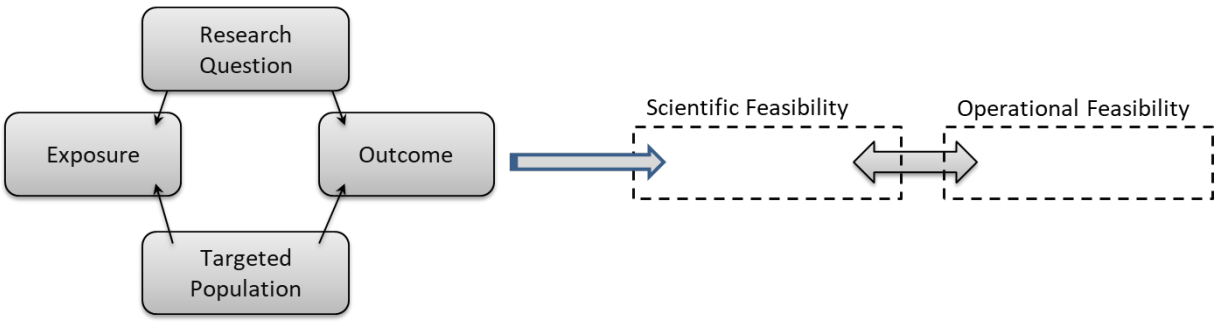
AE: Adverse Event; CPRD: Clinical Practice Research Datalink; GP: General Practice; HDSS: Health and Demographic Surveillance Sites; HES: Hospital Episode Sta- tistics; HPV: human papillomavirus; KD: Kawasaki Disease; NA: Not Applicable; PPV: Positive Predictive Value; SSA: Sub-Saharan africa; UK: United Kingdom.

Toolbox design

A pragmatic approach is proposed to support scientific reasoning and decision-making in the initiation and development of the feasibility assessment. The toolbox consists of two main components addressing both scientific and operational feasibility, comprising a series of specific questions to help identify strengths/limitations and to fill data gaps on key elements of the anticipated study design.

The scientific feasibility component addresses aspects related to exposure, outcome, and target population. The operational feasibility focuses on medical governance, logistical constraints for the vaccine manufacturer, and the need for potential partnerships or collaborations. Figure 1 presents a schematic view of the proposed toolbox.

Figure 1 Schematic representation of the toolbox



3. RESULTS

Lessons learned

Each feasibility assessment includes specific lessons learned, actions, or implementations (Table 2).

Study #1 (Exposure: HPV vaccine, Outcome: spontaneous abortion). A field study with primary data collection was initiated in the US to assess this association. However, due to very low vaccine uptake, the target sample size (*n* = 450 subjects) could not be reached within the 2-year time period requested by FDA to address the commitment. Given the time and resources that would have been necessary to prospectively accrue a sufficiently powered study population, an alternative retrospective database study in the CPRD GOLD database was proposed, as vaccine coverage in the United Kingdom (UK) was adequate to implement a post-authorization safety study (PASS). However, the feasibility assessment showed a lack of sensitivity (high rate of false negatives) in the vaccination records. This issue was

resolved by using a vaccinated control cohort with pregnancy onset after a sufficient post-vaccination period to exclude any possible vaccine effect. In-depth knowledge of the complexity of using the database was gained through the feasibility assessment, as well as through the actual study, which ultimately also benefited further studies with other exposure and/or outcome. Limitations related to this data source (e.g. lack of specificity of the exposure and outcome) were overcome by a modification of the cohort design, along with a detailed review of individual subject profiles and a case ascertainment by teratology experts blinded to vaccination status.

Study #2 (Exposure: HPV vaccine, Outcome: autoimmune diseases). Given the low incidence of the outcome in the target population of the vaccine, this study used a database design upfront. Pre-defined list of autoimmune conditions and sample size requirements were agreed with regulatory authorities (FDA). A robust feasibility assessment was performed to define algorithms and assess their accuracy. The positive predictive value (PPV) of the algorithms was 69%, highlighting the need for a robust case ascertainment plan to increase clinical endpoint specificity. A combined approach using the data retrieved by the algorithms and a review of the medical electronic records in addition to the associated free text (e.g. hospitals discharge and notes from general practices) were performed to ensure adequate case validation.

Study #3 (Exposure: H1N1 pandemic influenza vaccine, Outcome: solid organ transplant rejection). The study was implemented following a stepwise feasibility approach. The first step investigated ways of implementing a field study. Extensive surveys were conducted in specific settings (national transplant registries and hospitals specialized in transplantation) within five countries (UK, France, Brazil, Canada, and Germany). However, low survey response rates and paucity of medical/vaccination data were identified. An extended follow-up feasibility assessment was conducted in two of the five countries (UK and Brazil) using detailed site surveys to assess hospital type, standard of care, comprehensive patient information (compliance to treatment, drug regimen, history of infection…), and medical record

linkage. Despite several limitations, the feasibility assessment concluded that a field study could be conducted in one country (feasible in Brazil, but not in the UK, mostly due to small sample size). However, concerns about methodology and generalizability of the results discouraged the launch of the study and suggested that a retrospective database study was preferable. A further feasibility assessment in the CPRD confirmed the need to develop robust algorithms as well as include additional linked data from the Hospital Episodes Statistics (HES) database and complementary information from general practices through standardized questionnaires.

Study #4 (Exposure: Rotavirus vaccine, Outcome: intussusception). A hospital-based active surveillance system was implemented in Mexico to collect specific adverse events (AE). However, the active surveillance system showed inconsistencies in the enrollment of subjects over time. A feasibility assessment was initiated to ensure the performance of the active surveillance systems in the collection of two AEs of interest (intussusception and lower respiratory tract infections). In addition, the robustness of the data collection system was evaluated by the scientific validity of the results generated. The feasibility assessment was conducted as part of a pilot study in partnership with a company specializing in health information systems.

Study #5 (Exposure: Malaria vaccine, Outcome: auto- immune diseases, Kawasaki disease, intussusception, meningitis, and other pre-defined diseases). The feasibility assessment performed in Sub-Saharan Africa confirmed that a field study could be implemented through an existing network of health and demographic surveillance systems (HDSS) in African regions with low to moderate malaria endemicity. Missing key elements such as laboratory capacity, know-how in pharmacovigilance and a need for an expert panel for case ascertainment for some of the endpoints were identified.

For each of these post-licensure studies, the choice of the target country or geographical area was mainly dependent on the coverage of the vaccine of interest which further restricted a potential geographical

scope. Moreover, due to the complexity of some outcomes or the lack of background/incidence data, a systematic review of the literature also had to be performed as a preliminary step.

Recommendations: the toolbox

Based on the experience with these post-licensure studies, the working group proposed recommendations in the form of a toolbox as a pragmatic approach (Figure 2) for the development of feasibility assessments to implement appropriate study designs. The assessment tool is divided into two mutually interdependent categories: (i) the scientific feasibility; and (ii) the operational feasibility. Within each category, multiple boxes define specific topics and include a series of questions. Answers for each of the questions are aimed at improving the knowledge around potential methodological challenges and provide information on the likelihood of success of the design approach (Box 1). The scientific feasibility focuses on the outcome and the exposure while the operational feasibility helps identifying logistical issues and needs (e.g. collaborations/partnerships, timelines, governance, ethical aspects). Before making a final decision on the future study design, it is recommended to perform this exercise for two or three different study de- signs, including a field and a database study, if relevant. Box 1 developed based on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EnCePP) guidelines [21].

Box 1 developed based on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EnCePP) guidelines [21].

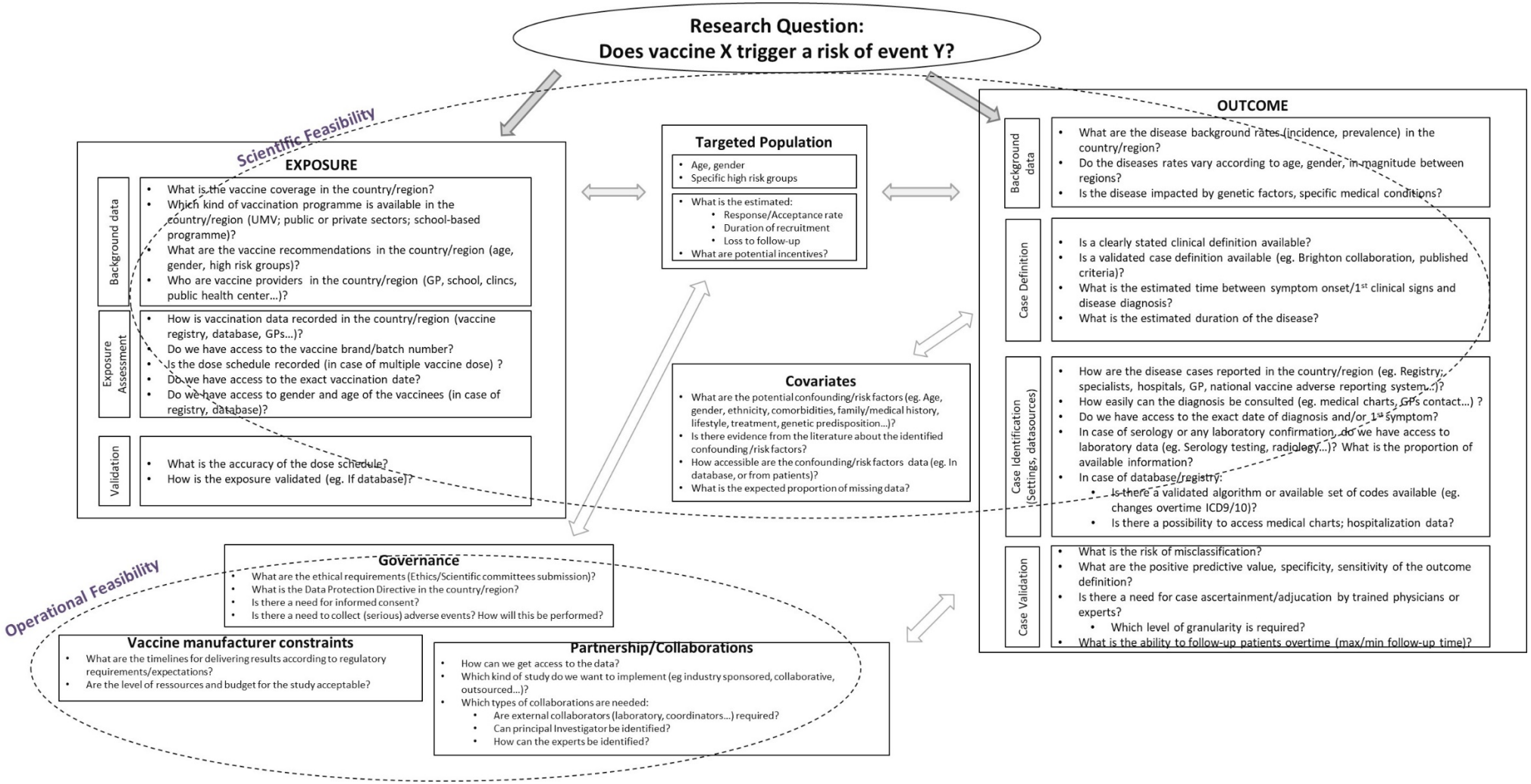
Box 1
Addressing scientific feasibility questions helps to define the appropriate study design and methodology:

- What is the most appropriate study design: prospective or retrospective; type of specific design, for example cohort (historical, concurrent, unmatched, matched, propensity scores), case–control (unmatched, matched, test-negative), and case-only (self-controlled case series, case coverage)?
- What is the most appropriate data collection strategy: primary (field study) or secondary data collection (large healthcare database)?
- What is an adequate risk period?
- Is a comparator required; if so, what is an adequate control group?
- What is the required sample size?
- What are the most appropriate statistical methods:
  - To control for bias and known confounding factors;
  - To take into account potential unknown or unmeasured confounding factors;
  - To control for missing data?
  - To perform sensitivity analyses
- What are the inclusion/exclusion criteria?
- What are the expected limitations of the study?

4. DISCUSSION

It is becoming routine that vaccine manufacturers are requested by regulatory authorities to perform specific studies to assess vaccine safety or effectiveness/impact. However, in some cases, the suggested designs may be unrealistic from an implementation perspective. The rationale, choice of study design, and implementation of an informative and meaningful PE study require consideration of several important factors. The advantages and limitations of using secondary (existing electronic healthcare data) or *de novo* field/primary data collection should be clearly stated and documented. In addition, a critical feasibility assessment should be considered and undertaken as a first step before embarking on a larger study.

Figure 2 Toolbox



For each of the study objectives, the degree of granularity of the feasibility assessment needs to be tailored depending on the available information. Based on the feasibility outcomes of the five examples of post-licensure studies for which a feasibility assessment was performed, we developed a toolbox to guide researchers in the design and implementation of a future study. Initially, we focused on technical and methodological aspects and on the understanding of the limitations of the available data (e.g. such as data accuracy and completeness, missing information), impact of existing known confounding factors, and opportunity for linkage with complementary data sources. Subsequently, we considered the feasibility assessment as a 'pilot study' to gain more insight into the specificity and sensitivity of the definition of the outcome of interest, data management flows, and external potential constraints (e.g. such as need for expert consultations, regulatory timelines, governance aspects).

Nevertheless, and importantly, the focus of the feasibility assessment should remain a technical evaluation and not a hypothesis testing. In our examples, the feasibility assessments were a 'dig-deeper evaluation' to understand the data content in the first place and secondly, to plan the future study to answer the research question successfully. For instance, in study#2, a full ascertainment of autoimmune disease cases was performed by a physician on a sub-sample of eligible cases to ensure a high PPV which was critical for the study's internal and external validity. In study #3, although a reasonable likelihood of success for the proposed field study was predicted, the representativeness and generalizability of the results were questionable. In addition, the feasibility assessment highlighted some limitations, such as lack of accurate reporting of the outcome of interest, which required development of an alternative study design. To date, the clinical definition criteria or diagnostic codes used to identify outcomes and exposures are not always included in scientific publications. However, the recent RECORD statements [16] recommend a systematic reporting of codes and algorithms to classify exposure, outcome, and confounders which will facilitate study outcome comparisons. Finally, the studies succeeded because of a strong collaboration/partnership with external experts as well as database owners. The roles and responsibilities of each of the stakeholders were clearly established at the time of the feasibility assessment.

Feasibility assessments are critical to ensure that the research question is adequately addressed and timely generates the expected robust evidence to support decision making. In the case of an inconclusive assessment, rational and appropriate answers are provided such as a proposal for a mitigation plan or an acknowledgment of missing information in a risk management plan. These answers are generally endorsed by regulatory agencies.

Feasibility assessments can constitute a constructive first step in discussions with regulators to define how to obtain the expected best possible and timely evidence. Decisions on statistical power and sample size, endpoints and clinical case definitions, or means of adjustment for bias and confounding, as well as adequacy of the proposed study design to meet the study objectives, can be agreed early on, thus potentially avoiding multiple study protocol review rounds and potential future amendments. Moreover, this would allow adapting timelines from the time of the study protocol development to the reporting and interpretation of the study results to be realistically planned and communicated. This process should ultimately improve the quality of study protocols, accelerating the endorsement process by regulatory authorities and ethical committees, and in turn, the start of the actual study. Ideally, the feasibility assessment report should remain publicly accessible for consultation and considered as an *ad-hoc* component of the study report (e.g. as a supplementary material with the study protocol and report registration and/or publication).

The above recommendations are based on examples of post-licensure safety studies. However, effective- ness or burden of disease studies would benefit from the same proposed toolbox, which can be used as a roadmap to guide scientific reasoning when designing an observational study.

5. CONCLUSION

With this report, the working group wishes to highlight and share recent experiences with feasibility assessments performed in the context of addressing commitments from regulatory authorities. A toolbox was designed to support the scientific reasoning when developing an observational study. In our examples, feasibility assessments led to a successful completion of the actual studies. Benefits of

collaboration between industry research teams, clinical experts, and database owners were largely acknowledged. Our final recommendation would be to formalize the feasibility assessment as a first step of a larger-scale study and as a complementary approach to existing guidelines (e.g. GPP, RECORD, good database selection [17], ENCePP etc.). The ultimate goal of this pragmatic approach is to contribute to advancing knowledge in pharmacoepidemiology and increasing public confidence in how the safety profile of licensed vaccines is evaluated.

References

1. European medicines agency. Guidelines on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 1). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf (Accessed on 12-Feb-2016).
2. EUR-Lex. Official Journal of the European Union. Regulations. Commission del- egated regulation (EU) No 357/2014. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0357&from=EN (Accessed on 12-Feb-2016).
3. European Network of Centers for Pharmacoepidemiology and Pharmacovigilance. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. http://www.encepp.eu/standards_and_guidances/ methodologicalGuide.shtml. (Accessed on 12-Feb-2016).
4. Food and Drug Administration Amendments Act (FDAAA) of 2004. http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm (Accessed on 12-Feb-2016).
5. Food and Drug Administration. Guidance for Industry. Process validation: gen- eral principles and practices. http://www.fda.gov/downloads/Drugs/…/Guid- ances/UCM070336.pdf (Accessed on 12-Feb-2016).
6. Alhat B. Pharmacovigilance: an overview. *Int J Res Pharm Chem* 2011; 1(4): 2231–2781.
7. Aprova os Guias de Farmacovigilância para a execução da RDC n°4, de 10.02.2009. INSTRUÇÃO NORMATIVA N° 14, DE 27 DE OUTUBRO DE 2009. http://portal.anvisa.gov.br/wps/wcm/connect/13e6a0804ad31c9aa21cafa337abae9d/Instrucao_Normativa_n_14_de_27_de_outubro_de_2009.pdf?MOD = AJPERES (Accessed on 12-Feb-2016).
8. Clinical Practice Research Datalink. https://www.cprd.com/home/ (Accessed on 12-Feb-2016).
9. European medicines agency. EMA to further clarify safety profile of human pap- illomavirus (HPV) vaccines. July 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/WC500189476.pdf ((Accessed on 12-Feb-2016).
10. Centers for Disease Control and Prevention. FluVaxView Interactive!. http://www.cdc.gov/flu/fluvaxview/interactive.htm (Accessed on 12-Feb-2016).
11. Carrasco-Garrido P, Gallardo-Pino C, Jumenez-Garcia R, *et al.* Incidence of adverse reactions to vaccines in a paediatric population. *Clin Drug Invest* 2004; 24(8): 457–463.

12. Shoenfeld Y, Agmon-Levin N. 'ASIA'—autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36(1): 4–8. doi:10.1016/j. jaut.2010.07.003.
13. Evans SJ. Pharmacoepidemiology. *Br J Clin Pharmacol* 2012; 73(6): 973–978. doi:10.1111/j.1365-2125.2012.04248.x.
14. ISPE. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf* 2008; 17(2): 200–208.
15. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Ob- servational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; 12(12): 1495–1499. doi:10.1016/j.ijsu.2014.07.013.
16. Benchimol EI, Smeeth L, Guttmann A, *et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RE- CORD) Statement. *PLoS Med* 2015; 12(10). doi:10.1371/journal. pmed.1001885.
17. PRISMA. Transparent reporting of systematic reviews and meta-analyses. http:// www.prisma-statement.org/ (Accessed on 12-Feb-2016).
18. Hall GC, Sauer B, Bourke A, *et al.* Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2012; 21(1): 1–10. doi:10.1002/pds.2229.
19. Thabane L, Ma J, Chu R, *et al.* A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010; 10: 1. doi:10.1186/1471-2288- 10-1.
20. ISPE. Call for manuscripts. http://campaign.r20.constantcontact.com/render? ca=a3b1a5b7-84ee-4c48-b565-7a963ed473df&c=ceee3810-4660-11e3-85fe- d4ae52a82222&ch=d15dff90-4660-11e3-86bb-d4ae52a82222. (Accessed on 12-Feb-2013).
21. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 3). EMA/95098/2010. Available at http:// www.encepp.eu/standards_and_guidances (Accessed on 12-Jul-2016).
22. Baril L, Rosillon D, Willame C, *et al.* Risk of spontaneous abortion and other pregnancy outcomes in 15–25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Vaccine* 2015; 33: 6884–6891. doi:10.1016/j.vaccine.2015.07.024.
23. Cohet C, Haguinet F, Dos Santos G, *et al.* Effect of the adjuvanted (AS03) A/H1N1 2009 influenza vaccine on the risk of rejection in solid organ transplant recipients in England: a self-controlled case series. *BMJ Open* 2016; 6(1): e009264. doi:10.1136/bmjopen-2015-009264.
24. Vélazquez FR, Colindres RE, Graiales C, *et al.* Post-marketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. *Pediatr Infect Dis J* 2012; 31(7): 736–744. doi:10.1097/ INF.0b013e318253add3.

Chapter 6: General Discussion

Real-World Data (RWD) networks and challenges

The safety surveillance of vaccines is a complex process which has showed drastic methodological improvements over the last decade. These methodological improvements were made at all stages of safety surveillance activities and include an extensive use of diverse existing healthcare data sources to detect and evaluate vaccine safety signals and the development of common methodological approaches in safety study using multi-data sources and collaborative approaches.

Over the recent years, real world data (RWD) have increasingly been used to generate evidence on the safety of vaccines for regulatory decision making [1]. In parallel, numerous data sources with various type of data has grown in the European setting with the development of novel methodological approaches. While safety studies were initially conducted using a single data source, the use of multi-data source studies and distributed data networks became a common standard for evidence generation [2]. The main advantage of multi-data sources studies is that they allow to gain statistical power to study rare outcomes or to study the effect of vaccines by regions, countries and in large special populations such as people with comorbidities. It increases study population size, being geographically dispersed and, therefore, maximizing the likelihood to detect and assess rare adverse events that may occur following vaccination. However, the applicability of multi-data sources studies is prone to limitations related to the observed heterogeneity across data sources which may be a challenge when data needs interpretation and contextualization. Heterogeneity across data sources is reflected at several layers such as the purpose for data collection, the type of data sources and origin of data and the structure of the medical records [3]. Medical data from existing healthcare data sources are not primarily collected for the purpose of medical research but rather to monitor the health of patients or for administrative purpose such as for reimbursement by private or public healthcare systems at national or regional levels. A variety of types of data source exists, it includes inpatient and/or outpatient medical diagnoses from hospitalization data sources, medical records from general practitioners or family pediatricians' data sources and record-linkage data sources that link hospitalization data and general practitioners' data or link data from registries [4]. Therefore, it is expected that some types of data sources will fit better to study specific medical events. As example, medical events that require emergency care will be more accurately captured in data sources containing hospitalization data than containing only primary care data. Heterogeneity in data sources is also observed at the level of data structure such as the type and format in which medical data are recorded (i.e., the use of various medical dictionaries and various coding systems). It is crucial to control for bias related to heterogeneity such as origin of data to ensure a correct interpretation of generated data source-specific estimates or eventually pooled estimates when conducting multi-data sources studies. The use of federated or distributed data network which utilizes common study protocol, common data structure through common data model (CDM), harmonized clinical definitions

of studied outcomes and common analytical programmes is one of the most effective tool to address issues related to heterogeneity [5-7]. Various strategies exist to execute multi-database studies which differ according to local execution of analysis *versus* centralized analysis, sharing of raw data *versus* CDM data storage and use of a general CDM *versus* study-specific CDM concept sets [8]. These strategies have been evolving over time, in the vaccine field from VAESCO, during H1N1 followed by the IMI-ADVANCE approach which both used a simple CDM. The IMI-ConCEPTION project modified the simple CDM to a generic CDM only requiring syntactic mapping [7]. In the IMI-ConCEPTION network, the data sources are held by data access providers and their use is driven on a study-by-study basis. The key features of the ConCEPTION CDM relies on the absence of unique standard vocabulary allowing to create concept sets originated from databanks. The use of the ConCEPTION CDM has been adopted by the VAC4EU network which has developed many tools and a community to run vaccine safety and effectiveness studies.

From a global perspective, the Vaccine Adverse Event Surveillance and Communication (VAESCO), ADVANCE and SOMNIA studies successfully demonstrated the feasibility to combine data from various existing healthcare data sources to assess vaccine safety signals [9-10]. Two VAESCO studies which, for the first, assessed the association between thrombocytopenic purpura and Measles, Mumps and Rubella vaccine and, for the second, assessed the association between GBS and H1N1 vaccine by using data sources from Europe showed consistency of the risk estimated across countries. Study sample size was increased by applying a standardized process for data collection or by pooling the data using meta-analytical approach [11-12]. Global studies were done for narcolepsy showing the strength of common data models [13]. Similarly, the ADVANCE proof-of-concept and database characterization studies combined data from hospital-linkage and primary care EU data sources [4]. The ADVANCE proof-of-concept study estimated risk associated with pertussis vaccination and showed comparable risk estimates with published data. The study demonstrated that the estimates slightly differed based on the originated data provenance suggesting that the study setting should also be considered for a correct data interpretation.

The findings reported in this thesis focus on the use of common analytics methods in distributed data network studies to generate background incidence rates that are needed for rapid evaluation of vaccine safety signal; on methodological considerations in safety signal evaluation studies with as a use case the safety evaluation of the bivalent HPV *Cervarix* vaccine; and on future perspectives for sustainable implementation of vaccine safety studies.

Background incidence rates for rapid evaluation of vaccine safety signal

With the successful implementation of the ADVANCE system which uses a simple CDM, we ran two studies, which are described in *Chapter 2.1 and 2.2,* to generate background incidence rates using the

system across several European countries. On top of generating incidence rates, we indirectly validated the system and demonstrated its robustness for conducting formal epidemiological studies. In *Chapter 2.1* and *2.2* of the thesis, we generated background incidence rates of rare diseases that are usually classified as adverse event of special interest (AESI) for vaccines, as they are of scientific, medical and public interest. Both studies were conducted through a distributed data network and included various types of data sources from several European countries. To overcome the observed heterogeneity across data sources, we applied common approaches which included the use of common protocol, CDM and common analytics. Common clinical case definitions and CDM were used to harmonize extraction of events. Each data access provider extracted events and converted into the CDM using, in the ACCESS study, a synthetic and semantic harmonization. Data were analysed locally using common analytics through R scripts and aggregated results were shared on a secure research environment for visualization. We computed pooled estimates according to the types of data source, and data provenance to highlight possible impact of the study setting. Through the studies, we highlighted the importance of considering the interplay between the setting where diseases are typically diagnosed and the setting that each data source captures. We observed that data sources containing exclusively primary care data underestimated the incidence of diseases that require hospitalization such as autoimmune diseases. On the other hand, data sources with just hospitalizations underestimated incidence of diseases that are mostly diagnosed in an outpatient setting.

Background incidence rates allow to contextualize safety signals that may emerged following vaccination in clinical or in real-world setting. They are used in observed-to-expected (O-E) analysis to calculate the number of expected cases of an event in a given population in the absence of vaccine intervention, which are then compared to the actual observed number of cases that occurred following vaccination [14,15]. As we demonstrated in our background incidence rates studies, most of the AESIs follow a specific pattern, increasing with age like for thromboembolic events in elderly or peaking in age group like for myo-pericarditis in young adults. The findings of the studies emphasized the importance of generating population-specific incidence rates such as children, pregnant women or individuals with comorbidities and, conducting population-specific stratified O-E analysis. In addition, population-specific background rates inform on potential confounders to take into account in vaccine safety evaluation studies. Background incidence rate studies also allow to measure the impact of environmental factors or public health interventions on the epidemiology of diseases and to understand diseases pattern over time emphasizing the importance to generate and update on a regular basis incidence data. More generally, background incidence rate studies are good indicators for fit-for-purpose data source assessment as they generate data that can be benchmarked to external references, also they allow to identify appropriate study setting for the detection and identification of potential adverse events that may occur following vaccination. In the final report of the ACCESS study

which is available on the Zenodo platform [16], incidence rates for each AESI were benchmarked against published references, where available, it allowed to understand whether generated data are in an expected range and whether a type of data source is more appropriate to identify a specific event. Although a wide range of data sources can be accessible for inclusion in a study, not all data sources are fit-for-purpose to address a specific research question. A feasibility assessment is usually required before implementing a formal epidemiological hypothesis testing study. The feasibility assessment helps to identify whether a study design choice is adequate to study a disease outcome or whether the population that is captured in the corresponding data source will be representative enough of the real-world setting, also accessibility to medical charts for outcome validation may be of importance. The adequacy of data sources will be further discussed in the future perspective section of this chapter.

Methodological considerations in vaccine safety signal evaluation studies: the use-case of the bivalent HPV vaccine

HPV vaccines were rapidly introduced into National Immunization Program (NIP) as a school-based program for adolescent females in European and non-European countries [17-19]. Since the launch of HPV vaccines, their risks and benefits have been continuously assessed by competent health authorities and vaccine manufacturers as per their obligations. To date, with the set of available evidence, HPV vaccines have well-established safety profiles with a favorable benefit-risk balance. In 2015, the EMA initiated a procedure following a request from the Danish Health and Medicines Authority which expressed concerns related to an increasing reporting of cases of Complex Regional Pain Syndrome (CRPS), a condition that affects limb, and Postural Orthostatic Tachycardia Syndrome (POTS,) a condition where the heart rate increases abnormally, and highlighted uncertainties on potential causal association with HPV vaccines [20,21]. Based on all available evidence including data from clinical trials, medical reports of patients and published research, the PRAC concluded on no causal association of these events and HPV vaccines [22-25]. Recently, new evidence on long-term safety of HPV vaccines have been made publicly available by Australian researchers [26]. Pre-selected AESIs including GBS, CPRS, POTS, venous thromboembolism, primary ovarian efficiency, and syncope following administration of HPV vaccines were examined from 11 years of post-marketing data using the Australian spontaneous reporting system database. The study did not reveal unexpected patterns that would suggest a causal association, except for syncope which occurred at higher rate in younger adolescents in the enhanced surveillance phase than previously observed. Long-term safety provides insights on potential unresolved safety questions that could not be addressed due to the extreme rarity and clinical complexity of an event such as POTS or for diseases that are long latent. Moreover, continuous assessments of the risks and benefits of the HPV vaccines during life cycle stage remain necessary due to extension of indication in subpopulations such as in males and extension of target

diseases indication such as for anal or oropharyngeal cancers which are diseases with a long natural history. In addition, newly formulated HPV vaccines are currently in clinical development with as target the improvement of formulation process to produce cost-effective HPV vaccines and ultimately ensure supply of vaccines worldwide [27]. These improvements at production level constitute the next generation of HPV vaccines for which safety assessments will also be required.

The first generation of HPV vaccines were of the first vaccines that used novel adjuvanted systems, for this reason, questions were raised on the risk of developing autoimmune diseases which are categorized as rare AEs (incidence rate ranges <1 to 10/100,000 person-years) and therefore not detectable during clinical development. To address these safety concerns, vaccine manufacturers were requested to conduct post-authorization or post-licensure safety studies as additional pharmacovigilance activities.

Chapter 3 of the thesis provides an overview of post-licensure observational safety studies that were implemented to assess the risk of autoimmune diseases and rare adverse events following HPV vaccination. We synthesized the methodologic approaches that were applied together with the data sources that were used. By conducting this review, we identified two important elements that inform on the validity and robustness of vaccine safety evaluation studies. One relates to analytical parameters that include study design, the size of the population that is available in a data source and, the risk window during which an adverse event is likely to occur and, the second relates to the validity of clinical case definitions that are used to identify adverse events in existing data sources.

Safety evaluation studies are formal epidemiological studies which are designed and powered specifically to test a hypothesis in an unbiased way and allow to characterize and quantify a potential safety signal. *Chapter 4* of the thesis describes three post-authorization safety studies that were conducted to assess the safety of the bivalent HPV *Cervarix* vaccine. Through the three post-authorization safety studies, we discussed methodological considerations of using existing healthcare data sources to address vaccine safety-related questions. The methodological considerations focus on the choice of study design and the use of harmonized clinical definitions, we also provide additional insights on bias linked to misclassification of exposure and the use of active comparators as alternative, and on the need for tailored statistical methods to deal with the 'zero-event' issue when assessing rare adverse events.

- *Several study designs can fit a single vaccine safety research question.*

The choice of study design to address a specific vaccine safety research question is usually guided by the nature of the events under assessment, the required population size and the available observation period. It has become more and more frequent to apply several study designs in a single study . Cohort and self-controlled case series (SCCS) designs are often applied as complementary methods because they can help to mitigate the threats related to internal validity within each study design [28]. The

cohort method is usually less suitable to assess rare events. However, it allows for the inclusion of large sample size and increases the statistical power for small risk quantification, it also allows to analyse multiple events following a single exposure. In *Chapter 4.1*, the risk of developing autoimmune diseases is evaluated through a cohort design and SCCS design. The study was set in the UK CPRD data source and the linked Hospital Episodes Statistics. The aim was to determine whether vaccinated females were exposed to an increase of risk of 19 autoimmune diseases, which were studied as two distinct composite endpoints given their low incidence rates, neuroinflammatory and ophthalmic diseases (1) and other autoimmune diseases (2), following administration of the bivalent HPV vaccine. By using the UK CPRD data source, it was expected that a large number of exposures to bivalent HPV will be captured since up to 80% vaccine coverage was observed in the UK through the NIP [29]. In addition, we used the SCCS design as an alternative method to analyse each autoimmune diseases as an individual endpoint, the method was applied under the condition that a minimum of 10 cases of an individual disease was detected. Case-only design are powerful method which only uses data from individuals who experienced the outcome of interest. In the SCCS, each individual acts as its own control allowing to implicitly control for all fixed confounders not varying with time [30], it compares the rate of adverse events during a risk interval with rates of events occurring during all remaining observational time (outside the risk interval). To generate valid and unbiased estimates, the SCCS should meet certain assumptions: 1) the occurrence of an event should not affect subsequent exposures (or event-dependent exposures); 2) events are rare or independently recurrent; 3) the occurrence of an event is constant over time (no impact of age or seasonality). A simplified version of the SCCS is the self-controlled risk interval (SCRI) design [31]. The SCRI restricts the analysis to vaccinated cases and is conducted over pre-specified risk and control intervals. The main advantage of the SCRI is that the analysis focuses exclusively on the pair 'exposure-event' of interest within a limited timeframe and then is less susceptible to time-varying confounders. However, the SCRI is usually less powerful due to the reduced unexposed observational time under assessment. When rare adverse events or events with long latent periods need further assessment, or when time matching is important case-control study designs may be most efficient [32]. In case-control design, individuals are included based on their outcome status and constitute the case and non-case/control study groups. Then the exposure is assessed in both groups. This design has the advantage to clearly define the case population according to specific clinical case definitions and it only observes a sample of the person-time in the source population to estimate the distribution of exposure. However, it is important that controls are selected from the same source-population that gives rise to the cases to ensure comparability, which should also be underlined through matching methods.

- *Harmonized clinical definitions can minimize bias linked to heterogeneity across studies.*

In *Chapter 4.2*, a meta-analysis was conducted to assess risk of autoimmune diseases following bivalent HPV vaccination. The meta-analysis included all evidence on bivalent HPV vaccine that were available to the vaccine manufacturer at that time and combined two types of data: data from clinical studies and data from observational post-licensure studies. The various nature of the studies and variation in used coding systems across studies induced predictable differences in the definitions of the clinical outcomes. As per the standard in the clinical setting, the MedDRA dictionary was used for clinical trials studies while for observational post-licensure studies the Read code classification or International Classification of Diseases 10th Revision (ICD-10) were used. Also, broad (or sensitive) and narrow (or specific) clinical case definitions were used non-uniformly across studies. In addition, the level of diagnostic certainty was not similar across studies with validated cases in clinical trial studies and limited or absence of validation case process in the observational studies.

In the clinical setting, each single individual case goes through a rigorous case ascertainment process which cannot necessarily be replicated in studies using real-world data. In studies using real-world data, pre-specified and computerized algorithms are used to identify events, exposures, and covariates of interest to build the analytical dataset. When using real-world data, validation of cases through medical charts review is often considered as a gold standard and preferably recommended by regulators. Case validation process allows to determine the positive predictive value (PPV) of computerized algorithms and may trigger an iterative process to refine the algorithm to ultimately ensure a high specificity and limit the risk of misclassification of outcomes [33,34]. In addition, PPV can also be used in quantitative bias analysis to adjust risk estimates for outcome misclassification [35]. However, due to resource or governance constraints, it is not always feasible to access additional medical information and, consequently validate the performance of computerized algorithms. Over the last years, tools have been developed to generate harmonized medical codelists such as CodeMapper [36] and to evaluate the performance of computerized algorithms such as PheValuator [37, 38]. While medical codelist creator tools have a proven experience in the vaccine field [39], further explorations of the PheValuator or similar validator tool are needed to test for its appropriateness and to understand whether the level of validity would satisfy health regulators requirements.

- <u>*Delayed exposure or active comparators can deal with misclassification of exposure*.</u>

  Reporting of exposure in existing healthcare data sources may be biased. Generally, an absence of medical records in existing healthcare data sources does not necessarily mean an absence of an event and, this limitation linked to missing data is particularly true for exposure such as vaccine or drug uptake. While disease diagnoses may be recorded with a delay in a data source, vaccine exposure may simply not be recorded or recorded in satellite data sources such as vaccine registry. In *Chapter 4.3*, the risk of spontaneous abortion was assessed in young women that were inadvertently exposed to the bivalent HPV vaccine. The study was conducted in the UK CPRD data source and applied a cohort

design with a 'delayed pregnancy-vaccine exposure' as comparator to overcome bias linked to misclassification of exposure. The 'delayed pregnancy-vaccine exposure' identified women who had a sufficiently long time between pregnancy and exposure and ensured a non-exposed vaccine status during pregnancy. Exposed and unexposed cohorts were built according to the first day of gestation and exposure to the bivalent HPV vaccine. Exposed women were those with the first day of gestation within -30 days and +45 days after any bivalent HPV vaccine dose and non-exposed were those with a first date of gestation between 120 days and 18 months after the last bivalent HPV vaccine dose.

In classical cohort designs using RWD, the unexposed cohort may consist of individuals which are not exposed to the vaccine under assessment meaning individuals for which the vaccine of interest is not recorded in the data source, but it needs to be certain these are truly unexposed and that data is not missing for other reasons. As we have seen during COVID-19 vaccine roll out, unexposed individuals may not be available for a long time for comparative assessment. Active vaccine comparators can be used to overcome the lack of 'unexposure', and bias linked to misclassification of exposure in a data source. Active vaccine comparators may consist of individuals exposed to another vaccine with the same target indication (i.e. a vaccine from another vaccine manufacturer with similar or different vaccine technology) or any other vaccines that are recommended for the population of interest mimicking a placebo arm. The use of vaccine comparators has been recently implemented in several observational studies assessing safety risks of COVID-19 vaccines [40,41].

Beside misclassification of vaccine exposure, when studying pregnancy, the identification of pregnancy onset may also be challenging. In *Chapter 4.3*, the identification of onset of pregnancy, last menstrual period (LMP), was made through any pregnancy-related medical records of the pregnant women, in addition to, an existing linkage mother-baby that links medical records of women to those of offspring. Moreover, birth registries are reliable data sources to retrieve data on live births, any teratogenic effects, LMP and duration of gestation [42]. For pregnancy outcomes other than live births, the recommended method to identify onset of pregnancy in a data source is to first identify the pregnancy outcome which then retrospectively flags pregnancy onset. In some data sources, an expected delivery date codes have been created, which can help to estimate the onset of pregnancy and to identify ongoing pregnancies and pregnancies with unknown outcome [43].

- *Assessment of rare adverse events requires tailored statistical methods.*

  An additional layer of complexity in the safety assessment of rare adverse events is the low incidence of the events of interest. Because of their low incidence, some events may not be detected in a data source or in a single data source study, therefore multi-data sources studies are used to increase study size and likelihood to identify rare events. When pooled estimates are computed through meta-analytic methods, the absence of events (zero cases) cannot be disregarded [44,45]. For example, in the meta-analysis describes in *Chapter 4.2*, we attempted to deal with the zero-event issue by applying

various statistical methods. Some studies that were included in the meta-analysis reported no event in one arm (single-zero) or even both arms (double-zero). To overcome the zero-event issue, three different statistical methods were applied to estimate pooled odds ratios which were: the continuity correction method, beta-binomial regression, and the 'crude' method as sensitivity analyses. The continuity correction method deals with single and double zero events by adding artificial continuity correction to the studies with zero cells. The beta-binomial regression method explicitly includes studies with zero-event without continuity correction, it assumes that a proportion is observed from a binomial distribution and each study contributes two proportions, one from the control and one from the 'treatment' arm. The 'crude' method also includes zero-event studies by aggregating all studies in a single table and computing effect estimates by applying standard methods. It ignores that data were collected from various studies and works under the assumption of a constant estimate across studies (fixed effects). The three methods generated estimates of similar magnitude but led to inconclusive evidence as one method suggested a slight increase of risk and the two others showed ambiguous results. This variation in estimates was mainly driven by the weighting of data from different studies.

Future perspectives

In the current health regulatory authority's context, multi-data sources studies are newly recommended methodological approaches to assess the safety of vaccines or drugs [46]. The European data source landscape is rich and diverse including data from primary care, hospital settings or pharmacy claims collected at national or regional level. The diversity of the EU data sources triggers the need to understand the appropriateness of data sources to address specific vaccine research's questions. In *Chapter 5* of the thesis, we emphasize the added value of conducting feasibility assessments as preliminary step before implementing formal epidemiological studies. We also recommend that the feasibility assessment should remain a technical evaluation that focuses on the scientific and operational feasibility without formal assessments. Metadata catalogues are also key documentations that provide a comprehensive description of data elements in an existing healthcare data source, it allows to increase the ability to judge the evidentiary value of a future observational study [47].

At the European level, many progresses have been made and, beyond evidence generation using real-world data, the fit-for-purpose and data quality are considered as the basis for generating trustful evidence.

Following the lessons learned from the H1N1 pandemic the IMI-funded ADVANCE project aimed at designing and establishing an ecosystem for vaccine monitoring in Europe, this was a collaboration of 47 partners including EMA and ECDC. In 2019 the VAccine monitoring Collaboration for Europe (VAC4EU) network was established as the sustainability solution of the successful implementation of the IMI-ADVANCE system [48]. The VAC4EU association is currently composed of 26 institutions from

9 European countries providing access to expertise and healthcare data sources, they work collaboratively using a similar system as the Vaccine Safety Datalink, institutions work together, rotate responsibilities, and use infrastructure provided by VAC4EU [49]. The research infrastructure includes tools such as the codemapper, a phenotype library with clinical event definitions, an analytical pipeline based on the ConcePTION CDM, remote research environment and community discussions. VAC4EU collaborated with the EU PE & PV network on several of the EMA procured COVID-19 vaccine studies such as the ACCESS project, the Early Covid-19 Vaccine Monitoring study for near real time monitoring of AESI, the Covid-19 Vaccine Monitoring study to assess safety signals and the COVE study, assessing COVID-19 vaccine effectiveness [50]. The overarching goal of ACCESS was to ensure readiness for the safety monitoring of COVID-19 vaccines. Materials such as template study protocols, clinical case definitions and background incidence rates for AESIs that were developed in ACCESS were transparently and publicly shared with the scientific community to promote and maximize harmonized approaches for the safety assessment of COVID-19 vaccines [51]. This initiative demonstrates the importance of fostering collaborations between vaccine's experts at EU level from diverse horizons (academic, public, and private sectors) and it also suggests the need for continuous efforts globally with existing vaccine expert groups such as the Global Vaccine Data Network, SPEAC or Brighton, with as example, the creation of central and global repository of case definitions to improve vaccine grade evidence.

In 2019, the Heads of Medicines Agencies and European Medicines Agency (HMA-EMA) launched a task force to describe the EU data landscape from a regulatory perspective and identify practical steps for the EU medicines regulatory network to optimize the use of existing healthcare data to support regulatory decision-making [52]. Among its top priority recommendations, the HMA-EMA Big Data Steering Group (BDSG) workplan includes to develop of a platform (DARWIN which stands for Data Analysis and Real-World Interrogation Network) to access and analyse EU healthcare data, to establish an EU framework for data quality and representativeness and, to enable data discoverability [53]. The implementation of DARWIN is a major achievement at the European level [54]. The data sources in DARWIN are currently growing. Studies in DARWIN will be conducted through a distributed data network using the Observational Medical Outcomes Partnership (OMOP) CDM which applies standardized vocabularies [55].

The appropriateness of data source(s) is two-fold, first to understand whether they are fit-for-purpose, which is based on the type of data elements available in a data source (i.e., data on exposure, outcome, covariates of interest) and data accessibility and, second, more importantly, to demonstrate quality of the used data. As part of the BDSG's effort, the project "Strengthening Use of Real-World Data in Medicines Development: Metadata for Data Discoverability and Study Replicability" (MINERVA) created a metadata catalogue of 10 selected EU data sources as a proof-of-concept catalogue to help

researchers and/or data access partners in their understanding of data sources when designing a study using RWD [56]. Metadata consists of a set of information about other data but which does not describe the content of the data. Metadata includes information on generation, location of a data set; key variables; data format, data provenance; documentation on storage, handling processes and governance. The expansion of the catalogue to the DARWIN data source network and its accessibility to the scientific community may be extremely helpful to validate the adequacy of data sources from an operational point of view, it will allow to understand whether data elements of interest or linked data can be accurately captured for a specific research question or from a governance standpoint whether a data source is accessible for industry-sponsor activity [57,58].

Regarding data quality, BDSG's effort established a framework for data quality which provides principles and procedures to assess data quality according to 5 main dimensions (reliability, extensiveness, coherence, timeliness, relevance) and related metrics which is a way to assess the value of a dimension [59,60]. Several research groups have developed tools for systematic measurement of data quality in data sources [61,62]. The developed quality check tools are, for most of them, based on the Kahn's framework which includes 3 levels of data quality checks: 1) Conformance to check for formatting or data structure; 2) Completeness to test for frequencies of data but without analyzing values themselves; 3) Plausibility to assess truthfulness of data values [63]. Applying various levels of data quality checks helps to understand the appropriateness of each data source in terms of needed data to create study variables and the level of validity of each variable. However, further progresses should be made to guide scientists in this field, as to date, no quality data thresholds or success criteria have been postulated to frame quality indicators.

The manufacturing process of the next generation of HPV vaccines will be cost-effective to ensure supply worldwide. It is anticipated that newly formulated HPV vaccines will be primarily supplied to low- and middle-income countries where pharmacovigilance system reporting is suboptimal, and vaccine adverse event surveillance is limited. In addition, in LMIC, there is a lack of visibility on capabilities in terms of data availability and accessibility for the implementation of vaccine safety surveillance studies. This emphasizes the need for global collaboration as safety surveillance is a necessary continuous process during vaccine life cycle and across borders.

Conclusions

Over the last decade, the assessment of vaccine safety has shown drastic methodological improvements which are illustrated in this thesis through the implementation of single data source studies to assess the safety of the bivalent HPV vaccine to multi-data sources studies on background incidence rates for rapid assessment of vaccines. The implementation of studies through distributed data network with the use of a common data model and common analytics has become the new norm.

However, improvements still need to be made globally to ensure reproducibility and comparability of study results, more harmonization in processes for conducting vaccine safety studies from regulatory requests to study implementation could contribute to this effort.

References

1. Arlett P, Kjaer J, Broich K, Cooke E. Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. *Clin Pharmacol Ther* 2022; 111(1): 21-3.
2. Sturkenboom M, Bahri P, Chiucchiuini A, Grove Krause T, Hahne S, Khromava A, Kokki M, Kramarz P, Kurz X, Larson HJ, de Lusignan S, Mahy P, Torcel-Pagnon L, Titievsky L, Bauchau V, consortium A. Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines. *Vaccine* 2020; 38 Suppl 2: B1-B7.
3. Pacurariu A, Plueschke K, McGettigan P, Morales DR, Slattery J, Vogl D, Goedecke T, Kurz X, Cave A. Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation. *BMJ Open* 2018; 8(9): e023090.
4. Sturkenboom M, Braeye T, van der Aa L, Danieli G, Dodd C, Duarte-Salles T, Emborg HD, Gheorghe M, Kahlert J, Gini R, Huerta-Alvarez C, Martin-Merino E, McGee C, de Lusignan S, Picelli G, Roberto G, Tramontan L, Villa M, Weibel D, Titievsky L. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations. *Vaccine* 2020; 38 Suppl 2: B8-B21.
5. Sentinel. Sentinel Common Data Model. https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model (accessed 03 April 2023).
6. Observational Health Data Sciences and Informatics. Standardized Data: The OMOP Common Data Model. https://www.ohdsi.org/data-standardization/ (accessed 03 April 2023).
7. Thurin NH, Pajouheshnia R, Roberto G, Dodd C, Hyeraci G, Bartolini C, Paoletti O, Nordeng H, Wallach-Kildemoes H, Ehrenstein V, Dudukina E, MacDonald T, De Paoli G, Loane M, Damase-Michel C, Beau AB, Droz-Perroteau C, Lassalle R, Bergman J, Swart K, Schink T, Cavero-Carbonell C, Barrachina-Bonet L, Gomez-Lumbreras A, Giner-Soriano M, Aragon M, Neville AJ, Puccini A, Pierini A, Ientile V, Trifiro G, Rissmann A, Leinonen MK, Martikainen V, Jordan S, Thayer D, Scanlon I, Georgiou ME, Cunnington M, Swertz M, Sturkenboom M, Gini R. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. *Clin Pharmacol Ther* 2022; 111(1): 321-31.
8. Gini R, Sturkenboom MCJ, Sultana J, Cave A, Landi A, Pacurariu A, Roberto G, Schink T, Candore G, Slattery J, Trifirò G; Working Group 3 of ENCePP (Inventory of EU data sources and methodological approaches for multisource studies). Different Strategies to Execute Multi-Database Studies for Medicines Surveillance in Real-World Setting: A Reflection on the European Model. Clin Pharmacol Ther. 2020 Aug;108(2):228-235. doi: 10.1002/cpt.1833. Epub 2020 May 5. PMID: 32243569; PMCID: PMC7484985.

9. DeStefano F, Chen RT, Izurieta HS, Raine JM. ADVANCE: The promises, pitfalls, and future prospects of a European distributed data network for immunization surveillance and research. *Vaccine* 2020; 38 Suppl 2(Suppl 2): v-vi.

10. Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M, Group V-GC-CS. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. *BMJ* 2011; 343: d3908.

11. Romio S, Weibel D, Dieleman JP, Olberg HK, de Vries CS, Sammon C, Andrews N, Svanstrom H, Molgaard-Nielsen D, Hviid A, Lapeyre-Mestre M, Sommet A, Saussier C, Castot A, Heijbel H, Arnheim-Dahlstrom L, Sparen P, Mosseveld M, Schuemie M, van der Maas N, Jacobs BC, Leino T, Kilpi T, Storsaeter J, Johansen K, Kramarz P, Bonhoeffer J, Sturkenboom MC. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccines: a multinational self-controlled case series in Europe. *PLoS One* 2014; 9(1): e82222.

12. Andrews N, Stowe J, Miller E, Svanstrom H, Johansen K, Bonhoeffer J, Hviid A, consortium V. A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark. *Vaccine* 2012; 30(19): 3042-6.

13. Weibel D, Sturkenboom M, Black S, de Ridder M, Dodd C, Bonhoeffer J, Vanrolleghem A, van der Maas N, Lammers GJ, Overeem S, Gentile A, Giglio N, Castellano V, Kwong JC, Murray BJ, Cauch-Dudek K, Juhasz D, Campitelli M, Datta AN, Kallweit U, Huang WT, Huang YS, Hsu CY, Chen HC, Giner-Soriano M, Morros R, Gaig C, Tio E, Perez-Vilar S, Diez-Domingo J, Puertas FJ, Svenson LW, Mahmud SM, Carleton B, Naus M, Arnheim-Dahlstrom L, Pedersen L, DeStefano F, Shimabukuro TT. Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines - Multi-country assessment. *Vaccine* 2018; 36(41): 6202-11.

14. Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. *Pharmacoepidemiol Drug Saf* 2016; 25(2): 215-22.

15. Black SB, Law B, Chen RT, Dekker CL, Sturkenboom M, Huang WT, Gurwith M, Poland G. The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety. *Vaccine* 2021; 39(19): 2712-8.

16. Willame CD, C; Gini, R; Durán, CE; Thomsen, RM; Wang, L; Gedebjerg, A; Kahlert, J; Ehrenstein, V; Bartolini, C; Droz, C; Moore, N; Haug, U; Schink, T; Diez-Domingo, J; Mira-Iglesias, A; Vergara-Hernández, C; Carreras, JJ; Villalobos, F; Pallejà, M; Aragón, M; Perez-Gutthann ,S; Arana, A; Giaquinto, C; Barbieri, E; Stona, L; Huerta, C; Pallejà, M; Aragón, M; García Poza, P; de Burgos, A; Martínez-González, M; Souverein, P; Gardarsdottir, H; Siiskonen, SJ; Weibel, D; Mahy, P; Klungel, O; Sturkenboom, MCJM. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines. Final report, 2021. Available on https://zenodo.org/record/5255870. Accessed on June 2023.

17. Human papillomavirus vaccines: WHO position paper, October 2014-Recommendations. *Vaccine* 2015; 33(36): 4383-4.
18. North AL, Niccolai LM. Human Papillomavirus Vaccination Requirements in US Schools: Recommendations for Moving Forward. *Am J Public Health* 2016; 106(10): 1765-70.
19. England PH. Human Papillomavirus (HPV) Vaccine Coverage in England, 2008/09 to 2013/14. A review of the full six years of the three-dose schedule. 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/774074/HPV_Vaccine_Coverage_in_England_200809_to_201314.pdf (accessed 03 April 2023).
20. European Medicines Agency. Notification to the PRAC/EMA secretariat of a referral under Article 20 of regulation (EC) 726/2004. 2015. https://www.ema.europa.eu/en/documents/referral/hpv-vaccines-article-20-procedure-notification_en.pdf (accessed 02 April 2023).
21. Ward D, Thorsen NM, Frisch M, Valentiner-Branth P, Molbak K, Hviid A. A cluster analysis of serious adverse event reports after human papillomavirus (HPV) vaccination in Danish girls and young women, September 2009 to August 2017. *Euro Surveill* 2019; 24(19).
22. Huygen F, Verschueren K, McCabe C, Stegmann JU, Zima J, Mahaux O, Van Holle L, Angelo MG. Investigating Reports of Complex Regional Pain Syndrome: An Analysis of HPV-16/18-Adjuvanted Vaccine Post-Licensure Data. *EBioMedicine* 2015; 2(9): 1114-21.
23. Weinbaum CM, Cano M. HPV Vaccination and Complex Regional Pain Syndrome: Lack of Evidence. *EBioMedicine* 2015; 2(9): 1014-5.
24. Vielot NA, Becker-Dreps S. Hazard of complex regional pain syndrome following human papillomavirus vaccination among adolescent girls in the United States: a case-cohort analysis of insurance claims data. *Expert Opin Drug Saf* 2020; 19(1): 107-12.
25. European Medicines Agency. Review concludes evidence does not support that HPV vaccines cause CRPS or POTS. 2015. https://www.ema.europa.eu/en/news/review-concludes-evidence-does-not-support-hpv-vaccines-cause-crps-pots (accessed 03 April 2023).
26. Phillips A, Hickie M, Totterdell J, Brotherton J, Dey A, Hill R, Snelling T, Macartney K. Adverse events following HPV vaccination: 11 years of surveillance in Australia. *Vaccine* 2020; 38(38): 6038-46.
27. Yousefi Z, Aria H, Ghaedrahmati F, Bakhtiari T, Azizi M, Bastan R, Hosseini R, Eskandari N. An Update on Human Papilloma Virus Vaccines: History, Types, Protection, and Efficacy. *Front Immunol* 2021; 12: 805695.
28. Checkoway H, Pearce N, Kriebel D. Selecting appropriate study designs to address specific research questions in occupational epidemiology. *Occup Environ Med* 2007; 64(9): 633-8.
29. UK Health Security Agency. Human papillomavirus (HPV) vaccination coverage in adolescents in England: 2021 to 2022. 2022; Volume 16 number 13.

30. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ* 2016; 354: i4515.

31. Yih K. Using the Self-Controlled Risk Interval (SCRI) Method to Study Vaccine Safety. 2017. https://www.sentinelinitiative.org/sites/default/files/Sentinel-ICPE-2017-Course-PRISM-SCRI-Studies.pdf (accessed 03 April 2023).

32. Setia MS. Methodology Series Module 2: Case-control Studies. *Indian J Dermatol* 2016; 61(2): 146-51.

33. Gini R, Dodd CN, Bollaerts K, Bartolini C, Roberto G, Huerta-Alvarez C, Martin-Merino E, Duarte-Salles T, Picelli G, Tramontan L, Danieli G, Correa A, McGee C, Becker BFH, Switzer C, Gandhi-Banga S, Bauwens J, van der Maas NAT, Spiteri G, Sdona E, Weibel D, Sturkenboom M. Quantifying outcome misclassification in multi-database studies: The case study of pertussis in the ADVANCE project. *Vaccine* 2020; 38 Suppl 2: B56-B64.

34. Girman CJ, Ritchey ME, Lo Re V, 3rd. Real-world data: Assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products. *Pharmacoepidemiol Drug Saf* 2022; 31(7): 717-20.

35. Lanes S, Beachler DC. Validation to correct for outcome misclassification bias. *Pharmacoepidemiol Drug Saf* 2023.

36. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom M, Kors JA, consortium A. CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project. *Pharmacoepidemiol Drug Saf* 2017; 26(8): 998-1005.

37. Swerdel JN, Hripcsak G, Ryan PB. PheValuator: Development and evaluation of a phenotype algorithm evaluator. *J Biomed Inform* 2019; 97: 103258.

38. Swerdel JN, Schuemie M, Murray G, Ryan PB. PheValuator 2.0: Methodological improvements for the PheValuator approach to semi-automated phenotype algorithm evaluation. *J Biomed Inform* 2022; 135: 104177.

39. Weibel D, Dodd C, Mahaux O, Haguinet F, De Smedt T, Duarte-Salles T, Picelli G, Tramontan L, Danieli G, Correa A, McGee C, Martin-Merino E, Huerta-Alvarez C, Berencsi K, Emborg HD, Bollaerts K, Bauchau V, Titievsky L, Sturkenboom M. ADVANCE system testing: Can safety studies be conducted using electronic healthcare data? An example using pertussis vaccination. *Vaccine* 2020; 38 Suppl 2: B38-B46.

40. Li X, Burn E, Duarte-Salles T, Yin C, Reich C, Delmestri A, Verhamme K, Rijnbeek P, Suchard MA, Li K, Mosseveld M, John LH, Mayer MA, Ramirez-Anguita JM, Cohet C, Strauss V, Prieto-Alhambra D. Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US. *BMJ* 2022; 379: e071594.

41. ENCePP. An Observational Post-Authorization Safety Study to Assess the Safety of Ad26.COV2.S Using European Healthcare Data through VAC4EU (COVID-19). EU PAS45362. 2022. https://www.encepp.eu/encepp/viewResource.htm?id=48839.
42. ENCePP. Guide on Methodological Standards in Pharmacoepidemiology. Annex 2. Guidance on methods for the evaluation of medicines in pregnancy and breastfeedingcitation. 2023.
43. Schink T, Wentzell N, Dathe K, Onken M, Haug U. Estimating the Beginning of Pregnancy in German Claims Data: Development of an Algorithm With a Focus on the Expected Delivery Date. *Front Public Health* 2020; 8: 350.
44. Ren Y, Lin L, Lian Q, Zou H, Chu H. Real-world Performance of Meta-analysis Methods for Double-Zero-Event Studies with Dichotomous Outcomes Using the Cochrane Database of Systematic Reviews. *J Gen Intern Med* 2019; 34(6): 960-8.
45. Kuss O. Statistical methods for meta-analyses including information from studies without any events-add nothing to nothing and succeed nevertheless. *Stat Med* 2015; 34(7): 1097-116.
46. DARWIN EU. 2023. https://www.darwin-eu.org/index.php. Access on June 2023.
47. European Medicines Agency. Conceptual Framework. Technical workshop on real-world metadata for regulatory purposes Virtual meeting, April 12, 2021. 2021. https://www.ema.europa.eu/en/documents/presentation/presentation-session-1-conceptual-framework-rosa-gini_en.pdf (accessed 03 April 2023).
48. Vaccine monitoring collaboration for Europe. 2019. Available on https://vac4eu.org/. Accessed on June 2023
49. Gianmarco Di Mauro RG, Patrick Mahy, Eva Molero, Miriam Sturkenboom, Daniel Weibel. VAC4EU: a pan-European research network for collaborative post-authorization vaccine safety and benefit monitoring. *ISoP* 2022.
50. ACCESS. Vaccine COVID-19 monitoring readiness. Available on: https://vac4eu.org/covid-19-vaccine-monitoring/. Accessed on June 2023.
51. VAC4EU. Dashboard Background rates of Adverse Events of Special Interest for COVID-19 vaccines. 2021.
52. European Medicines Agency. 2020. https://www.ema.europa.eu/en/about-us/how-we-work/big-data#hma/ema-big-data-steering-group-section (accessed 20 June 2023).
53. Heads of Medicines Agencies. Big Data Steering Group (BDSG): 2020 report, 2021.
54. European Medicines Agency. Data Analysis and Real World Interrogation Network (DARWIN EU) https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu (accessed 03 April 2023).

55. European Medicines Agency. DARWIN EU® has completed its first studies and is calling for new data partners. 2023. https://www.ema.europa.eu/en/news/darwin-eur-has-completed-its-first-studies-calling-new-data-partners20 Access on June 2023.

56. Lia Gutierrez AM, Romin Pajouheshnia, Vera Ehrenstein, Morris Swertz, Karin Gembert, Susana Perez-Gutthann On behalf of the MINERVA Project Consortium. MINERVA: Metadata for data dIscoverability aNd study rEplicability in obseRVAtional studies, 2021.

57. European Medicines Agency. Technical workshop on real-world metadata for regulatory purposes, 2021.

58. European Medicines Agency. List of metadata for Real World Data catalogues. 2022.

59. Heads of Medicines Agencies. Data Quality Framework for EU medicines regulation, 2022.

60. Enrique Bernal-Delgado SC, Thomas Engsig-Karup, Francisco Estupiñán-Romero, Nina Sahlertz Kristiansen, Jesper Bredmose Simonsen European Health Data Space Data Quality Framework, 2022.

61. Sentinel. How Sentinel Gets Its Data. https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data (accessed 03 April 2023).

62. Brown JS, Kahn M, Toh S. Data quality assessment for comparative effectiveness research in distributed data networks. Med Care. 2013 Aug;51(8 Suppl 3):S22-9. doi: 10.1097/MLR.0b013e31829b1e2c. PMID: 23793049; PMCID: PMC4306391.

63. Kahn MG, Callahan TJ, Barnard J, Bauck AE, Brown J, Davidson BN, Estiri H, Goerg C, Holve E, Johnson SG, Liaw ST, Hamilton-Lopez M, Meeker D, Ong TC, Ryan P, Shang N, Weiskopf NG, Weng C, Zozus MN, Schilling L. A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. *EGEMS (Wash DC)* 2016; 4(1): 1244.

Chapter 7: Summaries

7.1 English summary

Vaccines help to protect individuals and populations against harmful diseases. However, vaccines, as any other medicines, can trigger side effects or adverse events that range from mild to severe symptoms or diseases. Because severe adverse events are rare, they may go undetected during the clinical development phases which are conducted on a limited number of participants. Therefore, assessing risks associated to vaccines after their approval for use is necessary to provide reassurance on benefit-risk profile of vaccines and to maintain public confidence in vaccine programmes.

The monitoring of benefit-risk profiles of vaccines is a process that starts at early clinical development phases and includes passive, enhanced and active surveillance activities. Over the last years, the use of real-world data (RWD) and existing healthcare data sources has grown to assess vaccine safety post-licensure. RWD are, for instance, data electronically collected by physicians during routine clinical practice or disease diagnosis or procedures at hospital level or pharmacy claims. With collaboration initiatives at global level, the implementation of multi-data sources studies using RWD became a standard in vaccine safety assessment, which necessitates the development of methods such as common analytical approaches to overcome the observed heterogeneity across data sources.

In the general introduction (***Chapter 1***), I describe the importance of vaccination as one of the most effective preventive measures against infectious diseases and the pharmacoepidemiological concepts that are applied to detect and evaluate adverse events that may occur following vaccination. I emphasize the methodological improvements in vaccine safety assessment since the increasing use of collaborative approaches and implementation of multi-data sources studies. I also provide background information on the legislation on vaccine safety assessment in Europe outlining obligations for the European Medicines Agency (EMA) and for vaccine manufacturers to conduct appropriate pharmacovigilance activities once a vaccine is launched on a market.

Background incidence rates for vaccine safety assessment

Background incidence rates are useful to contextualize vaccine safety signals that may emerge post-vaccination. ***Chapter 2*** describes the implementation of multi-data sources studies that generated background incidence rates for a broad set of adverse events of special interest (AESI) for vaccines. Following the H1N1 pandemic in 2009, the need for robust surveillance systems to monitor benefits and risks of vaccines was highlighted as crucial by governments. In this context, the Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE), a public-private consortium, was launched by the Innovative Medicines Initiatives in 2013 which aimed to build a system to generate evidence on background rates, vaccine coverage and assess benefit-risk of vaccines using existing healthcare data sources in Europe. The study described in ***Chapter 2.1*** generated background

incidence rates of pre-selected autoimmune diseases using 7 European (EU) electronic healthcare data sources from 4 EU countries (Denmark, Italy, Spain and UK). Each data owner analyzed locally their data by applying a common data model and aggregated results were shared on a secure platform for visualization and pooling. Pooled estimates were computed according to the type of data (data collected by general practitioners or hospitalization record linkage data sources) to account for heterogeneity across data sources. The study demonstrated that the ADVANCE system can identify specific autoimmune diseases and can generate age, sex and time-specific incidence rates. More recently, following the COVID-19 pandemic in 2020, the ACCESS (The vACCine covid-19 monitoring readinESS) project was launched to prepare real-world monitoring of COVID-19 vaccines. The study in ***Chapter 2.2*** generated background incidence rates of 41 AESI for vaccines which are events of scientific, medical and public health interests. The study used a distributed data network of 10 data sources across 7 EU countries (Denmark, France, Germany, Italy, Netherlands, Spain and UK) and applied a common protocol, common data model and common analytics. Pooled estimates were computed according to the nature of the AESIs and the setting where the diseases are typically diagnosed (general practitioners or hospital-based databases or both), we concluded that background rates from data sources that show the highest level of completeness (primary care and specialist care) should be preferred for further safety assessment. Through the two background incidences rates studies, we highlighted the importance of dealing with heterogeneity in multi-data sources studies by applying harmonized clinical definitions, common methodology and common analytics and by considering the interplay between the setting where diseases are typically diagnosed and the setting that each data source captures. We observed that data sources containing exclusively primary care data underestimated the incidence of diseases that require hospitalization such as autoimmune diseases. On the other hand, data sources with just hospitalizations underestimated incidence of diseases that are mostly diagnosed in an outpatient setting. In addition, the background incidence rates studies demonstrated that most of the AESIs follow a specific age pattern which emphasizes the importance of generating population-specific incidence rates such as children, pregnant women, or individuals with comorbidities.

Methods for vaccine safety signal evaluation: the use-case of the bivalent HPV vaccine

A variety of methods can be implemented to assess the safety of vaccines. The systematic literature review described in ***Chapter 3*** provides an overview of study designs that were implemented to evaluate the risk of rare adverse events following HPV vaccination. The systematic review identified analytical parameters and the validity of clinical case definitions as being two important elements that inform on the validity and robustness of vaccine safety evaluation studies. The systematic review also highlighted the need for more systematic collaborations to monitor the safety of vaccines.

Since the launch of HPV vaccines, their risks and benefits have been continuously assessed by competent health authorities and vaccine manufacturers as per their obligations. To date, with the set of available evidence, HPV vaccines have well-established safety profiles with a favorable benefit-risk balance. **Chapter 4** describes three post-authorization safety studies that have been implemented to evaluate the risk of autoimmune diseases (***Chapter 4.1 and 4.2***) or the risk of spontaneous abortion (***Chapter 4.3***) following bivalent HPV vaccination.

In ***Chapter 4.1***, a cohort and a self-controlled case series designs were applied in the UK CPRD data source to assess the risk of autoimmune diseases following bivalent HPV vaccination. We demonstrated no evidence of an increased risk of autoimmune diseases in women aged 9 to 25 years. However, a statistically significant increased risk of autoimmune thyroiditis diseases following vaccination was observed when the analysis was conducted on validated cases only (relative risk: 3.75 [95%CI: 1.25-11.31]). The statistically significant increased risk was not confirmed in further post-hoc analyses. Additional real-world evidence on the safety of bivalent or quadrivalent HPV vaccines became publicly available and showed potential associations with Guillain Barré Syndrome (GBS), inflammatory bowel disease (IBD) and autoimmune thyroiditis diseases. For this reason, the meta-analysis described in ***Chapter 4.2*** has been conducted and included all evidence that were available at that time for the bivalent HPV vaccine, which included data from clinical and real-life settings. While a large of set data could be included, we could not draw any conclusion for GBS due to the very low number of observed cases and we observed no increased risk for IBD (odds ratio: 1.11 [95%CI: 0.75-1.66]) following bivalent HPV vaccination. We observed a 1.5-fold increased risk for autoimmune thyroiditis (odds ratio: 1.46 [95% CI: 1.22-1.76]), however, there was insufficient evidence to conclude on a potential causal association with the bivalent HPV vaccine. In ***Chapter 4.3***, a cohort design was implemented to analyze the risk of spontaneous abortion after bivalent HPV vaccination in the UK CPRD data source. We observed no evidence of an increased risk of spontaneous abortion (hazard ratio: 1.30 [95%CI: 0.79-2.12]) and other adverse pregnancy outcomes in young women inadvertently exposed to the bivalent HPV vaccine around gestation.

Recommendations for implementation of signal evaluation vaccine safety studies

Feasibility assessments are necessary steps before conducting a formal hypothesis testing epidemiological study. In ***Chapter 5***, we propose a pragmatic approach to conduct feasibility assessments. The toolbox focuses on two main components: the scientific feasibility and the operational feasibility, both comprising a series of questions to help overcoming methodological and operational challenges when post-licensure safety studies are implemented. With the increasing use of existing healthcare data sources to assess the safety of vaccines, it is of importance to test whether data sources are fit-for-purpose for a specific research question.

Discussion

Chapter 6 contextualizes in a broader perspective the findings of this thesis. In first instance, we emphasize the increasing use of multi-data sources studies and the use of distributed data networks to generate data on vaccine safety. The main advantage of multi-data sources studies is that they allow to gain statistical power to study rare outcomes by increasing study population size, and therefore maximizing the likelihood to detect and assess rare adverse events that may occur following vaccination. However, the applicability of multi-data sources studies has limitations related to the observed heterogeneity across data sources. Because a variety of types of data source exists which includes inpatient and/or outpatient medical diagnoses from hospitalization data sources, medical records from general practitioners or family pediatricians' data sources and record-linkage data sources that link hospitalization data and general practitioners' data or link data from registries, it is of importance to consider the data provenance and the setting where diseases are typically diagnosed for a correct data interpretation.

Second, we discuss and provide methodological considerations in vaccine safety signal evaluation studies, which are based on the experience from the bivalent HPV vaccine post-authorization safety studies described in Chapter 4. We highlight that harmonized clinical case definitions can minimize bias linked to heterogeneity across studies, misclassification of exposure can be overcome by using active comparators and tailored statistical methods should preferably be used when assessing rare adverse events.

Third, we discuss future perspective for the study of vaccines in the European context with the development of EU DARWIN and the conduct of fit-for-purpose data sources exercises.

To conclude, this thesis underlines the methodological improvements in vaccine safety assessment which should be maintained globally to ensure reproducibility and comparability of study results.

7.2 Nederlandse samenvatting

Vaccins helpen individuen en bevolkingsgroepen te beschermen tegen schadelijke ziekten. Vaccins kunnen echter, net als elk ander geneesmiddel, bijwerkingen veroorzaken die variëren van lichte tot ernstige symptomen of aandoeningen. Omdat ernstige bijwerkingen zelden voorkomen, kunnen ze onopgemerkt blijven tijdens de klinische ontwikkelingsfasen die slechts een beperkt aantal deelnemers omvatten. Daarom is de beoordeling van de risico's die verbonden zijn aan vaccins na goedkeuring voor gebruik noodzakelijk, dit om zekerheid te verkrijgen over het voordeel-risico profiel van deze vaccins en om het vertrouwen van het publiek in vaccinatieprogramma's te behouden.

Het opvolgen van het voordeel-risico profiel van vaccins is een proces dat begint in de vroege klinische ontwikkelingsfasen en omvat passieve, versterkte en actieve surveillanceactiviteiten. De afgelopen jaren is het gebruik van reële gegevens ('real world data', RWD) en bestaande bronnen van gezondheidszorggegevens toegenomen om de veiligheid van vaccins na het verlenen van de vergunning te beoordelen. RWD zijn bijvoorbeeld gegevens die door artsen elektronisch worden verzameld tijdens de routine klinische praktijk of diagnostiek van ziekten, procedures op ziekenhuisniveau of via apotheekaanvragen. Door samenwerkingsinitiatieven op mondiaal niveau is de uitvoering van studies met meerdere gegevensbronnen waarbij gebruik wordt gemaakt van RWD, de norm geworden voor de beoordeling van de veiligheid van vaccins, hetgeen de ontwikkeling vereist van methoden zoals bijvoorbeeld gemeenschappelijke analytische benaderingen om de waargenomen heterogeniteit tussen de verschillende gegevensbronnen op te lossen.

In de algemene inleiding (**hoofdstuk 1**) beschreef ik het belang van vaccinatie als een van de meest effectieve preventieve maatregelen tegen infectieziekten en de farmaco-epidemiologische concepten die worden toegepast om ongewenste bijwerkingen die zich na vaccinatie kunnen voordoen, op te sporen en te evalueren. Ik benadruk de methodologische verbeteringen bij de beoordeling van de veiligheid van vaccins sinds het toenemende gebruik van gezamenlijke benaderingen en de uitvoering van studies met meerdere gegevensbronnen. Ik geef ook achtergrondinformatie over de wetgeving inzake de beoordeling van de veiligheid van vaccins in Europa, waarin de verplichtingen zijn opgenomen voor het Europees Geneesmiddelenbureau (EMA) en voor fabrikanten van vaccins om passende geneesmiddelenbewakingsactiviteiten uit te voeren zodra een vaccin op de markt wordt gebracht.

Achtergrondincidentiecijfers voor de beoordeling van de veiligheid van het vaccin

Achtergrondincidentiepercentages zijn nuttig om de veiligheidssignalen voor het vaccin, die na vaccinatie kunnen optreden, in een gepaste context te plaatsen. In **hoofdstuk 2** wordt de implementatie beschreven van studies met meerdere gegevensbronnen die

achtergrondincidentiecijfers opleverden voor een uitgebreide reeks bijwerkingen die van bijzonder belang zijn voor vaccins. Na de H1N1-pandemie in 2009 werd de noodzaak van robuuste surveillancesystemen om de voordelen en risico's van vaccins te monitoren door de regeringen benadrukt als cruciaal. In deze context werd de versnelde ontwikkeling van VAccine beNefit-risk Collaboration in Europe (ADVANCE), een publiek-privaat consortium, in 2013 gelanceerd door het IMI. Dit had tot doel een systeem op te bouwen om bewijs te genereren over achtergrondpercentages, vaccindekking en de voordeel-risico verhouding van vaccins te beoordelen met behulp van bestaande gegevensbronnen over gezondheidszorg in Europa. Het in **hoofdstuk 2.1** beschreven onderzoek genereerde achtergrondincidentiepercentages van voorgeselecteerde auto-immuunziekten met behulp van 7 Europese (EU) elektronische gegevensbronnen over gezondheidszorg uit 4 EU-landen (Denemarken, Italië, Spanje en het Verenigd Koninkrijk). Elke data-eigenaar analyseerde lokaal zijn data door een gemeenschappelijk data model toe te passen en geaggregeerde resultaten werden gedeeld op een veilig platform voor visualisatie en pooling. Gepoolde schattingen werden berekend volgens het type gegevens (gegevens verzameld door huisartsen of door koppeling van ziekenhuisgegevens) om rekening te houden met heterogeniteit tussen gegevensbronnen. De studie toonde aan dat het ADVANCE-systeem specifieke auto-immuunziekten kan identificeren en leeftijds-, geslacht- en tijd-specifieke incidentiecijfers kan genereren. Meer recentelijk, na de COVID-19-pandemie in 2020, werd het ACCESS project (The vACCine covid-19 monitoring readinESS) gelanceerd om de monitoring van COVID-19-vaccins in de praktijk voor te bereiden. De studie in **hoofdstuk 2.2** leverde achtergrondincidentiepercentages op voor 41 bijwerkingen van speciaal belang (AESI), i.e. van wetenschappelijk, medisch en volksgezondheidsbelang. In de studie werd gebruikgemaakt van een verspreid datanetwerk van tien gegevensbronnen in zeven EU-landen (Denemarken, Frankrijk, Duitsland, Italië, Nederland, Spanje en het Verenigd Koninkrijk) en werden een gemeenschappelijk protocol, een gemeenschappelijk gegevensmodel en gemeenschappelijke analyses toegepast. De gepoolde schattingen werden berekend op basis van de aard van de AESI's en de omstandigheden waarin de ziekten doorgaans worden gediagnosticeerd (huisartsen, ziekenhuis of beide). We concludeerden dat achtergrondpercentages uit gegevensbronnen die het meest volledig zijn (eerstelijnszorg en specialistische zorg) de voorkeur verdienen voor verdere veiligheidsbeoordelingen. Door middel van de twee achtergrondincidentiestudies wezen we op het belang van het omgaan met heterogeniteit in onderzoeken met meerdere gegevensbronnen door geharmoniseerde klinische definities, een gemeenschappelijke methodologie en gemeenschappelijke analyses toe te passen en door de wisselwerking te overwegen tussen de omgeving waarin ziekten doorgaans worden gediagnosticeerd en de omgeving die elke gegevensbron registreert. We merkten op dat gegevensbronnen die uitsluitend gegevens uit de eerstelijnszorg bevatten, een onderschatting inhielden van de incidentie van ziekten die ziekenhuisopname vereisten, zoals auto-immuunziekten.

Anderzijds onderschatten gegevensbronnen met alleen ziekenhuisopnames de incidentie van ziekten die meestal worden gediagnosticeerd in een poliklinische setting. Bovendien is uit de studies naar achtergrondincidentiecijfers gebleken dat de meeste AESI's een specifiek leeftijdspatroon volgen, wat het belang benadrukt van het genereren van populatie-specifieke incidentiecijfers zoals kinderen, zwangere vrouwen of personen met co-morbiditeiten.

Methoden voor de evaluatie van het veiligheidssignaal van het vaccin: het use-case-geval van het bivalente HPV-vaccin

Er kunnen verschillende methoden worden toegepast om de veiligheid van vaccins te beoordelen. Het in **hoofdstuk 3** beschreven systematische literatuuronderzoek geeft een overzicht van de onderzoeksopzet die werd toegepast om het risico op zeldzame bijwerkingen na HPV-vaccinatie te evalueren. Bij de systematische evaluatie werden analytische parameters en de geldigheid van klinische gevalsdefinities geïdentificeerd als twee belangrijke elementen die informatie geven over de geldigheid en robuustheid van studies ter beoordeling van de veiligheid van vaccins. Uit de systematische evaluatie bleek ook dat er behoefte is aan meer systematische samenwerking om de veiligheid van vaccins op te volgen.

Sinds de lancering van HPV-vaccines zijn de risico's en voordelen ervan voortdurend geëvalueerd door de bevoegde gezondheidsautoriteiten en vaccinproducenten, in overeenstemming met hun verplichtingen. Tot op heden beschikken HPV-vaccins, op basis van de beschikbare gegevens, over bewezen veiligheidsprofielen met een gunstige voordeel-risico verhouding. **Hoofdstuk 4** beschrijft drie veiligheidsonderzoeken die na de toelating zijn uitgevoerd om het risico op auto-immuunziekten (**hoofdstuk 4.1 en 4.2**) of het risico op spontane abortus (**hoofdstuk 4.3**) na bivalente HPV-vaccinatie te evalueren. In **hoofdstuk 4.1** werden een cohorte en een zelf-gecontroleerde casusserie toegepast in de gegevensbron van de Britse CPRD om het risico op auto-immuunziekten na bivalente HPV-vaccinatie te beoordelen. We toonden geen bewijs van een verhoogd risico op auto-immuunziekten bij vrouwen van 9 tot 25 jaar. Er werd echter een statistisch significant verhoogd risico op auto-immuun thyreoïditis na vaccinatie waargenomen wanneer de analyse alleen werd uitgevoerd op gevalideerde gevallen (relatief risico: 3,75 [95 % BI: 1,25-11,31]). Het statistisch significant verhoogde risico werd niet bevestigd in verdere post-hoc analyses. Bijkomend bewijs van de veiligheid van bivalente of quadrivalente HPV-vaccins werd algemeen beschikbaar uit de praktijk en toonde potentiële associaties met het syndroom van Guillain-Barré (GBS), inflammatoire darmziekte (IBD) en auto-immuun thyreoïditis. Om deze redenen is de in **hoofdstuk 4.2** beschreven meta-analyse uitgevoerd die alle op dat moment beschikbare gegevens voor het bivalente HPV-vaccin bevatte, waaronder gegevens uit klinische en real-life omgevingen. Hoewel een groot aantal gegevens kon worden opgenomen, konden

we geen conclusies trekken voor GBS vanwege het zeer lage aantal waargenomen gevallen en we hebben geen verhoogd risico voor IBD waargenomen (odds ratio: 1,11 [95 % BI: 0,75-1,66]) na bivalente HPV-vaccinatie. We zagen een 1,5-voudig verhoogd risico op auto-immuun thyreoïditis (odds ratio: 1,46 [95 % BI: 1,22-1,76]), maar er was onvoldoende bewijs om tot een potentieel causaal verband met het bivalente HPV-vaccin te concluderen. In **hoofdstuk 4.3** werd een cohortontwerp geïmplementeerd om het risico op spontane abortus na bivalente HPV-vaccinatie te analyseren in de Britse CPRD-gegevensbron. We hebben geen aanwijzingen gevonden voor een verhoogd risico op spontane abortus (hazard ratio: 1,30 [95 % BI: 0,79-2,12]) en andere ongunstige zwangerschapsuitkomsten bij jonge vrouwen die onbedoeld waren blootgesteld aan het bivalente HPV-vaccin rond het moment van de zwangerschap.

Aanbevelingen voor de implementatie van signaalbeoordeling veiligheidsstudies met vaccins

Haalbaarheidsbeoordelingen zijn noodzakelijke stappen vooraleer een formele epidemiologische studie van de hypothese wordt uitgevoerd. In hoofdstuk 5 stellen we een pragmatische aanpak voor om haalbaarheidsbeoordelingen uit te voeren. De toolbox richt zich op twee hoofdcomponenten: de wetenschappelijke haalbaarheid en de operationele haalbaarheid, die beide bestaan uit een reeks vragen om methodologische en operationele uitdagingen te helpen overwinnen wanneer veiligheidsstudies na verlening van de vergunning worden uitgevoerd. Aangezien er steeds meer gebruik wordt gemaakt van bestaande bronnen van gezondheidszorggegevens om de veiligheid van vaccins te beoordelen, is het van belang te testen of gegevensbronnen geschikt zijn voor een specifieke onderzoeksvraag.

Discussie

Hoofdstuk 6 contextualiseert de bevindingen van deze thesis in een breder perspectief. In de eerste plaats benadrukken we het toenemende gebruik van studies met meerdere gegevensbronnen en het gebruik van verspreide gegevensnetwerken om gegevens over de veiligheid van vaccins te genereren. Het belangrijkste voordeel van studies met meerdere gegevensbronnen is dat ze het mogelijk maken statistische power te verkrijgen om zeldzame uitkomsten te bestuderen door de grootte van de onderzoekspopulatie te vergroten, en daardoor de kans te maximaliseren om zeldzame ongewenste voorvallen die zich na vaccinatie kunnen voordoen te detecteren en te beoordelen. De toepasbaarheid van onderzoek met meerdere gegevensbronnen heeft echter beperkingen met betrekking tot de waargenomen heterogeniteit tussen de gegevensbronnen. Omdat er verschillende soorten gegevensbronnen bestaan, waaronder medische diagnoses bij gehospitaliseerde en/of niet-gehospitaliseerde patiënten uit ziekenhuisgegevens, medische dossiers van huisartsen of gegevensbronnen van kinderartsen, registers die gegevens van ziekenhuisopnamen aan die van

huisartsen koppelen of gegevens uit verschillende registers koppelen, is het voor een correcte interpretatie van de gegevens van belang rekening te houden met de herkomst van de gegevens en de omgeving waarin ziekten doorgaans worden gediagnosticeerd.

Ten tweede bespreken en leveren we methodologische overwegingen in de evaluatiestudies van het veiligheidssignaal voor vaccins, die zijn gebaseerd op de ervaring uit de veiligheidsstudies na toelating met het bivalente HPV-vaccin zoals beschreven in hoofdstuk 4. Wij wijzen erop dat een geharmoniseerde definitie van klinische casussen vertekening met betrekking tot heterogeniteit tussen verschillende onderzoeken tot een minimum kan beperken, dat een verkeerde indeling van blootstelling kan worden verholpen door het gebruik van actieve referentieproducten en dat bij de beoordeling van zeldzame ongewenste voorvallen bij voorkeur statistische methoden op maat moeten worden gebruikt.

Ten derde bespreken we het toekomstperspectief voor het onderzoek naar vaccins in de Europese context met de ontwikkeling van EU DARWIN en de uitvoering van "fit-for-purpose"-oefeningen.

Tot slot wordt in dit proefschrift de nadruk gelegd op de methodologische verbeteringen bij de beoordeling van de veiligheid van vaccins, die wereldwijd moeten worden gehandhaafd om de reproduceerbaarheid en vergelijkbaarheid van de onderzoeksresultaten te garanderen.

Chapter 8: Appendices

8.1 List of publications

Publications based on studies described in this thesis

Willame C, Dodd C, van der Aa L, Picelli G, Emborg HD, Kahlert J, Gini R, Huerta C, Martín-Merino E, McGee C, de Lusignan S, Roberto G, Villa M, Weibel D, Titievsky L, Sturkenboom M. Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project. *Drug Saf* 2021; **44**(3): 383-95.

Willame C, Dodd C, Duran CE, Elbers R, Gini R, Bartolini C, Paoletti O, Wang L, Ehrenstein V, Kahlert J, Haug U, Schink T, Diez-Domingo J, Mira-Iglesias A, Carreras JJ, Vergara-Hernandez C, Giaquinto C, Barbieri E, Stona L, Huerta C, Martin-Perez M, Garcia-Poza P, de Burgos A, Martinez-Gonzalez M, Bryant V, Villalobos F, Palleja-Millan M, Aragon M, Carreras JJ, Souverein P, Thurin NH, Weibel D, Klungel OH, Sturkenboom M. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. *Vaccine* 2023; **41**(1): 251-62.

Willame C, Gadroen K, Bramer W, Weibel D, Sturkenboom M. Systematic Review and Meta-analysis of Postlicensure Observational Studies on Human Papillomavirus Vaccination and Autoimmune and Other Rare Adverse Events. *Pediatr Infect Dis J* 2020; **39**(4): 287-93.

Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, Boggon R, Bunge EM, Pladevall-Vila M, Baril L. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Hum Vaccin Immunother* 2016; **12**(11): 2862-71.

Rosillon D, **Willame C**, Tavares Da Silva F, Guignard A, Caterina S, Welby S, Struyf F. Meta-analysis of the risk of autoimmune thyroiditis, Guillain-Barre syndrome, and inflammatory bowel disease following vaccination with AS04-adjuvanted human papillomavirus 16/18 vaccine. *Pharmacoepidemiol Drug Saf* 2020; **29**(9): 1159-67.

Baril L, Rosillon D, **Willame C**, Angelo MG, Zima J, van den Bosch JH, Van Staa T, Boggon R, Bunge EM, Hernandez-Diaz S, Chambers CD. Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Vaccine* 2015; **33**(48): 6884-91.

Willame C, Baril L, van den Bosch J, Ferreira G, Williams R, Rosillon D, Cohet C. Importance of feasibility assessments before implementing non-interventional pharmacoepidemiologic studies of vaccines: lessons learned and recommendations for future studies. Pharmacoepidemiol Drug Saf. 2016 Dec;25(12):1397-1406.

Other relevant publications (by chronological order)

Cohet C, Rosillon D, **Willame C**, Haguinet F, Marenne MN, Fontaine S, Buyse H, Bauchau V, Baril L. Challenges in conducting post-authorisation safety studies (PASS): A vaccine manufacturer's view. *Vaccine* 2017; **35**(23): 3041-9.

Hoffman SR, Le T, Lockhart A, Sanusi A, Dal Santo L, Davis M, McKinney DA, Brown M, Poole C, **Willame C**, Smith JS. Patterns of persistent HPV infection after treatment for cervical intraepithelial neoplasia (CIN): A systematic review. *Int J Cancer* 2017; **141**(1): 8-23.

Willame C, Henry O, Lin L, Vetter V, Baril L, Praet N. Pain caused by measles, mumps, and rubella vaccines: A systematic literature review. *Vaccine* 2017; **35**(42): 5551-8.

Gvozdenovic E, Vetter V, **Willame C**, Rosillon D. Impact of history of febrile convulsions on the risk difference of febrile convulsions with the tetravalent measles-mumps-rubella-varicella vaccine: Post-hoc exploratory analysis of results from a matched-cohort study. *Vaccine* 2018; **36**(39): 5803-6.

Hoffman V, Abu-Elyazeed R, Enger C, Esposito D, Doherty M, Quinlan S, Skerry K, Holick C, Basile P, Friedland L, Praet N, Wery S, **Willame C**, Dore D, Rosillon D. Safety study of live, oral human rotavirus vaccine: A cohort study in United States health insurance plans. Hum Vaccin Immunother. 2018 Jul 3;14(7):1782-1790.

Willame C, Lin L, Vetter V, Baril L, Praet N. Reply to Lee et al.'s letter to the editor pertaining to our publication entitled "Pain caused by measles, mumps, and rubella vaccines: A systematic literature review". *Vaccine* 2018; **36**(45): 6589-90.

Willame C, Vonk Noordegraaf-Schouten M, Gvozdenović E, Kochems K, Oordt-Speets A, Praet N, van Hoorn R, Rosillon D. Effectiveness of the Oral Human Attenuated Rotavirus Vaccine: A Systematic Review and Meta-analysis-2006-2016. *Open Forum Infect Dis* 2018; **5**(11): ofy292.

Benninghoff B, Pereira P, **Willame C**. Letter to the editor concerning the article 'Association between rotavirus vaccination and risk of intussusception among neonates and infants: a systematic review and meta-analysis' (JAMA Netw Open. 2019;2(10):e1912458). *Hum Vaccin Immunother* 2020; **16**(10): 2502-3.

Povey M, Aris E, Cheuvart B, Hall G, Cohet C, **Willame C**. Effectiveness of "Priorix" Against Measles and Mumps Diseases in Children Born After 2004 in the United Kingdom: A Retrospective Case-control Study Using the Clinical Practice Research Datalink GOLD Database. *Pediatr Infect Dis J* 2021; **40**(6): 590-6.

Willame C, Cheuvart B, Aris E, Vetter V, Cohet C. Association between rotavirus gastroenteritis and intussusception: suggested evidence from a retrospective study in claims databases in the United States. *Hum Vaccin Immunother* 2021; **17**(1): 269-77.

Willame C, Weibel D, Sturkenboom MCJM. Authors' Reply to Juergen O Kirchner's Comment on "Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project". *Drug Saf*. 2023 May 27:1–3.

Posters and/or oral presentations

ICPE 2022 (oral presentation) – Leveraging data diversity to improve quality of evidence in a study of background incidence rates of adverse events of special interest for COVID-19 vaccines. C Willame, C Dodd, C Durán, R Elbers, R Gini, C Bartolini, O Paoletti, L Wang, V Ehrenstein, J Kahlert, U Haug, T Schink, J Diez-Domingo, A Mira-Iglesias, JJ Carreras, A Arana, C Vergara-Hernández, C Giaquinto, E Barbieri, L Stona, C Huerta, M Martín-Pérez, P García-Poza, A de Burgos, M Martínez-González, V Bryant, F Villalobos, M Pallejà-Millán, M Aragón, P Souverein, N Thurin, B Bolibar, R Thomsen, D Weibel, O Klungel, M Sturkenboom

ICPE 2022 (poster) - Heterogeneity across European electronic healthcare data sources: identification of adverse events of special interest (AESI) and impact in multi-databases assessment - An ACCESS study. C Willame, C Dodd, C Duran, R Elbers, R Gini, E Barbieri, N Thurin, L Wang, T Schink, F Villalobos, A Mira-Iglesias, P Souverein, M Martin-Perez, R Lasalle, J Jové, C Droz-Perroteau, P García-Poza, C Huerta, A de Burgos, M Martínez-González, V Bryant, D Weibel, O Klungel, M Sturkenboom

ICPE 2022 (poster) - Capacity for identifying Janssen Ad26.COV2.S COVID-19 vaccination in four US health insurance and state Immunization Information System databases: Preparation for a post authorization safety study. C Fuller, A Kawai, K Haynes, K Coughlin, R Hawrusik, C Horgan, J Reynolds, B Calingaert, C Johannes, B Layton, A Peterson, N Praet, C Willame, E Yost, C Brannan, C McMahill-

Walraven, M Guzman, A Jamal-allial, V Nair, Q Ma, M Selvan, R Seals, F Wang, R Platt, A Gilsenan, J Brown

ICPE 2021 (oral presentation) – Background incidence rates of Adverse Events of Special Interest for COVID-19 vaccine monitoring. C Willame, R Gini, C Duran, C Dodd, M Sturkenboom for the ACCESS consortium.

ESPID 2017 (poster) – Risk of febrile convulsion attributable to first dose of measles-mumps-rubella-varicella vaccine depending on subjects' history of febrile convulsion: an exploratory analysis. E Gvozdenovic, V Vetter, D Rosillon, C Willame

ICPE 2015 (poster) – Risk of autoimmune diseases (AD) after human papillomavirus (HPV)-16/18 AS04-Adjuvanted vaccine immunization in women aged 9 to 25 years in the United Kingdom: an observational cohort study. C Willame, D Rosillon, J Zima, MG Angelo, A Stuurman, H Vroling, T van Staa, R Boggon, E Bunge, M Pladevall-Vila, L Baril.

ICPE 2014 (poster) - Risk of spontaneous abortion in young women exposed to human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in the United Kingdom: an observational cohort study. D Rosillon, C Willame, MG Angelo, J Zima, JH van den Bosch, T van Staa, R Boggon, E Bunge, S Hernandez-Diaz, C Chambers, L Baril

ICPE 2014 (poster) - Design and Feasibility of a Study Using the Clinical Practice Research Datalink General Practice OnLine Database (CPRD GOLD) To Assess the Risk of New Onset of Auto-Immune Diseases (NOAD) Following Administration of the Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine. D Rosillon, C Willame, M Pladevall, J Zima, JH van den Bosch, E Bunge, T van Staa, R Boggon, L Baril

ICPE 2013 (poster) - Design and feasibility of a study using the Clinical Practice Research Datalink General Practice Online Database (CPRD GOLD) to assess the risk of spontaneous abortion (SA) following administration of the human papillomavirus (HPV) 16/18 AS04 adjuvanted vaccine. D Rosillon, C Willame, J Logie, S Taylor, V Bauchau, MG Angelo, J Zima, JH van den Bosch, T van Staa, R Boggon, C Chambers, S Hernandez-Diaz, L Baril

8.2 Acknowledgements

This thesis is a tremendous work that I started seven years ago. Of course, I could not have accomplished this work alone. Many people have been involved directly and indirectly in this work and I would like to thank all of them. I would like to thank all co-authors of each manuscript included in this thesis. I also would like to especially thank a few people:

Miriam and Daniel – for giving me this opportunity. I'm honored to have been able to complete my PhD with you as knowledgeable experts in the pharmacoepidemiology field. Even with your busy daily agenda, you managed to always find time for me and provide helpful inputs and viewpoints. I'm grateful for your time, advice and mentoring that guided me across all challenges I/we faced along this incredible journey. You pushed me to do the best I could.

Caitlin – for sharing your expertise and your positive mindset when we worked together on a big project during hard pandemic time.

Laurence Baril – for opening my professional career in epidemiology and pushing me to start a PhD. I still remember with some nostalgy time spent under your supervision at GSK.

Severine, my best friend - for all moments we spent together since more than 25 years, our endless friendly discussions, and your support in difficult moments.

My former GSK colleagues who became friends - Anne Van Beneden for your positive mindset which boosted me to refocus on this work. Catherine Cohet for your mentoring in pharmacoepidemiology and your inspiring ideas for relaxing weekends.

My former GSK colleague who is still a colleague - Nicolas Praet for the memorable lobster dinner and Caesar salad lunch in Boston but also for the trust you place in me during our daily working life.

Marc Ceuppens - for the kind introductory at Janssen Pharmaceutica and his undoubtful Dutch translation capabilities.

WPRC friends - for our running tours and hiking-trail weekends which helped me to breath between work, academic work and family obligations with a special thanks to Sophie and Bénédicte for your energy and kindness.

My parents - for encouraging me to always going forward, helping me gain independence and supporting me in my ambitions, ideas, and decisions. Joan, Célia and Bea – for our cheerful and rejuvenating family time. Maia, my daughter - who allows me to realize every day how much energy I have and who pushes me to always think with a positive mind. I cherish every day I spend with each of you.

8.3 About the author

Corinne Willame was born in 1980 in La Louvière, Belgium. In 2003, she completed a bachelor's degree in Biochemistry at the Haute Ecole Rennequin Sualem in Liège (Belgium) after which she started working at GlaxoSmithKline (GSK) as a laboratory technician in animals science and in pre-clinical executing biological assays such as ELISA, flow cytometry, cell culture. After three years spent in labs, she decided to go back to school at the Free University of Brussels where she pursued a Master's degree in Public Health. She obtained her graduation in 2009.

After her master graduation, she (re)joined GSK where she covered several roles starting in the pharmacovigilance department as a pharmacoepidemiologist where her activities focused on vaccines safety signal detection, then she transitioned to a biostatistical role during which she performed data analyses for post-authorization safety studies in large existing healthcare data sources. In 2014, she integrated the global epidemiology department at GSK where she started working as an epidemiologist on the Human papillomavirus vaccine conducting safety and effectiveness post-authorization activities and life-cycle management activities for other vaccines programmes. At that time, she was advised to perform a PhD thesis in epidemiology and then she contacted several universities to find a suitable university that could support her project. During the ICPE in 2014, she met with Miriam Sturkenboom who gave her the opportunity to start a PhD. While pursuing her PhD remotely from Belgium, she joined Janssen Pharmaceutica in 2020 where she worked on the implementation of the post-authorization plan for the COVID-19 vaccine, in addition to other vaccine programmes.

Corinne carried out her PhD project under the supervision of Miriam Sturkenboom and Daniel Weibel. Her research focused on the use of existing healthcare data sources to assess the risk of rare adverse events following vaccination and the implementation of multi-data source studies applying common methodological approaches.

Corinne spends her time outside of work taking care of Maia, her daughter, and doing yoga and running. She ran the 20 Km of Brussels in May 2023, her longest distance, with ambition to reiterate this effort in other locations.

Corinne currently lives in Brussels, together with her daughter, Maia. After completion of this PhD thesis, she will continue working as an epidemiologist at Janssen Pharmaceutica and she will start a yoga teacher programme in Brussels to obtain a certified yoga teacher license from the Yoga Alliance.