Vaccine-preventable diseases: evaluation of vaccination programmes and optimisation of surveillance

Nicoline van der Maas

Cover design	Dorien Gijsbertse en Nicoline van der Maas
Foto	iStock
Lay-out	Nicoline van der Maas
Printing	GVO drukkers, Ede, the Netherlands
ISBN	978-94-6332-351-2

The publication of this thesis was financially supported by the National Institute for Public Health and the Environment (RIVM).

Vaccine-preventable diseases: evaluation of vaccination programmes and optimisation of surveillance

Preventie door vaccinaties: evaluatie van vaccinatieprogramma's en verbetering van surveillance
(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 12 juni 2018 des middags te 4.15 uur

door

Nicoline Anita Theodora van der Maas

geboren op 19 april 1963 te 's-Hertogenbosch

Promotor:	Prof.dr. E.A.M. Sanders
Copromotoren:	Dr. H.E. de Melker Dr. W. van der Hoek

Chapter 1

General introduction

Vaccinations and mass immunisation programmes.

The earliest efforts to immunise persons to prevent disease date back to about 1000 AD. However, only after the 1902 formation of the Biological Control Act in the Unites States of America, which regulated manufacturers and required both licensing and inspections, were vaccines produced with more consistent quality (1). From 1914 onwards, there was licensing of bacterial vaccines (e.g. tetanus toxoid, vaccines against typhoid and pertussis) that fulfilled the criteria of the Biological Control Act. Since the 1920s, vaccines have spread across the globe. The first vaccination programmes dramatically reduced the number of deaths from disease and were crucial in establishing the concept of preventive public health measures (2). For example, in Australia diphtheria notifications and deaths plummeted in the 1930s due to infant and school-based immunisation programmes (3). Viral vaccines were also developed after the discovery of cell cultures that could grow viruses in 1930 (1). The increasing number of vaccines urged the development of combination vaccines containing antigens against several diseases in order to decrease the number of immunisations (4). The first combination vaccines, targeting diphtheria and tetanus (DT) and eventually pertussis (DTP) were licensed in 1947 and 1949, respectively. To date, many other combination vaccines are available for protection against multiple diseases. Alongside the increased use of vaccinations to prevent disease, criticism of vaccination has spread around the world, as shown in Figure 1 (5, 6).

Figure 1. The Cow Pock…or…the Wonderful Effects of the New Inoculation! A cartoon by James Gillray, published June 12, 1802 by H. Humphrey, St. James's Street.

As many vaccine-preventable diseases have the highest disease burden in early childhood (7), almost all countries have a universal childhood national immunisation programme in place, starting in the first months of life. In 1974, the Expanded Programme on Immunisation of the World Health Organisation (WHO) was established to ensure that all children in all countries benefited from lifesaving vaccines (8). In 1977, the goal was set to make immunisation against diphtheria, pertussis, tetanus, poliomyelitis, measles, and tuberculosis available to every child in the world by 1990. To date, this goal has not been achieved, but tremendous progress has been made. Major challenges to the Expanded Programme are accelerating and sustaining national immunisation efforts. These national immunisation efforts are also recognised as an essential aspect to reach WHO's Sustainable Development Goals concerning the reduction of child mortality (9).

The aim of sustained high national immunisation coverage is to decrease morbidity and mortality of the disease as much as possible in the target group, leading to interrupted transmission and herd immunity, if possible. If a disease is completely under control, eradication or elimination of disease can be discussed (10-12). Eradication refers to a situation where disease and its causal agent have been removed completely and permanently. Once the worldwide incidence has reached to zero for a certain amount of time, it can be discussed whether intervention measures

are no longer needed. In 1980, the goal of smallpox eradication was reached (2). For poliomyelitis, eradication efforts began in 1988 and the goal is nearby (13). For elimination to occur, the specific agent may still circulate but does not lead to disease because of vaccination programmes and herd immunity. Continued high vaccination coverage is needed to prevent re-establishment of transmission, and surveillance must be in place to detect outbreaks as soon as possible. The World Health Organisation aims to eliminate both measles and rubella, as has already been achieved in the Americas for measles. All six WHO regions have measles elimination goals, and three have also developed rubella elimination goals (14). Worldwide, the extent of control of the other diseases, targeted through mass vaccination programmes, differs per country.

Immunisation programmes in the Netherlands

In the Netherlands, two routine national immunisation programmes are in place. The National Immunisation Programme (NIP), also called 'Rijksvaccinatie programma', targets infants and children, and the seasonal influenza vaccination targets older adults and predefined risk groups.

The National Immunisation Programme

In 1952, routine childhood vaccination targeting diphtheria, tetanus, and pertussis was introduced in the Netherlands. The NIP officially started in 1957 (15, 16), following a large poliomyelitis outbreak in the preceding year (17). During the first years, infants received a primary series targeting diphtheria, tetanus, pertussis, and poliomyelitis (DTP-IPV) at three, four, and five months of age with booster doses at 11 months and four years of age (18). In 1965, the pertussis component was left out of the four year booster and a second dT-IPV booster dose at nine years of age was added to the programme. In 1987, after a short period of single vaccination against rubella (11-year-old girls) and measles (boys and girls) a measles-mumps-rubella (MMR) combination vaccine was implemented with two doses, i.e. one at 14 months and the second at nine years of age (19). In recent decades, vaccinations were introduced against Haemophilus influenza type b (Hib; 1993), Meningococcal serogroup C (MenC; 2002), 7 to 10 pneumococcal serotypes (pneumococcal conjugate vaccine; PCV7 in 2006, replaced by PCV10 in 2011). Lastly, vaccination against human papilloma virus (HPV, 2010; 12 year old girls) and universal hepatitis B (HBV, 2011) were implemented (16).

Over time, several adaptations in the NIP have been implemented, mainly in view of the re-emergence of pertussis. In 1999, the primary schedule was advanced to start at 6 to 9 weeks. In late 2001, an acellular pertussis (aP) component was added to the preschool dT-IPV booster at four years of age, and in 2005 we switched to vaccines

with aP during infancy from combination vaccines incorporating whole-cell pertussis (wcP) in the primary and booster infant series.

Currently, the Dutch NIP contains 14 vaccinations, given between two months and 12 years of age and targeting 12 diseases (Figure 2). All NIP vaccinations are free of charge, and participation is voluntary.

Phase 1	Injection 1	Injection 2
6-9 weeks	DTaP-IPV Hib HBV	PCV
3 months	DTaP-IPV Hib HBV	
4 months	DTaP-IPV Hib HBV	PCV
11 months	DTaP-IPV Hib HBV	PCV
14 months	MMR	MenC

Phase 2	Injection 1	Injection 2
4 years	DTaP-IPV	

Phase 3	Injection 1	Injection 2
9 years	DT-IPV	MMR

Phase 4	Injection 1	Injection 2
12 years	HPV*	HPV* (6 months later)

Meaning of the abbreviations

D	Diphtheria	HBV	Hepatitis B	MenC	Meningococcal C disease
aP	Pertussis (whooping cough)	PCV	Pneumoccal disease	HPV	Human papillomavirus
T	Tetanus	M	Mumps		
IPV	Poliomyelitis	M	Measles	*	Only for girls
Hib	*Haemophilus influenzae* type b	R	Rubella		

Figure 2. The National Immunisation Programme of the Netherlands in 2018.

Organisation of the National Immunisation Programme

All NIP vaccines are purchased from private manufacturers by the Department for Vaccine Supply and Prevention Programmes (Dienst Vaccins en Preventieprogramma's; DVP) within RIVM. The buying of these vaccines is subjected to a European tender procedure with a fixed contract duration (20). Therefore, product changes occur over time. This department also manages supply and distribution of all NIP vaccines, monitors cold chain procedures, and facilitates invitations for vaccination. Finally, it manages the national vaccination registry, incorporated in 'Praeventis'. The Dutch Centre for Infectious Disease Control (Centrum Infectieziektebestrijding) within RIVM is responsible for NIP management.

The NIP is fully embedded in regular child health care (jeugdgezondheidszorg), with high attendance (21). Coverage for all vaccinations steadily ranges between 90% and 96% (22) except for HPV among teenage girls, for which coverage ranges between 53% and 61%.

Influenza vaccination for older adults and risk groups

Alongside the NIP, there is the annual seasonal influenza vaccination, a routine mass vaccination programme during autumn. Influenza vaccination always has been a task

of general practitioners. Systematic invitation of target groups started in the early 1990s (23). Since 1996, on advice of the Health Council, the seasonal vaccination has been offered to healthy people 65 and above in addition to groups at risk for complications from influenza virus infection because of certain chronic medical conditions (24, 25). In 1997, the Dutch National Influenza Prevention Programme, or 'Nationaal Programma Grieppreventie' (NPG), was implemented. Since 2008, all individuals aged 60 years and older are invited. The National Influenza Prevention Programme Foundation (Stichting Nationaal Programma Grieppreventie) is responsible for the practical implementation of the NPG, whereas the Centre for Health and Society (as part of RIVM), coordinates the NPG as a whole. The vaccination is free of charge. Regarding the influenza vaccination programme, the Department for Vaccine Supply and Prevention Programmes has the same tasks and responsibilities as with respect to the NIP, except that registration of administered vaccines is not centralised but locally documented in the medical files of the general practitioners. Following an increase in coverage from 30% (1992) to 70% (2009), coverage went down to 53% in 2014 and 50% in 2015 (26, 27). The decrease is most pronounced in 60-65-year-old and otherwise healthy adults, whose coverage was 24% in 2015. In addition to the groups mentioned above, health care personnel in close contact to patients with an increased risk for a severe course of influenza are urged to be vaccinated against seasonal influenza. Their employers are responsible for offering this vaccination (28). Information on the uptake among health care workers is not systematically monitored, but the few available studies show extremely low uptake (29).

Vaccination campaigns during outbreaks

Besides these two routine mass vaccination programmes, vaccination campaigns are organised if necessary, e.g. during an outbreak. In the Netherlands, groups of Orthodox Protestants live in socio-geographically clustered communities and are critical towards vaccination on religious grounds. The resulting area of low vaccination coverage spreads from the south-west to the north-east of the country and is called the 'Bible Belt', with 75% of Orthodox Protestants living in these regions. The remaining 25% live in scattered clusters across the country (30). Because of this socio-geographic clustering, Orthodox Protestants do not profit from the herd protection provided elsewhere by high vaccination coverage in the general population. Outbreaks may occur if a NIP-targeted pathogen is introduced and the number of susceptible individuals is sufficient. For example, in 1999-2000 and in 2013-2014 measles outbreaks occurred in the Orthodox Protestant community (31, 32). During the most recent outbreak, early MMR was offered to 6-to-14-month-old infants living in municipalities with MMR1 vaccination coverage below 90%, to protect them against severe disease.

Outbreaks of poliomyelitis have been another problem in the Bible Belt. Since the instalment of the NIP (using only inactivated polio vaccine, or IPV), vaccination with oral polio vaccine (OPV) was used during poliomyelitis outbreaks in 1971, 1978 and 1992-1993 in the Bible Belt with 39, 110 and 71 cases, respectively (33-35).
Nationwide, even outside areas with low vaccination coverage, new strains of pathogens may emerge and rapidly spread. For instance, outbreaks of meningococcal serogroup C (MenC) disease were controlled using a polysaccharide MenC vaccine in 1998 (36) and a conjugated MenC vaccine in July 2001 (37). No vaccination was offered during two smaller outbreaks in late 2000 and early 2001 (38). The 2000-2001-outbreaks coincided with a general increase in notifications of meningococcal serogroup C disease (39). This increase resulted in a large mass vaccination campaign in 2002, using conjugated MenC vaccine. A catch-up campaign was organised for all children from one to 18 years of age, followed by NIP implementation of MenC vaccination at 14 months of age from September 2002 onwards (37). In 2018, due to an outbreak of MenW starting late 2015, the MenC vaccination at 14 months will be replaced by a MenACWY vaccination, and a booster MenACWY dose for adolescents will be added to the NIP (40, 41).
Similarly, in 2009 a new variant of an influenza A virus spread from Mexico to all other continents and reached the Netherlands in April of that year (42). Influenza A(H1N1)pdm09 vaccination was available from November 2009 and was used to protect groups who were most at risk. Besides all the people who were eligible for seasonal influenza vaccination, several other groups were eligible for H1N1-vaccination. Among them were 1. healthy pregnant women in their second and third trimester, 2. infants between six months and five years of age, 3. household members of infants below six months of age, and 4. household members of high risk patients.

Decision-making regarding composition of NIP, target groups for seasonal influenza, and vaccinations during outbreaks.

After a new vaccine is licensed and available, the Minister of Health, Welfare and Sports (VWS) may request the Dutch Health Council, together with the Health Care Insurance Board, to advise on the position of the vaccine within the entire spectrum of vaccination care in the Netherlands. Bearing in mind the public health nature of vaccination, factors that determine whether a vaccine should be part of a mass vaccination programme have been translated into seven selection criteria that are grouped under five thematic headings: seriousness and extent of the disease burden, effectiveness and safety, acceptability, efficiency, and priority of the vaccination (Table 2) (43). The Ministry of Health, Welfare and Sports finally decides on the advice of the Health Council.

Table 2. Criteria for inclusion of a vaccine in a mass vaccination programme in the Netherlands (44).

Seriousness and extent of the disease burden

1. The infectious disease causes considerable disease burden within the population.
    a. The infectious disease is serious for individuals, and
    b. The infectious disease affects or has the potential to affect a large number of people.

Effectiveness and safety of the vaccination

2. Vaccination may be expected to considerably reduce the disease burden within the population.
    a. The vaccine is effective for the prevention of disease or the reduction of symptoms.
    b. The necessary vaccination rate is attainable (if eradication/elimination or the creation of herd immunity is sought).
3. Any adverse effects associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4. The inconvenience or discomfort that an individual may be expected to experience in connection with his/her personal vaccination is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
5. The inconvenience or discomfort that an individual may be expected to experience in connection with the vaccination programme as a whole is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

Efficiency of the vaccination

6. The balance between the cost of vaccination and the associated health benefit compares favourably to that associated with other means of reducing the relevant disease burden.

Priority of the vaccination

7. Relative to other vaccinations that might also be selected for inclusion, provision of this vaccination serves an urgent public health need at reasonable individual and societal costs.

Usually, during outbreak situations, an outbreak management team (OMT) advises on temporary vaccination strategies to control the outbreak (45). If the advice is adopted

by the Administrative Advisory Board (Bestuurlijk Afstemmingsoverleg), the final decision to start the vaccination campaign is taken by the Ministry of Health, Welfare and Sports. This system of scaling up during outbreaks and crises was implemented shortly after the 1992-1993 outbreak of poliomyelitis. During the H1N1-pandemic in 2009, the Health Council and the Centre for Infectious Disease Control advised together on target groups and prioritisation (42).Evaluation of the National Immunization Programme, seasonal influenza vaccination, and mass vaccinations during outbreaks is an integral part of the task of the Centre for Infectious Disease Control. The Centre coordinates the control of infectious diseases, including effective prevention, close vigilance, and quick response in the event of an outbreak, and contributes to reducing health problems related to infectious diseases. It also provides the Health Council with up-to-date data on vaccine preventable diseases that are currently part of mass immunisation programmes or may be embedded in the near future. Indeed, in general the Health Council mentions in its advice the need for close monitoring of short- and long-term effects of the vaccinations, including safety.

Surveillance of mass immunisation programmes.

To measure the success of a vaccination programme, it is essential to monitor its impact. In particular, there is a need to verify if a vaccine has a continuous positive benefit/risk balance, not only in the target group, but also in the entire population and for a longer period of time. Therefore, continuous surveillance remains essential both for diseases under control (e.g. polio), diseases that remain endemic (e.g. pertussis, pneumococcal disease and influenza), potentially emerging vaccine-preventable diseases, and those that may re-emerge despite vaccination. Surveillance is defined as the ongoing systematic collection and analysis of data and the provision of information which leads to action being taken to prevent and control disease (46). There must be ongoing assessment of vaccination coverage, disease incidence, safety, pathogen, plus serological surveillance of the target population and the population as a whole (11). These surveillance systems are usually designed to monitor trends, detect and describe problems, and generate hypotheses to be tested in more refined research designs (12). Such systems are important, because immunisations change the epidemiology of diseases. For instance, due to a decrease in the force of infection, age of infection can increase and in some diseases lead to a more severe course (47). This occurred for example in Greece in the 1980s, when an increase in congenital rubella syndrome occurred due to suboptimal (i.e. 50%) uptake of MMR vaccination in infants. Furthermore, a new pathogen or a non-vaccine-preventable strain can occupy the niche that becomes available after vaccination. Likewise, a pathogen can change, leading to decreased vaccine effectiveness, as is currently shown for pneumococcal disease and also postulated for pertussis (16, 48, 49). Likewise, antibody levels and the duration of protection can differ between naturally infected and vaccinated

people. This is exemplified in decreased transfer of measles-specific maternal antibodies from mothers vaccinated with MMR compared to mothers who were naturally infected with measles (50, 51). This changing epidemiology may require fine-tuning or adaptation of the NIP.
Surveillance systems should be periodically reviewed based on their quality as well as their usefulness and cost (52). A vaccine surveillance system is useful if it can 1. detect trends signalling possible new problems, 2. detect outbreaks leading to control and prevention activities, 3. provide quantitative estimates of prevented morbidity and mortality, 4. identify factors involved in disease occurrence, 5. facilitate research that is likely to lead to control or prevention, or 6. permit assessment of the effects of control measures. Sensitivity, specificity, representativeness, timeliness, simplicity, flexibility, and acceptability should be taken into account when looking at quality. In the assessment of costs, direct and indirect costs should be involved, e.g. by using a social cost-benefit analysis.

Surveillance and epidemiological studies of the Dutch National Immunisation Programme and seasonal influenza vaccination programme

The Ministry of Health, Welfare and Sports has commissioned the Centre for Infectious Disease Control with the evaluation of the NIP, seasonal influenza vaccinations and mass vaccination campaigns during outbreaks. For this task, the Centre uses a surveillance system that is based on five pillars, by which we aim to answer several questions:

1. Vaccination coverage. How high is the vaccination coverage? Are there specific groups or regions were vaccination coverage is lower? Is the coverage high enough to sustain herd immunity? Do we meet WHO targets? What trends over time occur?

To this end, the Centre for Infectious Disease Control uses data from the individual-based electronic national vaccination registry 'Praeventis' to assess coverage of the National Immunisation Programme. Likewise, for coverage of seasonal influenza vaccination, data based on a sample of nearly 800,000 general practitioner's records are used.

2. Safety surveillance. What is the safety profile of vaccines in both the short and long term? Which new, rare, and/or severe adverse events are reported after vaccination? What is the frequency of milder and more commonly occurring adverse events? Which adverse events can be expected in view of the introduction of a new vaccine and what is their background rate?

The cornerstone of safety surveillance is the passive reporting system of adverse events following immunisation (AEFI), in place at the Dutch Pharmacovigilance Centre, also called 'Lareb'. Aggregated results of AEFI following NIP and influenza vaccinations are described in yearly reports and placed on the Lareb website (53). Furthermore, the Centre for Infectious Disease Control performs epidemiological studies to assess and quantify a possible association in case of safety signals (54). Tolerability surveys are carried out if new vaccines are introduced in the routine programme or in temporary outbreak control. Finally, background rates of AEFI are studied in advance of the introduction of a new vaccine to gain more perspective, especially when new groups become eligible for vaccinations (55-57).

3. Disease surveillance. What is the effectiveness of vaccinations in reducing the incidence of the target disease and its complications? How does effectiveness develop over time? Do all people eligible for vaccination, benefit equally? Is herd protection apparent?

For most NIP diseases, data are based on mandatory notifications by care providers. Data on 'influenza like illness' (ILI) or 'acute respiratory illness' (ARI), derived from the 'NIVEL Primary Care Database' (Netherlands institute for health services research) are used to monitor influenza (58). Furthermore, data from the National Reference Laboratory for bacterial meningitis and weekly reports of virological laboratories are used. Additional data on disease-specific hospitalisations and deaths give insight into more severe disease courses for all vaccine-preventable diseases. When vaccination data are also available, vaccine effectiveness can be calculated.

4. Pathogen surveillance. Do changes occur in circulating pathogens as result of vaccination pressure, and does this impact vaccine effectiveness? How closely are new-found pathogens related; is a common source plausible? What are the characteristics of influenza-positive samples during the influenza season?

Monitoring is based on evaluation of strain variations due to differences in phenotype and/or genotype.

5. Immunosurveillance. What are the risks for (re)emergence of diseases targeted by vaccination? How well is the population protected at present and in the future? Are some groups at increased risk for disease? Can potential problems be expected in view of changing dynamics in infectious disease after vaccination and age-specific antibody profile (e.g. waning immunity)?

To answer the above questions, the Centre for Infectious Disease Control periodically collects a blood sample and questionnaire data from a representative sample of the general population, i.e. PIENTER surveys, to assess seroprevalence acquired through natural infection or vaccination (16). This survey was performed in 1995-1996 (59) and in 2006-2007 (60). Data collection of the third survey was finished late 2017.

Oversampling of risk groups, e.g. people living in regions with low vaccine coverage and immigrants was performed.
This surveillance system is supplemented with more in-depth studies and research if necessary. For several surveillance aspects, the Centre for Infectious Disease Control collaborates with external partners. The combined information collected through the five surveillance pillars offers an integrated picture of the Dutch NIP and influenza vaccination programme. This picture gives insight into aspects and parts of the programmes that need more study or can be optimised.

Current status of vaccine-preventable diseases targeted through mass vaccinations.

Diphtheria and tetanus toxoid vaccinations were introduced in early 1950s. The two diseases are currently under control with only rare occasions of disease (16).
Regarding **tetanus**, protection in the general population is very high and sustained, perhaps enabling a widening of the 10-year interval between tetanus toxoid boosters, described in the tetanus post-exposure prophylaxis guideline (61). In this thesis, we investigated a bedside test for tetanus immunity, to support this optimisation of tetanus vaccinations.
With respect to **poliomyelitis**, despite the presence of the high-risk Orthodox Protestant community, the Netherlands as a whole is categorised as 'low-risk country' since 2011, based on high vaccination coverage and adequate surveillance being in place (62). The latest poliomyelitis outbreak occurred in 1992-1993 (35).
With respect to **measles and rubella**, elimination is challenging because vaccination coverage of at least 95% for both doses of MMR vaccine is required to maintain sufficient population immunity (63). For some years, vaccination coverage has been slowly declining (64). In 2016, coverage for the first MMR at 14 months of age and second MMR at 9 years of age was 94.8% and 92%, respectively. The latest rubella outbreak was in 2004-2005 (65), while the latest measles outbreak occurred in 2013-2014, both spreading in the Bible Belt area (32). During the last measles outbreak, children 6-14 months old living in municipalities with a low MMR1 coverage were offered early MMR vaccination, since young infants are at increased risk for severe disease. However, the literature shows that effectiveness of early MMR is age-dependant, being lower effectiveness at younger age (66, 67). Finally, information on the tolerability of this early MMR was very limited and derived mainly from studies in developing countries. Therefore, we aimed to assess effectiveness and tolerability of this early MMR as a temporary outbreak measure.
Mumps is an example of waning immunity after vaccination. Outbreaks occur on a regular basis, mainly among students who have received two MMR vaccinations (68, 69). Modelling studies showed that under specific conditions mumps could increase

among vaccinated individuals about 30 years after the introduction of vaccination because of suboptimal coverage or waning immunity (70, 71).

The most prominent example of vaccine failure is the worldwide re-emergence of **Bordetella pertussis** (72, 73). Despite high vaccination coverage, pertussis has resurged since the late 1990s, with additional epidemic peaks every three to four years. From 1996 onwards, the yearly number of notifications ranged between 2,573 (1998) and 13,828 (2012). There is an increase in incidence among adolescents and adults, who are an important source of transmission for infants not yet fully vaccinated (74, 75). An increase is also seen in very young infants, who are at highest risk for hospitalisation and severe morbidity and mortality (76). In our thesis, we assessed whether measures taken to stop the increase were effective and actually protected the not yet (fully) vaccinated infants. Preterm infants are at even higher risk for severe pertussis disease and overrepresented in infant pertussis hospitalisations (77, 78). In a medical record study on pertussis hospitalisations, we aimed to compare the pertussis disease burden in term and preterm infants, relate the clinical presentation to vaccination status, and compute vaccine effectiveness estimates for both groups. To quantify the underreporting of pertussis hospitalisation and death, particularly in the light of the possible introduction of maternal pertussis vaccination, we also performed a capture-recapture analysis using two sources for each outcome.

The incidence of invasive disease caused by the vaccine types of ***Streptococcus pneumoniae*** has decreased considerably since the introduction of PCV7 in 2006 and later switch to PCV10 in 2011, not only among vaccinated children, but also in other age categories, especially the elderly. However, this decrease is progressively eroded by the increase in disease due to non-vaccine serotypes, particularly in older adults and elderly (79). The impact on non-invasive and far more frequent pneumococcal respiratory disease, like pneumonia, is also monitored based on primary care and hospitalisation data (80).

Cases of ***Haemophilus influenza*** **type b**, **Meningococcus serogroup C disease,** and acute **Hepatitis B** are rare (16).

For the Netherlands, time after introduction of **HPV** vaccination is too short to draw firm conclusions. However, international data show that vaccine effectiveness against cervical lesions and genital warts is high (81). Follow-up of vaccinated and unvaccinated girls in the Netherlands shows high effectiveness against early endpoints of HPV, i.e. against persistent infections with HPV16 and 18. Given the continual media focus on adverse events following HPV vaccination, safety surveillance with respect to HPV vaccination is very important. Already at the start of the introduction, experts urged assessment of background rates of possible AEFI, especially immune-mediated disorders (55, 57). In this thesis, we describe the background rate of Multiple Sclerosis to evaluate potential future reports on adverse events in perspective (55, 56).

The incidence of **influenza**-like illness and **influenza** virus infection fluctuates from year to year. Vaccine effectiveness estimates vary over time, because circulating influenza strains do not always match with the strains included in the seasonal vaccines. The threat of a new pandemic always plays a role. Therefore, during the 2009 pandemic, the Centre for Infectious Disease Control participated in a European consortium that calculated background rates for a set of adverse events following immunisation (AEFI) with a known association with seasonal influenza and therefore of possible importance in the 2009 pandemic (83), again to put potential reports of adverse events into perspective (55, 56). For the Netherlands, we looked into the background rates for Guillain-Barré syndrome, an adverse event known to follow certain infections and particularly a swine flu vaccination programme in the USA in 1976 (84).
Lessons learned from the outbreak measures, taken during the 2009-pandemic are meaningful for both seasonal and pandemic influenza. Our study on adverse events following both vaccines in 2009 was set up to increase knowledge on the tolerability of serial administered influenza doses and differences between adjuvanted and non-adjuvanted vaccines. Likewise, the linkage study on adverse pregnancy outcomes following pandemic influenza vaccination during pregnancy was conducted to learn more about the safety of maternal influenza vaccination, a measure advised by the WHO but not yet implemented in the Netherlands.

Aim and outline of this thesis.

As described above, monitoring of NIP and influenza mass vaccination programmes is relevant to optimise vaccination strategies and keep programmes successful with high acceptance and trust by the public and professionals.
The aim of this thesis was to obtain insight into strengths and limitations of the various surveillance systems used to monitor the NIP and influenza programme and bring forward ideas on improvement of surveillance. It focusses on three aspects of surveillance of vaccine-preventable diseases: disease, safety, and immunosurveillance.
The first part of the thesis concerns disease surveillance and epidemiological studies on pertussis. The first study on pertussis disease is a surveillance study designed to obtain knowledge on pertussis epidemiology in relation to changes in the pertussis vaccination schedule **(chapter 2)**. We wanted to know whether the young, not yet (fully) vaccinated infants, who are at highest risk for severe disease, are well protected via the current pertussis vaccination schedule. Given the known underestimation of more severe disease courses, we tried to assess the completeness of records on pertussis hospitalisations and deaths, covered by several registries routinely used for surveillance in the light of possible introduction of additional vaccination measures, e.g. third-trimester maternal pertussis vaccination **(chapter 3)**. As preterm and term infants might profit differently from this maternal vaccination,

we obtained baseline information on the pertussis burden in these two groups **(chapter 4)**.

The next part of the thesis concerns early measles vaccination, which was offered during the latest measles outbreak. Because vaccine effectiveness estimates against laboratory-confirmed measles in infants below 9 months of age had not been reported using an observational study design in developed countries, we aimed to assess the effectiveness of this outbreak response measure **(chapter 5).** Likewise, because data on early MMR tolerability stem mainly from studies in developing countries, we looked into that aspect in **chapter 6**.

The next chapters deal with safety and preparedness for possible safety issues regarding two large mass vaccination campaigns launched in 2009: the catch-up campaign of HPV vaccination among girls 13 to 16 years old and the influenza A(H1N1) pandemic. Given the urgency of the latter, extensive information on the tolerability of pandemic vaccines was lacking. Yet safety was an issue because adjuvanted instead of non-adjuvanted vaccines were used, and new groups were vaccinated (e.g. pregnant women). Therefore we assessed the tolerability of seasonal influenza vaccination followed by two doses of pandemic vaccine **(chapter 7)** in adults who received these vaccinations from their general practitioners. Likewise, we studied the safety of pandemic vaccination during pregnancy for mother and infant, because vaccinating healthy pregnant women had never been advised in the Netherlands, and in general there is hesitancy to interfere during a pregnancy **(chapter 8).** To be able to put possible safety signals into perspective, we also assessed background rates of a range of adverse events following influenza vaccination, including Guillain-Barré syndrome **(chapter 9).** Likewise for the HPV vaccination campaign, preparedness for possible safety signals was important, because eligible girls formed a new age group for vaccination. Furthermore, adolescence coincides with increased incidence of several immune-mediated diseases, which could be attributed to the HPV vaccination, whereas in fact there is only a temporal association (55, 57). Again, therefore, we assessed background rates of several immune-mediated disorders, including Multiple Sclerosis **(chapter 10).**

The last part of this thesis includes two studies on immune-surveillance. We assessed the seroprotection against poliomyelitis in the light of ongoing eradication efforts **(chapter 11).** Lastly, we used a rapid test to assess immunity against tetanus to investigate the adherence to the Health Council guideline on tetanus post-exposure prophylaxis (T-PEP) and the eligibility to receive T-PEP based on the Health Council guideline **(chapter 12).**

In the discussion **(chapter 13)**, we will use study results and their strengths, and weaknesses to deliberate whether the current surveillance systems fulfil expectations or can be improved.

References

1. Coalition IA. vaccine timeline 1994 [Available from: http://www.immunise.org/timeline/]*
2. Service NH. the History of Vaccination [Available from: http://www.nhs.uk/conditions/vaccinations/pages/the-history-of-vaccination.aspx]
3. **Gilbert L**. Fact File; Immunisation and Vaccine Preventable Diseases Sydney2012 [Available from: https://www.rcpa.edu.au/getattachment/72fd414e-8e44-40ec-bea2-19d2a52e2a2f/Immunisation-and-Vaccine-Preventable-Diseases.aspx]
4. Combination vaccines for childhood immunisation: recommendations of the Advisory Committee on Immunisation Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). Pediatrics. 1999;103(5 Pt 1):1064-77.
5. Schwartz JL. New media, old messages: themes in the history of vaccine hesitancy and refusal. Virtual Mentor. 2012;14(1):50-5.
6. Dube E, Vivion M, MacDonald NE. Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. Expert Rev Vaccines. 2015;14(1):99-117.
7. **. 6th ed.** Plotkin S, Orenstein W, Offit PA, editors. Philadelphia: Elsevier Saunders; 2013.
8. Keja K, Chan C, Hayden G, Henderson RH. Expanded programme on immunisation. World Health Stat Q. 1988;41(2):59-63.
9. WHO. Sustainable Development Goals, Geneva: WHO. [3 November 2017]. Available from: http://www.who.int/sdg/en/]
10. Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ. 1998;76 Suppl 2:22-5.
11. Begg N, Miller E. Role of epidemiology in vaccine policy. Vaccine. 1990;8(3):180-9.
12. Chen RT, Orenstein WA. Epidemiologic methods in immunisation programs. Epidemiol Rev. 1996;18(2):99-117.
13. Initiative GPE: polio global eradication initiative [Available from: http://polioeradication.org/polio-today/]
14. Institute SV. Closing Immunity Gaps in Measles and Rubella Elimination [Available from: http://www.sabin.org/updates/blog/closing-immunity-gaps-measles-and-rubella-elimination]
15. Rumke HC, Visser HK. [Childhood vaccinations anno 2004. I. Effectiveness and acceptance of the Dutch National Vaccination Programme]. Ned Tijdschr Geneeskd. 2004;148(8):356-63.
16. Schurink-van 't Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands; surveillance and developments in 2016-2017. Bilthoven: National Institute for Public Health and the Environment; 2017. Report No.: 2017-0143.
17. Croon MC. Some epidemiological data collected from the epidemic of poliomyelitis in 1956. Additamenta Folia Med Neerl. 1963;2:102-8.
18. Gezondheidsraad. Poliomyelitis (revaccinatie met of zonder K-component). Den Haag: Gezondheidsraad; 1965. Report No.: 225.
19. van den Hof S, Conyn-van Spaendonck M, de Melker HE, Geubbels E, Suijkerbuijk AWM, Talsma E, et al. The effects of vaccination, the incidence of target diseases. Bilthoven: National Institute for Public Health and the Environment; 1998. Contract No.: 213676008.
20. Environment NIfPHat. Department for Vaccine Supply and Prevention Programmes Bilthoven [Available from: http://www.rivm.nl/en/About_RIVM/Organisation/Centres/Department_for_Vaccine_Supply_and Prevention_Programmes]

21. Verbrugge HP. Youth health care in The Netherlands: a bird's eye view. Pediatrics. 1990;86(6 Pt 2):1044-7.

22. Van Lier A, Geraedts JLE, Oomen P, Giesbers H, Van Vliet H, Drijfhout I, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2016. Bilthoven: National Institute for Public Health and the Environment; 2017. Report No.: 2017-0010.

23. Hak E, Hermens RP, van Essen GA, Kuyvenhoven MM, de Melker RA. Population-based prevention of influenza in Dutch general practice. Br J Gen Pract. 1997;47(419):363-6.

24. Preventie SNPG. griepvaccinatieprogramma [Available from: http://www.snpg.nl/over-snpg/historie/]

25. Tacken M, Mulder J, van den Hoogen H, Tiersma W, Donkers J, Verheij R, et al. Monitoring Nationaal Programma Griepprevention 2008. Utrecht: Landelijk Informatie Netwerk Huisartsenzorg 2009. Report No.: ISBN: 978-90-76316-505.

26. Sloot R, Hooiveld M, ten Veen P, Korevaar J. Vaccinatiegraad Nationaal Programma Griepprevention 2014. Utrecht: Nivel; 2015.

27. Heins M, Hooiveld M, Ten Veen P, Korevaar J. Monitor Vaccinatiegraad Nationaal Programma Griepprevention. Netherlands institute for health services research; 2015. Report No.: ISBN 978-94-6122-404-0.

28. Gezondheidsraad. Vaccinatie tegen seizoensgriep. Den Haag: Gezondheidsraad; 2011. Report No.: 2011/21.

29. van Gageldonk-Lafeber AB, Dijkstra F, van 't Veen H, Orchudesch M, van der Hoek W. [Low influenza vaccination coverage rate among hospital employees]. Ned Tijdschr Geneeskd. 2014;158:A7650.

30. Ruijs WL, Hautvast JL, van der Velden K, de Vos S, Knippenberg H, Hulscher ME. Religious subgroups influencing vaccination coverage in the Dutch Bible belt: an ecological study. BMC Public Health. 2011;11:102.

31. van den Hof S, Meffre CM, Conyn-van Spaendonck MA, Woonink F, de Melker HE, van Binnendijk RS. Measles outbreak in a community with very low vaccine coverage, the Netherlands. Emerg Infect Dis. 2001;7(3 Suppl):593-7.

32. Knol M, Urbanus A, Swart E, Mollema L, Ruijs W, van Binnendijk R, et al. Large ongoing measles outbreak in a religious community in the Netherlands since May 2013. Euro Surveill. 2013;18(36):pii=20580.

33. Bijkerk H, Draaisma FJ, Landheer T, van Os M. [Poliomyelitis epidemic in Staphorst]. Ned Tijdschr Geneeskd. 1972;116(14):549-58.

34. Bijkerk H, Draaisma FJ, van der Gugten AC, van Os M. [The poliomyelitis epidemic in 1978]. Ned Tijdschr Geneeskd. 1979;123(39):1700-14.

35. Oostvogel PM, van Wijngaarden JK, van der Avoort HG, Mulders MN, Conyn-van Spaendonck MA, Rumke HC, et al. Poliomyelitis outbreak in an unvaccinated community in The Netherlands, 1992-93. Lancet. 1994;344(8923):665-70.

36. Van Steenbergen JE, Kraayeveld AG, Spanjaard L. Vaccination campaign for meningococcal disease in a rural area in the Netherlands - January 1998. Euro Surveill. 1999;4(2):18-21.

37. de Greeff SC, de Melker HE, Spanjaard L, van den Hof S, Dankert J. [The first effect of the national vaccination campaign against meningococcal-C disease: a rapid and sharp decrease in the number of patients]. Ned Tijdschr Geneeskd. 2003;147(23):1132-5.

38. van Dijk E, Timen A, De Melker H, Kool J, Spanjaard L. Twee clusters van meningokokkenziekte door Neisseria meningitidis serogroep C in Nederland. Infectieziekten Bulletin. 2001;12(8):267-71.

39. Bijlsma MW, Bekker V, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. Epidemiology of invasive meningococcal disease in the Netherlands, 1960-2012: an analysis of national surveillance data. Lancet Infect Dis. 2014;14(9):805-12.
40. Knol M, Ruijs H, De Melker H, Berbers G, van der Ende A. Plotselinge toename van invasieve meningokokkenziekte serogroep W in 2015 en 2016. Infectieziekten bulletin. 2017;28(1):23/8.
41. Schippers EI. Maatregelen tegen meningokokkenziekte. den Haag: Ministerie van Volksgezondheid, Welzijn en Sport; 2017.
42. Stein ML, Van Vliet H, Timen A. Chronological overview of the 2009 H1N1 pandemic and the response of the Centre for Infectious Disease Control (Cib) of the National Institute for Public Health and the Environment (RIVM). Bilthoven: National Institute for Public Health and the Environment; 2010. Report No.: 2151320001/2010.
43. Houweling H, Verweij M, Ruitenberg EJ. Criteria for inclusion of vaccinations in public programmes. Vaccine. 2010;28(17):2924-31.
44. gezondheidsraad. de toekomst van het rijksvaccinatieprogramma; naar een programma voor alle leeftijden. Den Haag: Gezondheidsraad; 2007.
45. Control CfID. National Guidance for Infectious Disease Threats and Crises. Bilthoven: National Institute for Public Health and the Environment; 2011.
46. Organisation WH. Immunisation surveillance, assessment and monitoring [Available from: http://www.who.int/immunisation/monitoring_surveillance/en/]
47. Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. BMJ. 1999;319(7223):1462-7.
48. Mooi FR, Van Der Maas NA, De Melker HE. Pertussis resurgence: waning immunity and pathogen adaptation - two sides of the same coin. Epidemiol Infect. 2014;142(4):685-94.
49. Mooi FR, van Loo IH, van Gent M, He Q, Bart MJ, Heuvelman KJ, et al. Bordetella pertussis strains with increased toxin production associated with pertussis resurgence. Emerg Infect Dis. 2009;15(8):1206-13.
50. Mollema L, Smits GP, Berbers GA, Van Der Klis FR, Van Binnendijk RS, De Melker HE, et al. High risk of a large measles outbreak despite 30 years of measles vaccination in The Netherlands. Epidemiol Infect. 2014;142(5):1100-8.
51. Waaijenborg S, Hahne SJ, Mollema L, Smits GP, Berbers GA, van der Klis FR, et al. Waning of Maternal Antibodies Against Measles, Mumps, Rubella, and Varicella in Communities With Contrasting Vaccination Coverage. J Infect Dis. 2013.
52. Thacker SB, Parrish RG, Trowbridge FL. A method for evaluating systems of epidemiological surveillance. World Health Stat Q. 1988;41(1):11-8.
53. 'Lareb' NPC. Lareb rapportages en publicaties 's Hertogenbosch [Available from: http://www.lareb.nl/Vaccins/Lareb-rapportages-en-publicaties]
54. Schurink-Van't Klooster TM, de Ridder MA, Kemmeren JM, van der Lei J, Dekker F, Sturkenboom M, et al. Examining a possible association between human papilloma virus (HPV) vaccination and migraine: results of a cohort study in the Netherlands. Eur J Pediatr. 2015;174(5):641-9.
55. Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunisation in adolescent and young adults: a cohort study to illustrate what events might be mistaken for

adverse reactions. Pediatr Infect Dis J. 2007;26(11):979-84.

56. 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 immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009;374(9707):2115-22.

57. Callreus T, Svanstrom H, Nielsen NM, Poulsen S, Valentiner-Branth P, Hviid A. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. Vaccine. 2009;27(22):2954-8.

58. Teirlinck AC, van Asten L, Brandsema PS, Dijkstra F, Donker GA, Van Gageldonk-Lafeber AB, et al. Surveillance of influenza and other respiratory infections in the Netherlands: winter 2015/2016. Bilthoven: National Institute for Public Health and the Environment; 2016. Report No.: 2016-0071.

59. De Melker HE, Conyn-van Spaendonck MA. Immunosurveillance and the evaluation of national immunisation programmes: a population-based approach. Epidemiol Infect. 1998;121(3):637-43.

60. van der Klis FR, Mollema L, Berbers GA, de Melker HE, Coutinho RA. Second national serum bank for population-based seroprevalence studies in the Netherlands. Neth J Med. 2009;67(7):301-8.

61. Steens A, Mollema L, Berbers GA, van Gageldonk PG, van der Klis FR, de Melker HE. High tetanus antitoxin antibody concentrations in the Netherlands: a seroepidemiological study. Vaccine. 2010;28(49):7803-9.

62. World Health Organisation rOfE. 30th Meeting of the European Regional Certification Commission for Poliomyelitis Eradication. Copenhagen: WHO; 2016.

63. World Health Organisation rOfE. Eliminating measles and rubella and preventing congenital rubella infection; WHO European Region strategic plan 2005-2010. Copenhagen; 2005.

64. Van Lier A, Oomen P, Giesbers H, Van Vliet H, Drijfhout I, Zonnenberg-Hoff IF, et al. Immunisation Coverage* National Immunisation Programme in the Netherlands; year of report 2016. Bilthoven: National Institute for Public Health and the Environment; 2016. Report No.: 2016-0064.

65. Hahne S, Macey J, van Binnendijk R, Kohl R, Dolman S, van der Veen Y, et al. Rubella outbreak in the Netherlands, 2004-2005: high burden of congenital infection and spread to Canada. Pediatr Infect Dis J. 2009;28(9):795-800.

66. Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C, et al. Measles vaccine effectiveness in standard and early immunisation strategies, Niger, 1995. Pediatr Infect Dis J. 1998;17(11):1034-9.

67. de Serres G, Boulianne N, Ratnam S, Corriveau A. Effectiveness of vaccination at 6 to 11 months of age during an outbreak of measles. Pediatrics. 1996;97(2):232-5.

68. Brockhoff HJ, Mollema L, Sonder GJ, Postema CA, van Binnendijk RS, Kohl RH, et al. Mumps outbreak in a highly vaccinated student population, The Netherlands, 2004. Vaccine. 2010;28(17):2932-6.

69. Sane J, Gouma S, Koopmans M, de Melker H, Swaan C, van Binnendijk R, et al. Epidemic of mumps among vaccinated persons, The Netherlands, 2009-2012. Emerg Infect Dis. 2014;20(4):643-8.

70. Anderson RM, Crombie JA, Grenfell BT. The epidemiology of mumps in the UK: a preliminary study of virus transmission, herd immunity and the potential impact of immunisation. Epidemiol Infect. 1987;99(1):65-84.

71. Wijnker G. Mumps re-emergence among Dutch university students. Bilthoven: Utrecht University; 2012.

72. de Melker HE, Schellekens JFP, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van

Spaendonck MAE. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. Emerg Infect Dis. 2000;6(4):348-57.

73. de Greeff SC, de Melker HE, van Gageldonk PG, Schellekens JF, van der Klis FR, Mollema L, et al. Seroprevalence of Pertussis in the Netherlands: Evidence for Increased Circulation of Bordetella pertussis. PLoS One. 2010;5(12):e14183.

74. van der Maas NAT, Mooi FR, de Greeff SC, Berbers GAM, Conyn-Spaendonck MAE, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? Vaccine. 2013;31(41):4541-7.

75. de Greeff SC, Mooi FR, Westerhof A, Verbakel JM, Peeters MF, Heuvelman CJ, et al. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis. 2010;50(10):1339-45.

76. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. Ned Tijdschr Geneeskd. 1998;142(49):2657-60.

77. Riise OR, Laake I, Vestrheim D, Flem E, Moster D, Riise Bergsaker MA, et al. Risk of Pertussis in Relation to Degree of Prematurity in Children Less Than 2 Years of Age. Pediatr Infect Dis J. 2017;36(5):e151-e6.

78. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. Arch Dis Child. 2017.

79. Wagenvoort GH, Sanders EA, Vlaminckx BJ, Elberse KE, de Melker HE, van der Ende A, et al. Invasive pneumococcal disease: Clinical outcomes and patient characteristics 2-6 years after introduction of 7-valent pneumococcal conjugate vaccine compared to the pre-vaccine period, the Netherlands. Vaccine. 2016;34(8):1077-85.

80. van Gageldonk-Lafeber AB, Bogaerts MA, Verheij RA, van der Sande MA. Time trends in primary-care morbidity, hospitalisation and mortality due to pneumonia. Epidemiol Infect. 2009;137(10):1472-8.

81. Schurink-van 't Klooster TM, de Melker HE. HPV vaccination: Background information for the Dutch Health Council. Bilthoven: National Institute for Public Health and the Environment; 2017. Report No.: 2017-0020.

82. Schurink-van 't Klooster TM. the National Immunisation Programme in the Netherlands; surveillance and developments in 2015-2016. Bilthoven: National Institute for Public Health and the Environment; 2016. Report No.: 2016-0141.

83. Dieleman J, Sturkenboom M. Pandemic Influenza Vaccination Safety Assessment Network* Europe; Background Rates of Specific Events of Interest. 2010.

84. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barre syndrome reported in association with the administration of swine influenza vaccines. Am J Epidemiol. 1984;119(6):841-79.

Chapter 2

Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants?

Nicoline A.T. van der Maas
Frits R. Mooi
Sabine C. de Greeff
Guy A.M. Berbers
Marina A.E. Conyn-Spaendonck
Hester E. de Melker

Published in:
Vaccine. 2013;31(41):4541-7
(DOI 10.1016/j.vaccine.2013.07.060)

Abstract

Background
Pertussis has resurged in the Netherlands since 1996. Several measures, i.e. acceleration of the schedule, introduction of a preschool acellular pertussis booster and change from an infant whole cell to an acellular pertussis combination vaccine were implemented in the National Immunisation Programme to decrease disease burden, in particular among very young infants who have the highest morbidity and mortality of pertussis. Nevertheless, a large outbreak occurred in 2011-2012.

Methods.
1996-2010 was divided in 3-year-periods to assess the impact of the measures taken, using notifications and hospitalisations. These results were compared with 2011-2012. Mean Incidence rates (IRs) per 100,000 were calculated.

Results.
Although the measures taken resulted in decreased IRs among the targeted age groups after implementation, overall mean IRs of notifications increased from 32 (1996-2004) to 37 (2005-2010) and 63 (2011-2012). Young infants, not yet vaccinated, did not benefit; during the 2011-2012 outbreak, IR in 0-2-month-olds amounted to 259.6. IR among persons over 9 years of age increased from 6.8 (1996-1999) to 59.1 (2011-2012). For hospitalisations overall mean IRs decreased from 1.95 per 100,000 (1997-2004) to 0.88 (2005-2010) and 0.76 (2011).

Conclusion.
The measures taken reduced IRs of notifications and hospitalisations among groups eligible for vaccination, but had no effect on the increasing IRs in adolescents and adults. This trend is also observed in other countries. The high IRs in 2012 in adolescents and adults probably resulted in increased transmission to infants, who are at risk for contracting severe pertussis. Therefore, additional measures to protect this group should be considered.

Introduction

Pertussis or whooping cough is characterised by a catarrhal phase which is followed by a phase with persistent paroxysmal coughing. In typical cases, coughing may be followed by inspiratory whooping and vomiting. Pertussis may be complicated by cyanosis, apnoea, pneumonia or seizures. Even encephalopathy or death may occur, albeit infrequently.[1] Severe pertussis usually occurs in young infants. In adolescents and adults pertussis usually has a mild and more atypical disease course.[2, 3] Since the 1950s, vaccination programmes have been introduced worldwide. First whole cell pertussis vaccines (WCVs) were used, later, in the 1990s, many western countries switched to acellular pertussis vaccines (ACVs) with a more favourable safety profile.[4, 5]

Despite constant high vaccine coverage, pertussis has resurged in many countries, including the Netherlands.[6-9] Pertussis was originally defined as a childhood disease, but the largest increase in pertussis incidence is nowadays found in adolescents and adults.

In the Netherlands pertussis notifications increased suddenly in 1996 and since then remained at a higher level, with additional peaks every 3-4 years.[10] In 2012, a particular high and broad peak in notifications was observed, starting at the end of 2011 and continuing in 2012. In contrast to the usual seasonal pattern with peaks in late summer and autumn, the incidence stayed at a high level during winter and spring, and decreased only after August 2012. [11] In view of the resurgence of pertussis since 1996 in the Netherlands, several measures were taken to reduce disease burden, with special focus on protecting the most vulnerable, not (completely) vaccinated infants. In 1999, an accelerated schedule of the National Immunisation Programme (NIP) was implemented, in which the first vaccination was given at two instead of three months. From November 2001 onwards, ACV was administered to four-year-olds, simultaneously with the booster Diphtheria-Tetanus-Inactivated Poliovirus (DT-IPV) vaccine. Finally, in 2005 the DTP-IPV-*Haemophilus influenzae* type b (Hib) combination vaccine including WCV was replaced by a combination with ACV at 2, 3, 4 and 11 months of age. This article aims to evaluate the impact of these measures on the pertussis burden, using surveillance data on hospitalisations and notifications by law routinely collected since 1975. We discuss the possible impact of additional measures in view of improvement of the control of pertussis, in infants too young to be vaccinated who have the highest morbidity and mortality.

Methods and materials

Notifications

Pertussis is notifiable by law since 1976. In the mandatory reports, among others, information on vaccination status is available. We included data from 1996-2012 since

in this period a stable case-definition for notification was used, which includes a clinical picture compatible with pertussis combined with laboratory confirmation of *Bordetella (para)pertussis* infection or contact with a laboratory confirmed patient with a *B.(para)pertussis* infection in the last three weeks. Laboratory confirmation can be based on isolation of the bacterium, detection of DNA by polymerase chain reaction (PCR), a ≥4-fold rise in IgG antibodies against pertussis toxin (Ptx) in paired serum samples, or a single serum sample with IgG-anti-Ptx concentrations above a defined age-specific cut-off value.[12] The relative distribution of diagnoses based on culture or PCR, serology as well as epidemiological linked cases (i.e. ~5%, ~90%, ~5% respectively) has been stable over the years under study.

Hospitalisations

Hospitalisation data in the period 1997 to 2011 were retrieved from the National Medical Registration (LMR). LMR collects discharge diagnoses of all patients admitted to the hospital. Only inpatient diagnoses are registered. Diseases are registered as main or side diagnosis according to International Classification of Diseases (ICD-9) coding. Coverage was ~ 99% until mid-2005; thereafter coverage has fluctuated around 90%. Age specific data were available since 1997. Patient records with code 0330 or 0331 (whooping cough caused by *B.pertussis* and *B.parapertussis, respectively)* and 0338 or 0339 (whooping cough caused by other specified or an unspecified organism, respectively) were included.

Statistical analysis

To assess the impact of the measures taken, we divided 1996-2010 in five periods of three years.(Box 1) Three of the five periods, 1999-2001, 2002-2004 and 2005-2007, coincided with a change in the NIP. We calculated mean incidences per 100,000 for each period, which diminished the influence of peak incidences every 2-3 year; peak years were 1996, 1999, 2001, 2004, 2007 and 2008. To relate these results to the current situation, we also present mean IRs for 2011-2012. For hospitalisations the first period consisted of two years (1997 and 1998) and data on 2012 were not available yet.

1996-1998	1999-2001	2002-2004	2005-2007	2008-2010	2011-2012
infant WCV[a]	infant WCV[a]	infant WCV[a]	**infant ACV[b]**	infant ACV[b]	infant ACV[b]
start NIP 3 m	**start NIP 2 m**	start NIP 2 m	start NIP 2 m	start NIP 2 m	start NIP 2 m
no booster 4y	no booster 4y	**ACV[c] booster 4y**	ACV[c] booster 4y	ACV[c] booster 4y	ACV[c] booster 4y

Box 1. Overview of used schedules and vaccines in the defined periods. Changes between successive periods are in bold.

[a]=DTwP-IPV (+Hib) vaccine/RIVM+NVI
[b]=from January 1st 2005 til December 31st 2005 Infanrix-IPV-Hib/GSK was administered during infancy. From January 1st 2006 till 2008 Pediacel /SP MSD was administered. From 2008 onwards Pediacel was gradually replaced by Infanrix-IPV-Hib again. From October 1st 2011 onwards all infants received Infanrix hexa/GSK.
[c]=Untill July 2006 single aP/GSK was used as a booster. From August 2006 till 2008 Triaxis Polio/SP MSD was administered. Thereafter this was gradually replaced by Infanrix-IPV/GSK.

Mean incidences were calculated using numerators from the respective registries and age specific denominators, retrieved from CBS (www.statline.nl), being the number of inhabitants in the specific period.
For comparing incidences in different periods or age categories, risk ratios (relative risk, RR) were calculated with 95% confidence intervals (95%CI). Changes were regarded as significant if the 95%CI did not include '1'.
Vaccine effectiveness (VE) was estimated using the 'screening-method'. [13]

$$VE = 1 - PCV/(1-PCV)*(1-PPV)/PPV$$

PCV= proportion of cases vaccinated
PPV=proportion of population vaccinated

For infant vaccinations and the booster dose at four years of age, PPV was set at 96% and 92%, respectively.[14] If PCV exceeded PPV, estimation of VE was not possible.
Calculations were performed using SAS version 9.3, Excel and Episheet.

Results

The overall mean incidence per 100,000 of notifications increased from 32 (1996-2004) to 37 (2005-2010) and 63 (2011-2012). For hospitalisations overall mean incidence decreased from 1.95 (1997-2004) to 0.88 (2005-2010) and 0.76 (2011)(Figure 1).

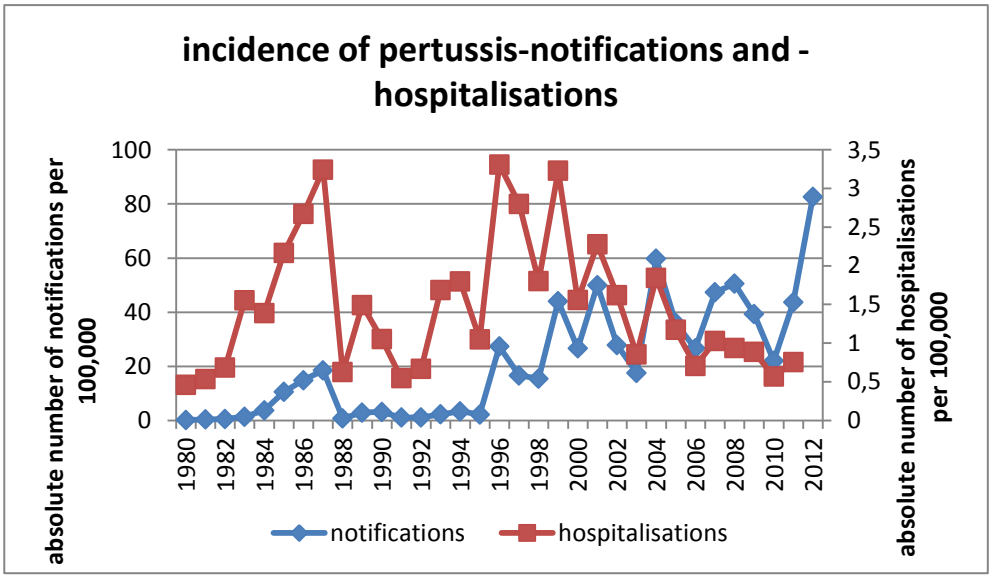


Figure 1. Overall incidence of notifications (left Y-axis) and hospitalisations per 100,000 (right Y-axis) for 1996-2012 and 1997-2011, respectively.

Age specific incidences fluctuated over time with peaks every 2-3 years in the period 1996-2004 (Figure 2A and 2B). After the peak in 2004, for those of 4-6 and ≥10 years as well as those 0-2 months of age peaks occurred in 2008, with the largest peak occurring in the young infants. For the age groups 3 months to 3 years of age a decreasing trend was observed from 2004 until 2010-2011 with no discernible peaks. Thereafter, an increase was seen again.

Acceleration of the vaccination schedule in 1999

The incidences in 0-2-month-olds for notifications and hospitalisations increased in 1999-2001 compared to 1996-1998. (Table1 and 2). In 3-5 month old infants, incidences for notifications and hospitalisations decreased, comparing 1996-1998 and 1999-2001.

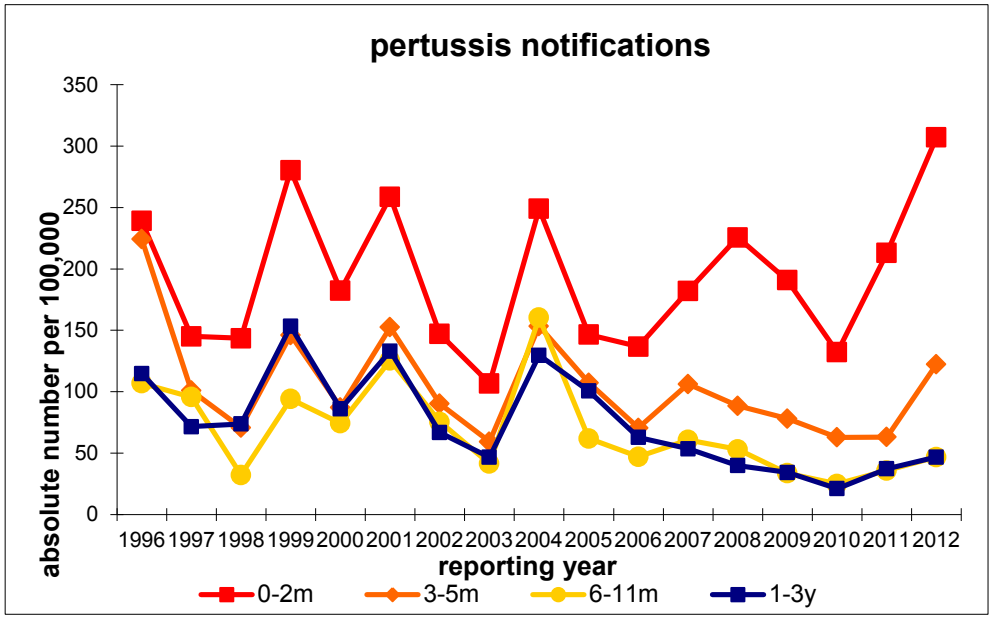


Figure 2A. Incidence of notifications per 100,000 for 0-2, 3-5 and 6-11 month-olds and 1-3 year-olds for 1996-2012.

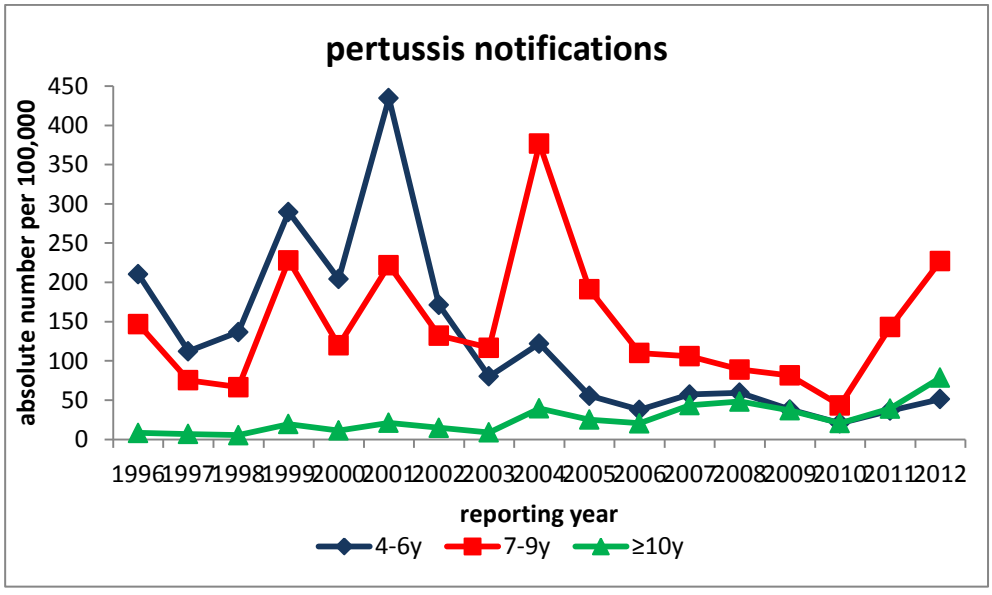


Figure 2B. Incidence of notifications per 100,000 for 4-6, 7-9 and ≥10-year-olds for 1996-2012.

Table 1. Mean incidences per 100,000 (95%CI) of notifications per age category in 1996-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2010, 2011-2012 and risk ratios (relative risk; RR) of subsequent periods.

Mean incidence of notifications	0-2m	3-5m	6-11m	1-3y	4-6y	7-9y	≥10y
1996-1998	175.8 (140.4-218.0)	131.9 (101.5-168.9)	78.1 (61.7-98.4)	86.7 (79.5-94.8)	153.2 (143.3-163.3)	96.4 (88.3-104.4)	6.8 (6.4-7.3)
Change NIP	**Acceleration schedule**						
1999-2001	240.6 (199.8-287.2)	128.8 (98.9-163.4)	98.3 (80.2-119.9)	124.1 (115.3-133.4)	309.5 (295.2-323.7)	189.9 (178.9-201.1)	17.3 (16.6-18.0)
Change NIP	**Booster 4 yr olds**						
2002-2004	167.6 (134.2-207.7)	101.0 (75.0-132.5)	92.5 (74.2-112.6)	81.0 (74.0-88.4)	124.5 (115.5-133.6)	208.6 (196.3-219.7)	21.0 (20.3-21.8)
Change NIP	**Change to ACV for infants**						
2005-2007	155.2 (121.5-194.8)	94.7 (69.7-127.8)	56.6 (42.1-73.6)	72.3 (66.0-79.9)	50.1 (44.7-56.1)	135.7 (126.1-145.1)	29.8 (28.9-30.7)
2008-2010	182.9 (146.3-227.0)	76.5 (53.2-106.3)	37.2 (25.7-51.9)	31.8 (27.3-36.8)	39.3 (34.7-45.1)	71.3 (64.7-78.3)	35.4 (34.3-36.3)
2011-2012	259.6 (215.9-309.7)	92.4 (67.5-123.6)	41.8 (30.0-56.7)	42.0 (36.9-47.6)	44.0 (38.8-49.7)	185.0 (174.3-196.1)	59.1 (57.9-60.4)
RR 9901-9698	**1.37 (1.04-1.81)**	0.97 (0.69-1.37)	1.26 (0.93-1.69)	**1.43 (1.28-1.60)**	**2.02 (1.87-2.19)**	**1.97 (1.78-2.19)**	**2.54 (2.36-2.74)**
RR 0204-9901	**0.70 (0.53-0.92)**	0.79 (0.55-1.13)	0.93 (0.70-1.24)	**0.65 (0.58-0.73)**	**0.40 (0.37-0.44)**	**1.09 (1.01-1.19)**	**1.21 (1.15-1.28)**
RR 0507-0204	0.92 (0.67-1.26)	0.95 (0.63-1.42)	**0.61 (0.44-0.86)**	0.90 (0.79-1.02)	**0.40 (0.35-0.46)**	**0.65 (0.60-0.71)**	**1.42 (1.35-1.48)**
RR 0810-0507	1.18	0.80	0.65	**0.44**	**0.79**	**0.53**	**1.18**

	(0.86-1.62)	(0.51-1.24)	(0.43-1.01)	(0.37-0.52)	(0.67-0.94)	(0.47-0.59)	(1.14-1.23)
RR 1112-0810	1.42 (1.07-1.87)	1.21 (0.77-1.89)	1.13 (0.71-1.79)	1.32 (1.09-1.61)	1.11 (0.93-1.33)	2.60 (2.32-2.90)	1.68 (1.62-1.73)

Table 2. Mean incidences per 100,000 (95%CI) of hospitalisations per age category in 1997-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2010, 2011 and risk ratios (relative risk; RR) of subsequent periods.

Mean incidence of hospitalisations	0-2m	3-5m	6-11m	1-3y	4-6y	7-9y	≥10y
1997-1998	278.4 (232.9-329.6)	145.5 (114.1-185.0)	38.8 (27.2-53.3)	10.2 (7.9-13.3)	6.0 (4.2-8.3)	1.7 (0.8-3.2)	0.10 (0.06-1.69)
Change NIP	**Acceleration schedule**						
1999-2001	343.5 (294.0-398.0)	131.0 (102.4-167.8)	27.5 (18.3-39.9)	6.3 (4.4-8.7)	4.4 (2.9-6.5)	1.6 (0.8-3.1)	0.1 (0.05-0.17)
Change NIP	**Booster 4 yr olds**						
2002-2004	191.7 (155.5-233.9)	87.6 (63.2-116.7)	32.6 (22.4-45.8)	4.1 (2.6-6.0)	1.7 (0.8-3.1)	1.5 (0.7-2.9)	0.1 (0.05-0.17)
Change NIP	**Change to ACV**						
2005-2007	161.3 (127.1-201.9)	65.1 (44.7-93.4)	13.4 (7.3-23.6)	2.2 (1.2-3.7)	0.5 (0.1-1.4)	0.8 (0.3-2.0)	0.1 (0.07-0.19)
2008-2010	155.7 (121.0-195.5)	47.3 (30.1-72.7)	13.1 (6.8-22.9)	1.1 (0.4-2.3)	0.7 (0.2-1.7)	0.2 (0.004-0.9)	0.1 (0.06-0.17)
2011	150.0 (116.7-189.8)	45.7 (28.3-69.8)	7.6 (3.1-15.7)	2.0 (0.99-3.6)	0 (0-0.7)	0.2 (0.004-0.92)	0.1 (0.05-0.16)
RR 9901-9798	1.23 (0.98-1.55)	0.89 (0.64-1.24)	0.71 (0.44-1.17)	**0.61 (0.40-0.92)**	0.73 (0.44-1.21)	0.97 (0.40-2.32)	0.91 (0.43-1.94)
RR 0204-9901	**0.56 (0.44-0.72)**	**0.67 (0.46-0.98)**	1.18 (0.71-1.95)	0.65 (0.39-1.07)	**0.38 (0.18-0.79)**	0.91 (0.37-2.24)	1.05 (0.50-2.24)
RR 0507-0204	0.84 (0.62-1.14)	0.76 (0.48-1.20)	**0.42 (0.22-0.80)**	0.54 (0.28-1.05)	0.29 (0.08-1.06)	0.56 (0.19-1.67)	1.20 (0.59-2.43)
RR 0810-0507	0.96	0.73	0.95	0.49	1.38	0.19	0.87

	(0.70-1.33)	(0.42-1.26)	(0.43-2.08)	(0.19-1.30)	(0.31-6.16)	(0.02-1.66)	(0.43-1.74)
RR 11-0810	0.97 (0.69-1.35)	0.95 (0.52-1.73)	0.58 (0.23-1.48)	1.85 (0.68-4.99)	0 (---)	1.01 (0.06-16.12)	0.94 (0.45-1.94)

The decrease in incidences of notifications in 3-5-month-olds compared to 0-2-month-olds was significant for 1999-2001 (RR 0.53; 95%CI 0.39-0.72). Comparing these two age categories for 1996-1998 resulted in a non-significant decrease. For hospitalisations, the incidence in 3-5-month-olds was significantly lower than in 0-2-month-olds in both periods (1996-1998 RR 0.53; 95%CI 0.39-0.70 and 1999-2001 RR 0.38; 95%CI 0.29-0.50). Among 6-11-month-olds a non-significant increase in incidence of notifications was seen when 1996-1998 and 1999-2001 were compared. In the age categories 1-3-year-olds (RR 1.43; 95%CI 1.28-1.60), 4-6-year-olds (RR 2.02; 95%CI 1.87-2.19), 7-9-year-olds (RR 1.97; 95%CI 1.78-2.19) and ≥ 10-year-olds (RR 2.54; 95%CI 2.36-2.74) a significant increase in incidences of notifications was observed comparing these respective periods. Incidences of hospitalisations decreased slightly or showed no change, except in 1-3-year-olds, in which a significant decrease was seen (RR 0.61; 95%CI 0.40-0.92) comparing 1997-1998 and 1999-2001.

Implementation of the booster dose at four years of age in November 2001

After the introduction of a preschool ACV booster in November 2001, the mean incidence of notifications and hospitalisations in 4-6-year-olds decreased comparing the period2002-2004 with 2008-2010 (Table1 and 2). Comparing 2002-2004 (post-introduction) to 1999-2001 (pre-introduction) revealed a significant decrease in incidences of notifications and hospitalisations in 4-6-year-olds with respective RRs of 0.40 (95%CI 0.37-0.44) and 0.38 (95%CI 0.18-0.79).

Furthermore, the mean incidence of notifications in 0-2-month-olds decreased significantly (RR 0.70; 95%CI 0.53-0.92), when pre- and post-introduction periods were compared. In 3-5-month-olds a non-significant decrease was visible, comparing these periods. Incidences of hospitalisations for 1999-2001 compared to 2002-2004 decreased significantly (RR 0.56; 95%CI 0.44-0.72 and RR 0.67; 95%CI 0.46-0.98) in 0-2 and 3-5-month-olds, respectively.

In 7-9-year-olds, incidences of notifications increased significantly comparing the periods 1999-2001 and 2002-2004. Thereafter, mean incidence of notifications in 7-9-year-olds decreased significantly, most likely due to the fact that during these years 7-9-year-olds were eligible for the preschool ACV. Incidences of hospitalisations of this age group showed non-significant changes over the periods..

In ≥ 10 year old people incidences of notifications and hospitalisations increased in 2002-2004 compared to1999-2001. This increase was only significant for notifications (RR 1.21; 95%CI 1.15-1.28).

Mean vaccine effectiveness (VE) of the booster dose decreased with time since last vaccination, being 82%, 76%, 63%, 59% and 52% for 5, 6, 7, 8 and 9-year-olds, respectively. (Table 3).

Table 3. Estimation of vaccine effectiveness of the preschool booster by the 'screening method' for 6-11-year-olds per year.

Age\reporting year	'04	'05	'06	'07	'08	'09	'10	'11
5y	77	71	82	86	80	84	83	92
6y	74	70	80	79	71	61	89	87
7y		68	57	68	71	51	61	67
8y			67	75	56	47	35	72
9y				73	63	36	49	37
10y					60	-	13	26
11y						-	11	-
12y							45	-
13y								1

Change from a Dutch whole cell vaccine to acellular vaccine in infancy on January, 1st 2005

After the implementation of ACV in the primary series in 2005, incidences of notifications and hospitalisations in 0-2-month-olds showed non-significant changes comparing 2005-2007 and 2008-2010 (Table 1 and 2).

In 3-5-month-olds a decrease in mean incidence of notifications was seen comparing 2002-2004, 2005-2007and 2008-2010. The same pattern was seen in incidences of hospitalisations. None of these decreases was significant.

After the switch from WCV to ACV the incidences of both notifications and hospitalisations decreased significantly in 6-11 month old infants between the periods 2002-2004 and 2005-2007 (RR of notifications 0.61; 95%CI 0.44-0.86 and of hospitalisations 0.42; 95%CI 0.22-0.80). In 2008-2010 the decrease continued in both registries, although non-significant.

In 1-3 year old children, incidences of notifications decreased comparing 2002-2004, 2005-2007 and 2008-2010. The last decrease was significant (RR 0.44; 95%CI 0.37-0.52), probably because during 2008-2010 a larger part of this age category was eligible for infant ACV. Incidences of hospitalisations showed a non-significant decreasing trend in 1-3-year-olds in the periods concomitant with the introduction of infant ACV.

In ≥ 10-year-olds, the incidence of notifications increased significantly from 2005-2007 to 2008-2010 (RR 1.18; 95%CI 1.14-1.23). No significant changes in hospitalisations were observed.

After the introduction of ACV, mean VE per 3-years-period of the primary series increased, ranging from 33-73%, 27-48% and 24-51% for 1-, 2-, and 3-year-olds

before introduction to 86-92%, 75-91% and 65-85% for the respective ages after implementation.

Outbreak 2011-2012

In 2011-2012, all age categories under study showed an increase in incidences of notifications compared to 2008-2010 (Table 1). In 3-5 and 6-11-month-olds, and 4-6 year old children this increase was not significant.

In 0-2-month-olds the incidence increased from 183 to 260 (RR 1.42; 95%CI 1.07-1.87), in 1-3-year-olds from 32 to 42 (RR 1.32; 95%CI 1.09-1.61), in 7-9-year-olds from 71 to 185 (RR 2.60; 95%CI 2.32-2.90) and in persons ≥ 10 years of age from 35 to 59 (RR 1.68; 95%CI 1.62-1.73) comparing 2008-2010 and 2011-2012. Age specific incidences for hospitalisations showed non-significant changes when comparing 2011 to 2008-2010 (Table 2).

Discussion.

Despite various changes in the pertussis vaccination schedule as implemented in the period 1996 to 2012, our routine surveillance data showed an increase in overall IRs of notifications (32, 37 and 63 in 1996-2004, 2005-2010 and 2011-2012). During the outbreak in 2011-2012, a possible positive impact in the target groups caused by the changes, i.e. earlier start of NIP, preschool ACV booster vaccination and change from an infant Dutch WCV to ACV, may have been nullified by the large upsurge of pertussis in infants too young to be vaccinated and in those above 9 years of age. With regard to more severe pertussis, resulting in hospitalisation, the positive impact in age groups targeted for measures was evident, however. Fortunately, only a small rise was observed in the total number of hospitalisations due to pertussis in 2011.

The earlier start of the NIP resulted in a significant decrease in IRs of notifications and hospitalisations, comparing the age groups of 0-2 and 3-5 months pre- and post-acceleration. The implementation of an ACV preschool booster resulted in a decrease of IRs of notifications and hospitalisations in all age categories from 0-2 months up to 4-6 years, except for hospitalisations in 6-11-month-olds. The decrease in young infants implies an indirect effect of the introduction of a booster dose at 4 years of age. De Greeff et al. showed the importance of siblings in the transmission of pertussis.[15] However, we also observed that the estimated vaccine effectiveness (VE) declined after ~ 4 years, suggesting only a limited period of protection by the preschool booster and therefore a short period of reduced transmission. A limited durability of protection by the preschool booster was also observed in two recent outbreak studies.[16, 17]

The transition to an ACV in the primary infant vaccination series in 2005 decreased IRs of notifications and hospitalisations in the age groups 2-5 months up to 3 years. In

contrast to the period before introduction of ACV in the primary schedule, VE remained high until the age at which the preschool booster is administered. These data confirmed that the Dutch WCV, as previously reported, had relative low effectiveness.[10] No further indirect effect of this measure on unvaccinated infants was observed.

The resurgence of pertussis observed in the Netherlands, is seen in many other countries across the world, mostly as a result of a steady increase of pertussis in adolescents and adults, but also due to peaks in the youngest age groups. [6, 8, 9] Recent outbreaks, for instance in USA and UK [18, 19] triggered the discussion about additional measures to protect the young, not yet fully immunised infants, who are most at risk for contracting severe pertussis. In both US and UK pregnant women are advised to be vaccinated. [19, 20] Other countries adopted booster doses for adolescents and adults, including cocooning strategies. However, in general uptake has been low and recently Australia decided to stop pertussis vaccination in adults because no effect was seen on pertussis in young infants.[21, 22] (http://www.news.com.au/breaking-news/states-ending-free-parent-whooping-vaccine/story-e6frfku0-1226350174856)

This resurgence is probably associated with waning immunity, because the duration of immunity after vaccination is limited.[23, 24] Furthermore, adaptation of *B.pertussis* [25], in particular the emergence of strains that produce more Ptx may play a role.[26, 27] Ptx suppresses the innate and adaptive immune system, resulting in increased infection and transmission, especially when anti-Ptx-antibody levels have waned.[27, 28] These strains with increased Ptx production are found worldwide.[29, 30] Recently, also strains emerged, which lack one or more of the vaccine antigens.[31-33] The impact of the emergence of these strains is not yet known.

Strengths and limitations

Of course, in addition to waning immunity and pathogen adaptation, several other causes may play a role in the increase of pertussis notifications such as improved diagnostics and increased awareness.[6, 34] All notifications in the Netherlands require laboratory confirmation or an epidemiologic link to a laboratory confirmed pertussis case. The latter only occurs in about 5% of the notifications. The frequencies of the laboratory diagnostics did not change during the years under study, with about 90% of the notifications confirmed by serology and ~ 5% by PCR or culture. Therefore, better diagnostics probably had little influence on the pertussis increase.

Furthermore, the case-definition for notification did not change during the study period. In addition the age-specific hospital admission data showed a similar trend compared to age-specific notifications; i.e. hospital admissions decreased among the age-groups targeted for additional measures and increased slightly for older age groups. The less evident increase in hospital admissions in older people is probably associated with low hospitalisation among this group. Many adults show a mild

clinical picture of pertussis, thereby outnumbering an increase in severe pertussis, needing hospitalisation.

Results of two large Dutch cross sectional population based serosurveys confirmed the changes found in age specific pertussis IRs of notifications. [3] Presumably due to the introduction of ACV at infancy and a preschool booster at 4 years of age, inducing a better serological immune response compared to the Dutch whole cell vaccine, an increase of children with high antibody levels against Pertussis toxin (Ptx) was seen in 2006-2007 compared to 1995-1996. However, these surveys also demonstrated an increase in anti-Ptx antibodies in the population older than 9 years. As anti-Ptx antibodies induced by vaccination have largely disappeared in 9-year-olds [23], this increase suggested higher infection rates in the latter period. In 2006-2007, 9.3% of these persons had an antibody level, indicative for a pertussis infection in the past year compared to 4.0% in 1995-1996. These seroprevalence data imply that the increased notifications among adolescents and adults reflect a real increase.

In a sensitivity analysis we further disentangled the effect of time and the true vaccination effect. We took the group of 10 years and older as reference for the time effect, because this group mainly consists of people, vaccinated with a relative weak Dutch whole cell vaccine during infancy and therefore, the influence of vaccination on incidences is negligible. All RRs of noticiations in this group are above '1'. We adjusted for this natural increase over time by dividing the RR of the other age groups by the RR of the over-9-years. This resulted in a further lowering of RRs, originally below '1', so even further confirming the positive effects of changes in the vaccination schedule. On the other hand, the increase in IR that we saw in some age groups is attenuated by adjusting for this time effect. These adjusted RRs showed that the impact of the changes in vaccination schedule might have been larger than visible in the changes in incidence between periods, shown by our RRs. On the other hand for public health purposes observed incidences and differences are also relevant information.

Our data on hospitalisations could be an underestimation, due to decreased coverage of this surveillance source since 2005. However, information on the number of patients hospitalized, as registered in the notifications, showed no major changes since 2005 (data not shown). Therefore, we think the impact of the possible underestimation will be limited. Finally, use of antibiotics could have influenced the hospitalisation rates. In the Netherlands, national guidelines on diagnosis and treatment of pertussis are in place and no major changes were implemented during the period under study.(http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M78_svk.htm and http://www.rivm.nl/Bibliotheek/Professioneel_Praktisch/Richtlijnen/Infectieziekten/LCI_richtlijnen/LCI_richtlijn_Pertussis_kinkhoest) Because most general practitioners and municipal health doctors follow these guidelines, we think the

influence of changed use of antibiotics on the decrease in hospitalisation will be minor.

In conclusion, we showed that measures taken to reduce pertussis burden in the Netherlands decreased infection rates in children, eligible for vaccination. However, rates in adolescents and adults steadily increased, while rates in infants not yet (fully) vaccinated remain high and showed an increase in the 2011-2012 epidemic. Therefore, additional measures must be considered to reduce the pertussis burden. Based on the current literature, maternal immunisation seems most effective. However, before wide scale introduction of maternal vaccination, further studies on the levels of antibodies, required for protection, persistence of maternal antibodies in infants, safety issues, interference and acceptation of this vaccination are needed.

Acknowledgement.
The authors want to thank dr. M.J. Knol, senior epidemiologist at the Dutch Centre for Infectious Disease Control, for her valuable input to the revision of the first draft of this manuscript.

References

1. Vegelin AL, van Vught AJ, Wolfs TF, Kimpen JL, Geelen SP. [Pertussis in young infants]. Ned Tijdschr Geneeskd. 1998;142(49):2657-60. Epub 1999/03/05. Kinkhoest bij de jonge zuigeling.

2. De Serres G, Shadmani R, Duval B, Boulianne N, Dery P, Douville Fradet M, et al. Morbidity of pertussis in adolescents and adults. J Infect Dis. 2000;182(1):174-9. Epub 2000/07/07.

3. de Greeff SC, de Melker HE, van Gageldonk PG, Schellekens JF, van der Klis FR, Mollema L, et al. Seroprevalence of Pertussis in the Netherlands: Evidence for Increased Circulation of Bordetella pertussis. PLoS One. 2010;5(12):e14183. Epub 2010/12/15.

4. Zhang L, Prietsch SO, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. Cochrane Database Syst Rev. 2011(1):CD001478. Epub 2011/01/21.

5. Edwards KM, Meade BD, Decker MD, Reed GF, Rennels MB, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. Pediatrics. 1995;96(3 Pt 2):548-57. Epub 1995/09/01.

6. Cherry JD. Epidemic pertussis in 2012--the resurgence of a vaccine-preventable disease. N Engl J Med. 2012;367(9):785-7. Epub 2012/08/17.

7. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. Emerg Infect Dis. 2000;6(4):348-57. Epub 2000/07/25.

8. Grant CC, Reid S. Pertussis continues to put New Zealand's immunisation strategy to the test. N Z Med J. 2010;123(1313):46-61. Epub 2010/06/29.

9. Moerman L, Leventhal A, Slater PE, Anis E, Yishai R, Marva E. The re-emergence of pertussis in Israel. Isr Med Assoc J. 2006;8(5):308-11. Epub 2006/06/30.

10. van 't Klooster TM, De Melker H. The National Immunization Programme in the Netherlands; developments in 2011. Bilthoven: National Institute for Public Health and the Environment, 2011 Contract No.: 210021015/2011.

11. Environment NIfPHat. http://www.rivm.nl/Onderwerpen/Ziekten_Aandoeningen/K/Kinkhoest. 2012.

12. Guiso N, Berbers G, Fry NK, He Q, Riffelmann M, Wirsing von Konig CH. What to do and what not to do in serological diagnosis of pertussis: recommendations from EU reference laboratories. Eur J Clin Microbiol Infect Dis. 2011;30(3):307-12. Epub 2010/11/12.

13. Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol. 1993;22(4):742-6. Epub 1993/08/01.

14. Van Lier A, Oomen PJ, Giesbers H, Drijfhout IH, De Hoogh PAAM, de Melker HE. Immunization coverage National Immunization Programme in the Netherlands. Bilthoven: National Institute for Public Health and the Environment, 2012 201001001/2012.

15. de Greeff SC, Mooi FR, Westerhof A, Verbakel JM, Peeters MF, Heuvelman CJ, et al. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis. 2010;50(10):1339-45. Epub 2010/04/08.

16. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med. 2012;367(11):1012-9. Epub 2012/09/14.

17. Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis. 2012;54(12):1730-5. Epub 2012/03/17.

18. whooping cough vaccination; coverage may be widened. Br Med J (Clin Res Ed). 2012;345(7868):E5201.

19. Billingsley M. Pregnant women in UK are offered whooping cough vaccine to protect newborns. BMJ. 2012;345:e6594. Epub 2012/10/10.

20. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. MMWR Morb Mortal Wkly Rep. 2011;60(1):13-5. Epub 2011/01/14.

21. Wei SC, Tatti K, Cushing K, Rosen J, Brown K, Cassiday P, et al. Effectiveness of adolescent and adult tetanus, reduced-dose diphtheria, and acellular pertussis vaccine against pertussis. Clin Infect Dis. 2010;51(3):315-21. Epub 2010/06/29.

22. Ulloa-Gutierrez R, Gentile A, Avila-Aguero ML. Pertussis cocoon strategy: would it be useful for Latin America and other developing countries? Expert Rev Vaccines. 2012;11(12):1393-6. Epub 2012/12/21.

23. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. Pediatr Infect Dis J. 2005;24(5 Suppl):S58-61. Epub 2005/05/07.

24. Hendrikx LH, Berbers GA, Veenhoven RH, Sanders EA, Buisman AM. IgG responses after booster vaccination with different pertussis vaccines in Dutch children 4 years of age: effect of vaccine antigen content. Vaccine. 2009;27(47):6530-6. Epub 2009/09/05.

25. Mooi FR. Bordetella pertussis and vaccination: the persistence of a genetically monomorphic pathogen. Infect Genet Evol. 2010;10(1):36-49. Epub 2009/11/03.

26. van Gent M, Bart MJ, van der Heide HG, Heuvelman KJ, Kallonen T, He Q, et al. SNP-based typing: a useful tool to study Bordetella pertussis populations. PLoS One. 2011;6(5):e20340. Epub 2011/06/08.

27. Mooi FR, van Loo IH, van Gent M, He Q, Bart MJ, Heuvelman KJ, et al. Bordetella pertussis strains with increased toxin production associated with pertussis resurgence. Emerg Infect Dis. 2009;15(8):1206-13. Epub 2009/09/16.

28. Carbonetti NH, Artamonova GV, Van Rooijen N, Ayala VI. Pertussis toxin targets airway macrophages to promote Bordetella pertussis infection of the respiratory tract. Infect Immun. 2007;75(4):1713-20. Epub 2007/01/24.

29. Schmidtke AJ, Boney KO, Martin SW, Skoff TH, Tondella ML, Tatti KM. Population Diversity among Bordetella pertussis Isolates, United States, 1935-2009. Emerg Infect Dis. 2012;18(8):1248-55. Epub 2012/07/31.

30. Kallonen T, Mertsola J, Mooi FR, He Q. Rapid detection of the recently emerged Bordetella pertussis strains with the ptxP3 pertussis toxin promoter allele by real-time PCR. Clin Microbiol Infect. 2012;18(10):E377-9. Epub 2012/08/23.

31. Barkoff AM, Mertsola J, Guillot S, Guiso N, Berbers G, He Q. Appearance of Bordetella pertussis Strains Not Expressing the Vaccine Antigen Pertactin in Finland. Clin Vaccine Immunol. 2012;19(10):1703-4. Epub 2012/08/24.

32. Bouchez V, Brun D, Cantinelli T, Dore G, Njamkepo E, Guiso N. First report and detailed characterization of B. pertussis isolates not expressing Pertussis Toxin or Pertactin. Vaccine. 2009;27(43):6034-41. Epub 2009/08/12.

33. Queenan AM, Cassiday PK, Evangelista A. Pertactin-negative variants of Bordetella pertussis in the United States. N Engl J Med. 2013;368(6):583-4. Epub 2013/02/08.

34. Berbers GA, de Greeff SC, Mooi FR. Improving pertussis vaccination. Hum Vaccin. 2009;5(7):497-503. Epub 2009/02/27.

Chapter 3

Severe underestimation of pertussis related hospitalizations and deaths in the Netherlands: a capture-recapture analysis

Nicoline A.T. van der Maas
Joske Hoes
Elisabeth A.M. Sanders
Hester E. de Melker

Published in:
Vaccine. 2017;24(35):4162-6.
(DOI: 10.1016/j.vaccine.2017.06.037)

Abstract

Objective

Despite vaccination, pertussis has remained endemic, sometimes leading to severe disease. We aimed to quantify the completeness of reporting (CoR) of pertussis hospitalizations and deaths in the Netherlands.

Study design

CoR was estimated using capture-recapture analyses. Hospitalizations (2007-2014) from the National Registration Hospital Care (hospital data) were matched to the notifiable Infectious Disease case registry (notifications) providing (month and) year of birth, gender and postal code. Deaths (1996-2014) from Statistics Netherlands (death registry) were matched to notifications using gender, age, year of death and notification date. Cases <2 years (y) and ≥2y were analysed separately. Chao's estimator estimated the total population, which was used to calculate CoR.

Results

Using strict matching criteria, we found 461 matches among 876 (hospital data) and 757 (notifications) hospitalizations <2y. The population estimate of hospitalised infants was 1446, resulting in CoR between 52% and 61%. For hospitalizations ≥2y (246; hospital data and 264; notifications) 43 matches were found, with a population estimate of 1512 and CoR between 16.5% and 22%.

Among thirteen (death registry) and eight (notifications) deaths <2y, seven cases overlapped. The population estimate was 16. CoR of the two sources was 50%-81%. With two (death registry) and eight (notifications) deaths ≥2y without overlap, the population estimate was 26 and CoR 8%-31%.

Conclusion

Results showed substantial underestimation of pertussis hospitalizations and deaths. This has to be taken into account in evaluation of current and future immunization programs.

Introduction

Pertussis is a respiratory tract infection, commonly caused by *Bordetella pertussis* [1]. Typical pertussis illness including paroxysmal coughing mainly affects young children who are not (fully) vaccinated, who are also at the highest risk for severe morbidity and mortality. Still, pertussis can also occur as a milder infection or even asymptomatic in older children, adolescents and adults.

To prevent severe disease and mortality, routine vaccination against pertussis was introduced in the National Immunization Program of the Netherlands in 1957 [2]. Up to 2005, a whole cell pertussis combination vaccine was used [3], but at present, an acellular pertussis combination vaccine, targeting diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* type b, and Hepatitis B (DTaP-IPV-Hib-HBV) at 2, 3, 4 and 11 months of age is offered, with vaccination coverage above 95% [4]. Since 2001, the National Immunization Program also includes an acellular pertussis booster for 4-year-olds because of the observed high incidence of pertussis in this age group [5]. The vaccination coverage of the booster amounts to approximately 92% [4]. Despite these changes and uninterrupted high vaccine coverage from 1980 onwards, an increase of pertussis is observed, not only in the Netherlands, but also worldwide [6, 7]. This increase occurs in all ages, with epidemic peaks every 2 to 3 years [3]. Surveillance data also show that infants, too young to be (fully) vaccinated, show increasing pertussis incidence rates from 2005 onwards with 64 (2013) and 222 (2014) notifications per 100,000.

To evaluate the potential impact of vaccination strategies, adequate data on morbidity of severe pertussis infection and mortality caused by pertussis are essential. However, different sources to assess severe morbidity and mortality vary in their completeness of reporting [8, 9]. Therefore, the aim of this study is to quantify the completeness of reporting (CoR) of hospitalization and death caused by pertussis in the Netherlands by means of capture-recapture analyses.

Methods

Setting

Reports of pertussis were derived from three databases with national coverage.

Data of the National Registration Hospital Care (hospital data) and of the 'Online System for Infectious diseases Reporting within the Infectious diseases Surveillance System' (notifications) were used in the analysis of hospitalizations. CoR was studied over the period from 2007 up to 2014, during which all pertussis vaccines within the National Immunization Program were acellular and date of birth was available in hospital data.

Data of notifications and of Statistics Netherlands (death registry) were used in the analysis of deaths. CoR was studied between 1996 and 2014. The case definition for pertussis has remained the same since 1996 [8].
No medical ethical approval was needed because only routinely collected data were used and people were not imposed to specific deed.

Data sources

National Registration Hospital Care data (hospital data)
Hospital data is collected by Dutch Hospital Data. This database registers medical and administrative information from hospitalized patients in the Netherlands [10]. From 2007 onwards, the rate of nationally participating hospitals fluctuated around 90% [11]. Main diagnosis as well as date of birth, four digits of the zip code, gender, and date of hospital admission is registered. Cases within the hospital data were included for analysis when a patient was diagnosed with whooping cough according to the International Classification of Diseases (ICD) codes, i.e. ICD-9 0330 or ICD-10 A370 (caused by *B. pertussis*), ICD-9 0331 or ICD-10 A371 (*B. parapertussis*), ICD-9 0338 or ICD-10 A378 (other specified organism) or ICD-9 0339 or ICD-10 A379 (other unspecified organism).

Notification data
Notification data is part of the national surveillance system for notifiable infectious diseases in the Netherlands. Information on reported cases in the system includes year of birth, four digits of the zip code, gender, date of disease onset and vaccination status. Month of birth is only provided in cases <2y of age. Furthermore, information on hospitalizations or death of the reported case is registered if known. Cases were included when a patient was notified for pertussis. Criteria for notification are 1. Clinical symptoms of pertussis (i.e. coughing for at least two weeks or either paroxysmal coughing, inspiratory whooping or vomiting after coughing) and 2. Laboratory confirmation using culture, PCR or serology or 3. Close contact to a laboratory confirmed case in the previous three weeks. Only patients which were hospitalized or death according to the notification system, were included in the respective analyses.

Data of Statistics Netherlands (death registry)
Statistics Netherlands collects and presents data and national statistics on societal and demographic aspects for scientific and political purposes [12]. Information on deceased individuals includes cause of death, gender, year of death, and age or age category at death. Cases were included for analyses when pertussis was reported as the cause of death (ICD-10 code A37).

Linkage procedure

Hospitalized cases

Prior to the actual linking procedure, the database of hospitalizations was checked for double entries of the same individual based on date of birth, gender, four digits of the zip code, date of hospitalization, date of discharge, and hospital code. Only first hospitalizations were included.

Furthermore, about 25% of notifications were supplemented with an imputed day of disease onset because this was missing. Here, the median interval between disease onset and notification from the records with a known day of disease onset (i.e. 43 days) was subtracted from the notification date.

For infants <2y, matching variables were four digits of the zip code, gender, and month and year of birth. For cases ≥2y, matching variables were identical, though without the month of birth. Matched hospitalized cases were classified as certain, likely, probable and unlikely matches (Table 1). Cases with identical matching variables and a maximum of 30 days (d) between a known day of disease onset and hospitalization were classified as certain matches. Cases with identical matching variables and an imputed day of disease onset were classified as likely matches if the interval between disease onset and hospitalization was 30d at most. Cases with an interval of 31-45d were classified as probable matches if all matching variables were identical irrespective of a known or imputed day of disease onset.

Furthermore, if there was one logical deviation in matching variables, e.g. typing errors like zip code 8013 instead of 8031, and the interval between disease onset and hospitalization was 45d at most, likelihood of matching was lowered by one category. Likewise, in case of two deviations the likelihood decreased by two categories.

Table 1: Combinations of criteria per matching category.

	0 deviations	**1 deviation**	**2 deviations**
Known disease onset, <31 days from hospitalization	Certain match	Likely match	Probable match
Imputed disease onset, <31 days from hospitalization	Likely match	Probable match	Unlikely match
Known disease onset, 31-45 days from hospitalization	Probable match	Unlikely match	No match
Imputed disease onset, 31-45 days from hospitalization	Probable match	Unlikely match	No match

First, certain matches were matched using the statistical software. Remaining cases were categorized according to matching criteria manually by two researchers independently (JH and NvdM). For these manually matched records, the Kappa statistic for observer agreement was calculated and conflicting cases were discussed until agreement was reached [13]. Analyses were performed using the number of matched cases after full agreement.

Deceased cases

Deceased cases were linked manually across the notifications and the death registry using the variables gender, year of death (available in death registry), date of notification (available in notifications), and age. Cases were linked when the date of notification was within the year of death, and all other variables were identical.

Statistical analyses

Descriptive statistics were performed regarding age and gender of included cases. Capture-recapture analyses were performed using Chao's lower bound estimator for total population size [14, 15]. The total population size (N) including the unreported cases, is estimated by identifying the number of unique cases in each source and the number of overlapping cases [14, 16]. The applied formula and corresponding 95% confidence interval (95%CI) are defined by:

Chao's lower bound estimator: $N = n + \frac{f1^2}{4f2}$

95% Confidence interval: $N \pm Z \sqrt{(\frac{f1^2}{4f2} (\frac{f1}{2f2} + 1)^2)}$

Hereby n represents the total captures, f1 represents the number of cases uniquely captured by source one plus source two, and f2 represents the number of cases that were captured by both sources.

For hospitalizations, estimates were provided for 1. certain matches only, 2. Certain and likely matches combined, 3. Certain, likely and proble matches combined and 4. All matches combined. The estimates of the total population sizes were used to calculate the completeness of reporting (CoR) of the different sources separately as a percentage of the total estimated population.

Cases were analysed in two age groups: a group with individuals less than 2 years (y) of age and a group with individuals of 2y or older. All analyses were performed using SPSS version 22.0.

Results

Hospitalizations in infants < 2 year of age

The number of infants, hospitalized for pertussis in 2007-2014 <2y equalled 876 (422 males) in the hospital data, after removal of multiple hospitalizations (n=160). Among the notifications, 757 hospitalized cases (359 males) were identified (Table 2). Median age was 2.0 months (m) in the hospital data compared with 1.0 m in the notifications. The kappa statistic on likely, probable and unlikely matches equalled 0.88 ($n_{agreement}$ =681, $n_{conflicting}$ = 30).

Table 2: Absolute number, median age (SD, range) and gender of hospitalized cases in the hospitalisation database and notifications between 2007 and 2014 divided by age group.

	Hospital data	**Notifications**
<2 years (n)	**876**	**757**
Median age, months (SD)	2.0 m (3.0)	1.0 m (3.3)
Gender, males (%)	422 (48%)	359 (47%)*
≥2 years (n)	**246**	**264**
Median age, years (SD; range)	23.5 y (27.5;2-88)	40.0 y (27.3; 2-89)
Gender, males (%)	118 (48%)	114 (43%)
Total (n)	**1122**	**1021**

*: sex was unknown for two notifications

Matches ranged between 461 (certain matches) and 542 (all matches; Table 3). This corresponded with a population estimate ranging between 1446 for certain matches and 1230 for all matches, indicating a CoR for hospital data between 61% and 71% for the respective matching categories. Likewise, within the notifications 52% to 62% was reported, respectively (Table 3).

Hospitalizations in people ≥ 2 year of age

Hospitalized cases ≥2y amounted to 246 cases (118 males) in the hospital data after removal of multiple hospitalizations (n=14) compared with 264 cases (114 males) within the notifications (Table 2). Median ages were 23.5y (range 2-88y) and 40.0y (range 2-89y) in the respective groups. The kappa statistic equalled 0.74 ($n_{agreement}$ = 414, $n_{conflicting}$ = 10).

Matches amounted to 43 for certain matches and 55 for all matching categories. The corresponding population estimate was1512 and 1182. CoR of hospital data amounted to 16.5% for certain matches and 21% for all matches. Likewise, CoR of notifications were 17.5% and 22%, respectively (Table 3).

Table 3: Number of uniquely captured hospitalized cases from hospitalisation database and notifications, matches from both databases, total hospitalized population estimates and completeness of reporting of hospitalisation data and notifications, for the period 2007-2014 and stratified by age group and matching category.

	Unique hospital data	Unique notifications	Matches	Chao's estimator (95% CI)	Completeness Hospital data (95%CI)	Completeness notifications (95%CI)
				<2 years		
Certain	415	296	461	1446 (1389–1503)	61% (58%-63%)	52% (50%-55%)
Likely	387	268	489	1363 (1315–1411)	64% (62%-67%)	56% (53%-58%)
Probably	335	216	541	1232 (1197–1267)	71% (69%-74%)	61% (59%-64%)
Unlikely	334	215	542	1230 (1195-1265)	71% (69%-74%)	62% (59%-64%)
				≥2 years		
Certain	203	221	43	1512 (1136-1888)	16.5% (14.5%-18%)	17.5% (16%-19%)
Likely	199	217	47	1444 (1106–1782)	17% (15%-19%)	18% (16%-20%)
Probably	192	210	54	1204 (951–1457)	20% (18%-23%)	22% (20%-24%)
Unlikely	191	209	55	1182 (937–1427)	21% (19%-23%)	22% (20%-25%)

Deaths in infants < 2 year of age

The number of reported deaths <2y between 1996 and 2014 equalled 13 (five males) in the death registry, and eight (four males) in the notifications (Table 4). Seven cases overlapped leading to a population estimate of 16. This indicated a CoR of 81% within the death registry, and 50% in the notifications.

Deaths in people ≥ 2 year of age

For the age group ≥2y, two deaths (both female; 10-15y and 75-80y old) were reported in the death registry, compared to eight deaths (three males; range 7-87y) in the notifications (Table 4). No overlapping cases could be identified and thus, Chao's estimator could not be calculated. Using Chapman's formula as an alternative [17], a total population estimate of 26 deaths was obtained. Hence, the CoR was 8% and 31% for the death registry and notifications, respectively.

Discussion

We studied the completeness of reporting (CoR) of hospitalizations and deaths due to pertussis in the Netherlands and showed that severe pertussis requiring hospitalization or resulting in death is substantially underestimated by combining data from three nationwide registries with information on hospitalizations and deaths. Furthermore, the CoR strongly varied between age groups and sources. For infants <2y, the estimated number of hospitalized cases was 1.5-2 times higher than reported within hospital data or notifications alone, with hospital data being more complete than notifications. For people ≥2y, the estimate was even 4-6 times higher for both sources. Likewise, for infants <2y who died following pertussis, the estimate was 1.2–2 times higher than reported through the death registry and notifications, respectively. Hereby, the death registry was more complete than the notifications. For people ≥2y, the estimate was 3-13 times higher with a higher CoR for notifications than for the death registry.

Comparable studies for hospitalized pertussis cases conducted in the United Kingdom (UK), the United States (US), and New Zealand showed a CoR of 29.6%, 23-32%, and 81-84%, respectively [18-20]. The UK and US percentages, both including all age groups, are comparable with the CoR we found in people ≥2y (16.5-22%). However, our findings for infants (CoR 52-71%) are more consistent with the New Zealand study, which focused on infants <12 months old.

In the UK, half (40-55%) of the estimated number of deaths were reported [9], compared to one third (23-33%) in the US [20]. The study population in the UK included children, and their CoR is comparable to the completeness we found for infants <2y (50-81%).

Table 4: Uniquely captured deceased cases from SN and notifications, matches from both databases, total deceased population estimates and completeness of reporting for the period 1996-2014 and stratified by age group.

Age (years)	Unique SN	Unique notifications	Matches	Chao's estimator (95%C.I.)	Completeness SN	Completeness notifications
<2	6	1	7	16 (12 - 20)	81%	50%
≥2	2	8	0	26 (0 - 55)*	8%	31%

*Calculated with Chapman's formula

However, a more recent paper on underestimation of deaths (all ages) in England found a much higher CoR (69%-79%) [21]. The completeness for the older deceased in the Netherlands (8-31%) seems to be consistent with the findings in the US (all age groups). However, similarities and dissimilarities in results of different countries must be interpreted with caution because of differences in surveillance systems and reporting criteria.

Striking differences in CoR between the sources exist; for hospitalized cases, the hospitalization registry has the highest completeness for infants <2y (61-71%), while the reporting rate was lower within the notifications (52-62%).

Several reasons for underreporting in the registries may play a role. Pertussis notifications, covering pertussis in primary care as well as hospitalizations, are based on laboratory confirmation and Municipal Health Services report as early as possible. Municipal Health Services sometimes do not receive follow-up information on hospitalizations and deaths and therefore cannot incorporate this information in the notification. If additional information on hospitalization and death becomes available, additional actions from several professionals are needed to incorporate this in the notification system, which are not always carried out. Also, diagnostics for pertussis are often not performed, since this has no consequences for treatment. For these reasons, both for notifications and hospitalizations, under-ascertainment of pertussis must be taken into account. For pertussis as the cause of or death, misclassification is also likely to be the case. Because pertussis is an unclear cause of death, at least in adults, many doctors or coroners will not report pertussis as the cause of death; they might use pneumonia or other complications related to pertussis instead [9, 22].

The reliability of the capture-recapture estimates depends on the possible violation of the underlying assumptions. First, independency of sources is assumed. In our study, positive dependency between sources is likely. Reporting parties mainly involve healthcare professionals reporting to both sources. Therefore, our results might underestimate the true hospitalized and deceased population.

The second assumption implies that every individual should have homogeneous chances for being captured by a certain source [16]. As differences in reporting and ascertainment are well established between young infants and older individuals, stratified analyses were conducted to prevent violation of this assumption. The cut-off at 2y was also chosen because different matching criteria could be used in both groups. Furthermore, all individuals should be within the time-space unit of study and no false positive cases should be in the study population. Inclusion of cases was based on the medical diagnosis and ICD codes. In general, in the Netherlands, pertussis diagnosis is laboratory confirmed (data not shown). Therefore, we think false positives are of minor influence. Finally, capture-recapture analysis assumes a closed study population. Due to the length of the study period, violation of this assumption is

inevitable. This might have resulted in an overestimation of the true population size [23, 24].

Cases should be matched properly to obtain an adequate estimate [16]. Ideally, linkage is based on a unique identifier to prevent mismatch of cases, but due to privacy legislation, in the Netherlands such a number is not available. Due to the lack of additional information on the deceased in the death registry such as date of birth or four digits of the zip code, some uncertainty remained in the linkage, i.e. the possibility of inclusion of false positive- and false negative matches. Twins in the datasets might have complicated linking as well. In addition, we might have missed hospitalized matches based on the range between disease onset and hospitalization. Rare cases in which more time between disease onset and hospitalization elapsed (>45d), were not matched. Moreover, the exclusion of multiple hospital registrations might also have caused missing matches, as only first hospitalizations were included. However, it was assumed that the missing of matching due to this exclusion was limited, as in regular cases, the disease onset would be closest in time to the first hospitalization.

Besides the capture-recapture assumptions, limitations to the current study include the incompleteness of the National Registration Hospital Care data; approximately 90% of all Dutch hospitals supply data. Therefore, our total population estimates can be either an over-estimation because matches were missed, or an underestimation of the real number of cases, since 10% of the entire population might not be included. Because the notifications are extracted from a nationwide registry that was linked to hospital data with 90% coverage, over-estimation of the total population estimate is more likely than under-estimation. Moreover, a two-source capture-recapture analysis was used, which could not include possible interactions between sources. In theory, a person could have different postal codes in the respective registries, e.g. due to a divorce of moving, unjust preventing a match. However, in the Netherlands, all people are only registered at their main home address and only records with a restricted, narrow time interval of 45 days were included. Therefore, we think these aspects had very limited impact on our results. Finally, the ICD codes that were used for case inclusion might have contained false-positives. These might have caused the over-estimations.

Despite these limitations, we think our data give a crude estimate of the CoR for hospitalizations and deaths and indicate substantial underreporting.

Increased awareness of occurrence of pertussis by public and professionals, increased diagnostics, correct registration of the diagnosis and sufficient follow up time to include hospitalizations and death in the notifications can help to decrease underreporting in the registries used. This is important in view of a reliable evaluation of the current National Immunization Program and possible changes in the programme, e.g. the introduction of pertussis vaccination during pregnancy.

References

1. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev. 2005;18(2):326-82.

2. de Greeff SC, Mooi FR, Westerhof A, Verbakel JM, Peeters MF, Heuvelman CJ, et al. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis. 2010;50(10):1339-45. Epub 2010/04/08.

3. van der Maas NA, Mooi FR, de Greeff SC, Berbers GA, Spaendonck MA, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? Vaccine. 2013;31(41):4541-7. Epub 2013/08/13.

4. Van Lier A, Oomen P, Giesbers H, Van Vliet H, Drijfhout I, Zonnenberg-Hoff IF, et al. Immunisation coverage National Immunisation Programme in the Netherlands; year of report 2016. Bilthoven: National Institute for Public Health and the Environment, 2016 2016-0064.

5. de Greeff SC, Mooi FR, Schellekens JF, de Melker HE. Impact of acellular pertussis preschool booster vaccination on disease burden of pertussis in The Netherlands. Pediatr Infect Dis J. 2008;27(3):218-23. Epub 2008/02/19.

6. Mooi FR, Van Der Maas NA, De Melker HE. Pertussis resurgence: waning immunity and pathogen adaptation - two sides of the same coin. Epidemiol Infect. 2014;142(4):685-94.

7. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. Emerg Infect Dis. 2000;6(4):348-57. Epub 2000/07/25.

8. de Melker HE, Versteegh FG, Schellekens JF, Teunis PF, Kretzschmar M. The incidence of Bordetella pertussis infections estimated in the population from a combination of serological surveys. J Infect. 2006;53(2):106-13. Epub 2005/12/15.

9. Crowcroft NS, Andrews N, Rooney C, Brisson M, Miller E. Deaths from pertussis are underestimated in England. Arch Dis Child. 2002;86(5):336-8. Epub 2002/04/24.

10. Data DH. Gebruikershandleiding Landelijke Basisregistratie Ziekenhuiszorg (LBZ) 2014. Utrecht: Dutch Hospital Data; 2014 [10-10-2016]; Available from: https://www.dhd.nl/klanten/klantenservice/handleidingen_formulieren/Documents/Handleiding%20LBZ.pdf.

11. Schurink-van 't Klooster TM. the National Immunisation Programme in the Netherlands; surveillance and developments in 2015-2016. Bilthoven: National Institute for Public Health and the Environment, 2016 2016-0141.

12. Netherlands S. Gebieden in Nederland [Areas in the Netherlands]. Den Haag: statistics Netherlands; [cited 2017 13-04-2017]; Available from: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=81498ned&D1=0-1,47-48&D2=a&HDR=T&STB=G1&VW=T.

13. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

14. Brittain S, Bohning D. Estimators in capture–recapture studies with two sources. AStA Advances in Statistical Analysis. 2008;93(1):23-47.

15. Chao A. Estimating the population size for capture-recapture data with unequal catchability. Biometrics. 1987;43(4):783-91.

16. Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. Epidemiol Rev. 1995;17(2):243-64.

17. Chapman DG. The estimation of biological populations. the Annals of Mathematical Statistics. 1954;25:1-15.

18. Devine MJ, Bellis MA, Tocque K, Syed Q. Whooping cough surveillance in the north west of England. Commun Dis Public Health. 1998;1(2):121-5.
19. Somerville RL, Grant CC, Grimwood K, Murdoch D, Graham D, Jackson P, et al. Infants hospitalised with pertussis: estimating the true disease burden. J Paediatr Child Health. 2007;43(9):617-22. Epub 2007/07/05.
20. Sutter RW, Cochi SL. Pertussis hospitalizations and mortality in the United States, 1985-1988. Evaluation of the completeness of national reporting. JAMA. 1992;267(3):386-91.
21. van Hoek A, Campbell H, Amirthalingam G, Andrews N, Miller E. The number of deaths among infants under one year of age in England with pertussis: results of a capture/recapture analysis for the period 2001 to 2011. Euro Surveill. 2013;18(9). Epub 2013/03/09.
22. Kristensen M, van Lier A, Eilers R, McDonald SA, Opstelten W, van der Maas N, et al. Burden of four vaccine preventable diseases in older adults. Vaccine. 2016;34(7):942-9.
23. van Hest NA, Grant AD, Smit F, Story A, Richardus JH. Estimating infectious diseases incidence: validity of capture-recapture analysis and truncated models for incomplete count data. Epidemiol Infect. 2008;136(1):14-22.
24. van Hest NA, Smit F, Baars HW, De Vries G, De Haas PE, Westenend PJ, et al. Completeness of notification of tuberculosis in The Netherlands: how reliable is record-linkage and capture-recapture analysis? Epidemiol Infect. 2007;135(6):1021-9.

Chapter 4

Pertussis hospitalizations among term and preterm infants: clinical course and vaccine effectiveness.

Nicoline A.T. van der Maas
Elisabeth A. M. Sanders
Florens G. A. Versteegh
Albertine Baauw
Anneke Westerhof
Hester E. de Melker

Submitted to CID

Abstract

Background

Pertussis causes severe disease in young unvaccinated infants with preterms potentially at highest risk. We studied the clinics of infants hospitalized for pertussis, related to gestational age (GA) and vaccination.

Methods

Hospitalization data of pertussis patients (0-2y) over 2005-2014 were linked to the vaccination registry. Multivariable logistic regression was used to study the association between GA and vaccination history on the clinical disease course. We compared vaccine effectiveness (VE) against pertussis hospitalization between terms and preterms using the screening method.

Results

Of all 1187 records, medical data from 676 were retrieved. Of these, 12% concerned preterms with 8% preterms present in Dutch birth cohorts. Median age at admission was 3m for preterms and 2m for terms ($p<0.001$). Preterms more often had received pertussis vaccinations (62% vs 44%; $p=0.01$) and were more often diagnosed with coinfection (37% vs 21%; $p=0.01$). Preterms tended to suffer more often from complications or required artificial respiration and intensive care (ICU) admittance, with longer ICU stay (15d vs 9d; $p=0.004$).

Vaccinated infants had a lower median length of stay and crude risks of apneas, artificial respiration, additional oxygen and ICU admittance. VE against pertussis hospitalizations of the first vaccination was 95% (95%CI 93%-96%) and 73% (95%CI 20%-91%) in terms and preterms, respectively.

Conclusions

Infants hospitalized for pertussis suffer from severe disease. Preterms were overrepresented with higher need for intensive treatment and less VE of first vaccination. This stresses the need for alternative prevention, in particular maternal pertussis vaccination, to effectively reduce pertussis in both groups.

Introduction

Pertussis or whooping cough is a highly contagious respiratory tract infection, mostly caused by *Bordetella pertussis* and less frequently by *Bordetella parapertussis* [1].Before mass immunization programmes, in particular infants and children contracted pertussis in the first years of life with a clinical course characterized by uncontrollable coughing attacks, often accompanied by paroxysms, post-tussive vomiting and inspiratory whooping. Vaccination with continuous high vaccination coverage led to a substantial decrease of pertussis among infants and children [2, 3], but newborns too young to be (fully) vaccinated remain at high risk for severe complications, including apnea, cyanosis, pneumonia, encephalopathy or even death. This risk is increasing due to the worldwide pertussis reemergence in the nineties of the previous century, even under high vaccination coverage among all age groups with transmission of disease from household members to newborns. Today, high pertussis incidences in young infants are observed with peaks in disease incidence every two to three years [3-5]. For this reason, many countries nowadays offer maternal pertussis vaccination to protect newborns. In the Netherlands, the Dutch Health Council also advised to offer maternal pertussis vaccination in the 3rd trimester of pregnancy. While this strategy is overall very effective in prevention of pertussis in early infancy, preterms may benefit less due to less transfer time of protective antibodies from mother to child before delivery [6, 7]. In the light of the introduction of maternal vaccination strategy against pertussis in The Netherlands, we sought to gain more insight into the current pertussis burden among hospitalized infants, with special attention for preterm infants.

Methods and materials

Data sources

National Registration Hospital care

Hospital Care data include main diagnosis as well as date of birth, four digits of the zip code, gender, and date of admission of hospitalized patients or outpatient treatment [8]. We extracted medical records of 0-2 year old patients with a primary diagnosis of whooping cough between 2005 and 2014 according to the International Classification of Diseases (ICD) codes, i.e. ICD-9 0330 or ICD-10 A370 (caused by *B. pertussis*), ICD-9 0331 or ICD-10 A371 (*B. parapertussis*), ICD-9 0338 or ICD-10 A378 (other specified organism) or ICD-9 0339 or ICD-10 A379 (other unspecified organism).

Setting, data collection and linkage

After written approval from the hospital board, data extraction from medical records was performed by trained medical students, supervised by a medical doctor (NvdM). Besides date of birth, sex and postal code, demographic data on gestational age (GA) and birth weight were collected. Furthermore, clinical symptoms at admission, date of

admission and discharge, diagnostics to confirm pertussis and details about the medical situation, complications, treatments and clinical status at discharge were extracted.
Medical record data were linked to the national vaccination registry, including all 0-18y old children. Changes in residence are archived within the register. In both datasets, pseudonyms were created based on date of birth, sex and postal code. Of infants who moved over time, pseudonyms were created based on all known postal codes to a maximum of six.
To ensure privacy, a Trusted Third Party was used for steps in data collection and data linking. (Figure 1) Researchers were only allowed to use age in rounded months.
Medical ethical approval was not needed because people were not subjected to imposed rules or acts. Informed consent of patients was not necessary because the study served public interest and asking permission was not feasible[9].

Statistical analysis

Differences in general characteristics and clinical aspects of pertussis between preterms, defined as born before 37w GA, and terms were described and tested using Pearson's Chi Square or Fisher's exact test for dichotomous and categorical variables and student t-test or Wilcoxon rank test for continuous variables.
Multivariable logistic regression was performed to assess the association between preterm delivery and the clinical picture of pertussis and to study the association between pertussis vaccination and clinical characteristics stratified by gestational age. Both analyses were adjusted for age at hospitalization and coinfections.
Vaccine effectiveness (VE), stratified for preterms and terms, was computed using the screening method [10]. Hereby we used monthly cumulative coverage estimates of a timely first dose, stratified by preterms and terms [11].
In the main analysis, children without exact GA but with written information of a term pregnancy and infants without information on GA were both classified as terms. In sensitivity analyses, we only included children with known GA.
Analyses were performed using SAS version 9.4. A p-value <0.05 was considered statistically significant. Furthermore, terms were set as reference in all analyses.

Results

General descriptives

Of the 87 invited hospitals, 4/8 university-, 19/26 top clinical- and 27/51 local hospitals participated. Overall, data of 57% of eligible cases (676/1187) were available.

GA was known for 61% of all children. Of the remaining 39% GA, information on a term pregnancy was recorded in 8.6%. When all medical records were taken into account, 11.8% (95%CI 9.6%-14.4%; n=80) were born preterm (median GA 35w, range 26w – 36w) compared to an overall 7.8% prematurity in birth cohorts in the Netherlands [12].

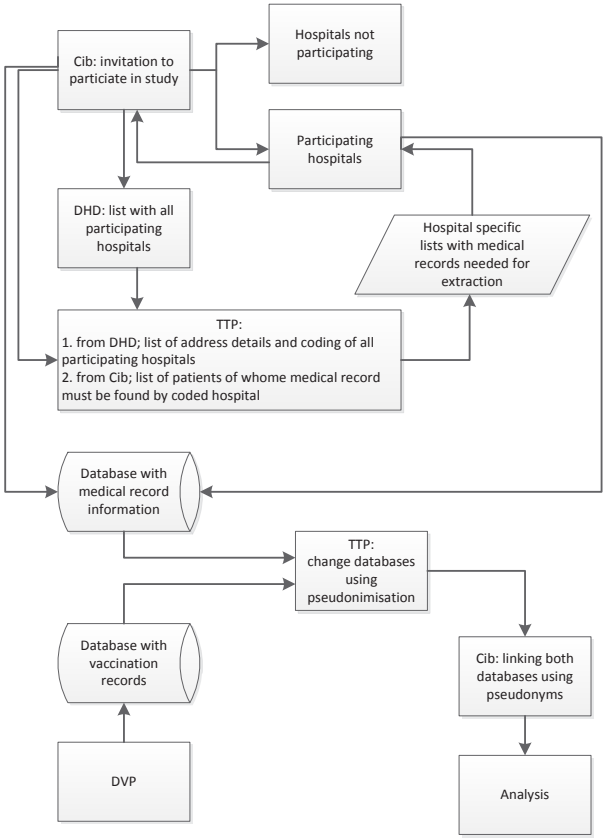


Figure 1. Flowchart of study logistics
CIb = Centre for Infectious Disease Control TTP = Trusted Third Party
DHD = Dutch Hospital Data, collector of hospital discharge data
DVP = Department for Vaccine Supply and Prevention Programmes, manager of vaccination registry

Among term and preterm infants, respectively 81% and 75% of medical records could be linked to vaccination data. Pseudonyms of the remaining records were too unspecific for reliable linkage.

Main analyses (n=676)

Hospitalization

Median age at hospitalization was 2 months. (Table 1) Terms were hospitalized at younger age. Median duration of hospitalization was 5 and 6 days for terms and preterms, respectively. Overall, 46% of infants were vaccinated at admission, with statistically significant higher frequencies in preterms than in terms.

Clinical course and treatment

On admittance, 93% of infants were coughing, with 73% also having coughing attacks. (Table 1) Other classical pertussis symptoms such as wheezing, whooping, vomiting and apneas were reported in up to 35% of the patients. With the exception of cyanosis that was more often reported in terms than in preterms (44% vs 31%; p=0.03), we found no differences in solicited symptoms ad admission between terms and preterms.

Complications, like bradycardia, respiratory insufficiency and desaturation, feeding problems and weight loss and pneumonia were reported in 9% of infants, with a slightly (not-significant) higher frequency in preterms. (Table 1) Two term infants, too young to be eligible for vaccination, had died due to pertussis.

Twenty percent of infants already had received antibiotics before admission, while 81% received antibiotics during hospitalization. (Table 1) Though preterms were slightly more often treated with intravenous antibiotics, start and duration of antibiotics was comparable between the two groups. We found similar need for additional oxygen (37% vs 34%) and admittance to pediatric intensive care unit (PICU; 13% vs 10%), though a trend to more often need of artificial respiration was observed in preterms compared to terms(14% vs 7%; p=0.05). Duration of ICU stay was longer in preterms than in terms (median 15 vs 9 days; p=0.004).

At discharge, 77% of infants still suffered from complaints, with the vast majority still coughing. (Table 1) Likewise, 14% needed re-admittance within 6 weeks after discharge. Both frequencies were somewhat lower in preterms compared to terms.

Diagnostics

For 91% of infants, information on diagnostics to confirm pertussis was found in the medical record.(Table 1) In 5% we found evidence of all three diagnostic procedures (i.e. culture, polymerase chain reaction (PCR) and serology), whereas in 25% and 64% of infants evidence of respectively two and one diagnostic was found.

Leukocyte data were available for one third of the medical records, with median highest value of 17.2 (range 4.3-106.1) with somewhat lower values in preterms. (Table 1) Likewise, C-reactive protein (CRP) was available for 21% of records with lower median CRP in terms than preterms (4.7 vs 15; p=0.007).

In 53% of the infants, diagnostics for other pathogens were performed. (Tables 1&2) Overall, preterms were more often tested (61% vs 51%; p0.2) and diagnosed (36.7%

vs 20.6%; p=0.01) with coinfections than terms. Respiratory syncytial virus (RSV), influenzavirus, adenovirus, human meta-pneumovirus, para-influenzavirus, rhinovirus and mycoplasma pneumoniae were observed in 21% to 57% of tested cases, with RSV, para-influenzavirus and Chlamydia trachomatis more often observed in preterms, although Chlamydia was only rarely observed. (Table2)

Assessment of the influence of age at hospitalization and coinfections on the clinical picture

Multivariable logistic regression analysis on clinical course and treatment of pertussis, adjusted for age at hospitalization and coinfections, did not change the trends, described above. (Table 3) In case of apnea, preterms showed an increased risk after adjustment (OR 1.8; 95%CI 1.0-3.3).

Being vaccinated was associated with a reduction in the median duration of hospitalization among both terms (9 vs 3 days; p<0.0001) and preterms (13 vs 5 days; p=0.01). A lower median duration of Intensive Care admission was found among vaccinated preterms (8 vs20 days; p=0.1), but not in terms. Vaccination was significantly associated with a lower crude risk of apneas, artificial respiration, additional oxygen and ICU admittance both in terms and preterms. (Table 4) Furthermore, vaccination appeared to reduce the crude risk of complications and prescription of antibiotics during admission in terms, but the crude risk of antibiotic prescription before admission appeared higher among the vaccinated term group. After adjustment for coinfections and age at admittance, differences were no longer significant except the lower need of oxygen treatment in vaccinated terms.

Influence of vaccination and vaccine effectiveness

Among preterm infants, vaccine effectiveness (VE) of the first infant dose, i.e.at 2 months of age, was 73% (95%CI 20%-91%) compared to 95% (95%CI 93%-96%) among term infants. (Table 5) VE of the second dose of the primary vaccination series did not differ between the groups.

Sensitivity analyses; n=468

Taken into account only those infants with known gestational age, findings of the analyses were similar, i.e. analyses in relation to preterm delivery (n=468), vaccination status (n=379) and VE estimates (not all data shown). (Table1, 2 and 5)

Table 1. Clinical course, diagnostic tests and treatment of pertussis in term and preterm infants. Denominator is the number of infants in the group, given in the column headings, unless specified in the respective cells.

	Total group (n=676)	Probable and certain term infants (n=596)[a]	Certain term infants (n=388)[b]	Preterm infants (n=80)
Characteristics of hospitalization, clinical course and treatment				
Boys; n (%)[1]	335 (49.6%)	295 (49.5%)	185 (47.7%)	40 (50%
Age at hospitalization in months; median (range)	2.0 (0-36)	2.0 (0-35)	2.0 (0-35)	3.0 (0-25)[c,d]
Duration of total hospitalization in days; median (range)	5.0 (1-51)	5.0 (1-51)	5.0 (1-51)	6.0 (1-49)
Admission intensive care unit (ICU); n (%)	69 (10.2%)	59 (9.9%)	50 (12.9%)	10 (12.5%)
Duration ICU stay in days; median (range)	9 (2-34)	9 (2-25)	9 (2-25)	15 (8-34)[c,d]
Vaccinated at admission; n (%)	250/541 (46.2%)	213/481 (44.3%)	130/319 (40.7%)	37/60 (61.7%)[c,d]
Coughing attacks; n (%)	494 (73.1%	438 (73.5%)	280 (72.2%)	56 (70.0%)
Apnea; n (%)	110 (16.3%)	92 (15.4%)	71 (18.3%)	18 (22.5%)
Whooping; n (%)	24 (3.6%)	23 (3.9%)	18 (4.6%)	1 (1.3%)
Vomiting; n (%)	238 (35.2%)	210 (35.2%)	146 (37.6%)	28 (35.0%)
Wheezing at inspiration; n (%)	49 (7.3%)	42 (7.1%)	33 (8.5%)	7 (8.8%)
Collapse; n (%)	8 (1.2%)	6 (1.0%)	5 (1.3%)	2 (2.5%)
Cyanosis; n (%)	284 (42.0%)	259 (43.5%)	176 (45.4%)	25 (31.3%)[c,d]
Fever; n (%)	60 (8.9%)	52 (8.7%)	33 (8.5%)	8 (10.0%)
Feeding problems; n (%)	212 (31.4%)	185 (31.0%)	133 (34.3%)	27 (33.8%)
Any complication[e]; n (%)	63 (9.3%)	53 (8.9%)	39 (10.1%)	10 (12.5%)
Antibiotics before admission; n (%)	131/657 (19.9%)	114/580 (19.7%)	66/377 (17.5%)	18/77 (23.4%)
Antibiotics during admission; n (%)	543/674 (80.5%)	475/587 (80.9%)	313/382 (81.9%)	68/78 (87.2%)
Intravenous antibiotics during admission; n (%)	12/403 (3.0%)	9/357 (2.5%)	6/244 (2.5%)	3/46 (6.5 %)

Duration of antibiotic use in days; median (range)	6 (0-28)	6 (0-28)	5 (0-28)	5.5 (1-18)
Artificial respiration; n (%)	50/654 (7.7%)	39/577 (6.8%)	32/375 (8.5%)	11/77 (14.3%)[c]
Additional oxygen; n (%)	226/661 (34.2%)	198/585 (33.9%)	150/382 (39.3%)	28 (36.8%)
Symptoms remaining; n (%)	518 (76.6%)	460 (77.2%)	298 (76.8%)	58 (72.5%)
Re-admittance <6w after discharge; n (%)	94 (14.0%)	85 (14.3%)	56 (14.4%)	9 (11.4%)
Diagnostics				
Pertussis test; Culture, PCR and serology; n (%)	34 (5.0%)	31 (5.2%)	24 (6.2%)	3 (3.8%)
Pertussis test; Culture and PCR; n (%)	59 (8.7%)	52 (8.7%)	40 (10.3%)	7 (8.8%)
Pertussis test; PCR and serology; n (%)	84 (12.4%)	73 (12.2%)	41 (10.6%)	11 (13.8%)
Pertussis test; Culture and serology; n (%)	24 (3.6%)	24 (4.0%)	17 (4.4%)	0 (0%)
Pertussis test; Culture; n (%)	37 (5.5%)	29 (4.9%)	18 (4.6%)	8 (10%)
Pertussis test; PCR; n (%)	329 (48.7%)	290 (48.7%)	194 (50%)	39 (48.8%)
Pertussis test; Serology; n (%)	69 (10.2%)	61 (10.2%)	36 (9.3%)	8 (10%)
Unknown diagnostic test for pertussis; n (%)	40 (5.9%)	36 (6.0%)	18 (4.6%)	4 (5%)
Result leukocyte counting result; n (%)	225/476 (47.3%)	200/421 (47%)	141/276 (51.1%)	25/55 (45%)
Leukocyte count; median (range)	17.2 (4.3-106.1)	17.7 (5.3-106.1)	17.2 (5.3-74.3)	13.5 (4.3-64.0)
result C-reactive protein; n (%)	142/392 (36.2%)	119/344 (35%)	81/231 (35.1%)	23/48 (48%)
C-reactive protein; median (range)	5 (0-415)	4.7 (0-415)	5 (0-415)	15 (0-363)[c,d]
Positive co-infections; n (%)	81/355 (22.8%)	63/306 (20.6%)	46/208 (22.1%)	18/49 (36.7%)[c,d]
Prescribed antibiotics before admission				
Amoxicillin	49/132 (37%)	38/114 (33%)	23/66 (35%)	11/18 (65%)
Azithromycin	24/132 (18%)	21/114 (18%)	17/66 (26%)	3/18 (18%)
Ceftriaxone	1/132 (1%)	1/114 (1%)	1/66 (2%)	
Clarithromycin	41/132 (31%)	38/114 (33%)	17/66 (26%)	3/18 (18%)

Erythromycin	7/132 (5%)	6/114 (5%)	2/66 (3%)	1/18 (6%)
Feneticillin	1/132 (1%)	1/114 (1%)	1/66 (2%)	
Trimethoprim	1/132 (1%)	1/114 (1%)	1/66 (2%)	
unknown	7/132 (5%)	8/114 (7%)	4/66 (6%)	0/18 (0%)
Prescribed antibiotics during admission				
Amoxicillin	11/543 (2%)	10/475 (2%)	7/313 (2%)	1/68 (1%)
Azithromycin	170/543 (31%)	146/475 (31%)	98/313 (31%)	24/68 (35%)
Cephotaxim	1/543 (0.2%)			1/68 (1%)
Clarithromycin	314/543 (58%)	280/475 (59%)	184/313 (59%)	34/68 (50%)
Erythromycin	44/543 (8%)	37/475 (8%)	23/313 (7%)	7/68 (10%)
unknown	3/543 (0.6%)	2/475 (0.4%)	1/313 (0.3%)	1/68 (1%)
Specific complications				
conjunctivitis	5 (0.7%)	5 (0.8%)	1 (0.3%)	0 (0%)
convulsion	5 (0.7%)	5 (0.8%)	4 (1.0%)	0 (0%)
encephalopathy	1 (0.2%)	1 (0.2%)	1 (0.3%)	0 (0%)
pneumonia	11 (1.6%)	9 (1.5%)	7 (1.8%)	2 (2.5%)
otitis media	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
death	2 (0.3%)	2 (0.3%)	2 (0.5%)	0 (0%)
bradycardia	8 (1.2%)	7 (1.2%)	6 (1.6%)	1 (1.3%)
cardio-respiratory insufficiency	7 (1.0%)	5 (0.8%)	4 (1.0)	2 (2.5%)
desaturation	20 (3.0%)	18 (3.0%)	14 (3.6%)	2 (2.5%)
feeding problems	5 (0.7%)	2 (0.3%)	0 (0%)	3 (3.8%)
weight loss	12 (1.8%)	11 (1.9%)	8 (2.1%)	1 (1.3%)
dehydration	1 (0.2%)	1 (0.2%)	1 (0.3%)	0 (0%)

drip-feed	4 (0.6%)	2 (0.3%)	1 (0.3%)	2 (2.5%)
gastroenteritis	3 (0.4%)	2 (0.3%)	2 (0.5%)	1 (1.3%)
sepsis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
hyperleukocytosis	2 (0.3%)	1 (0.2%)	0 (0%)	1 (1.3%)
metabolic alkalosis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
hypotonia	2 (0.3%)	1 (0.2%)	1 (0.3%)	1 (1.3%)

[a]: term infants in main analysis

[b]: term infants in the sensitivity analysis

[c]: significant difference ($p<0.05$) between certain+ probable terms and preterms (main analysis)

[d]: significant difference ($p<0.05$) between certain terms and preterms (sensitivity analysis)

[e]: specific complications are listed at the end of the table

Table 2. Number (%) of co-infections in term and preterm infants. Denominators are specified per cell.

	Total group (n=676)	**Probable and certain term infants (n=596)[a]**	**Certain term infants (n=388)[b]**	**Preterm infants (n=80)**
Respiratory syncytial virus	62/293 (21%)	49/257 (19%)	34/169 (20%)	13/36 (36%)[c,d]
Influenza	38/112 (34%)	29/93 (31%)	22/62 (35%)	9/19 (47%)
Adenovirus	35/98 (36%)	27/82 (33%)	18/51 (35%)	8/16 (50%)
Human metapneumovirus	28/81 (35%)	22/68 (32%)	12/37 (32%)	6/13 (46%)
parainfluenzavirus	25/76 (33%)	18/65 (28%)	12/43 (28%)	7/11 (64%)[c,d]
Rhinovirus	40/70 (57%)	33/59 (56%)	25/40 (63%)	7/11 (64%)
Mycoplasma pneumoniae	19/65 (29%)	15/55 (27%)	10/33 (30%)	4/10 (40%)
Astrovirus	0/1 (0%)	not tested	not tested	0/1 (0%)
Bocavirus	9/16 (56%)	5/12 (42%)	4/9 (44%)	4/4 (100%)
Campylobacter	0/3 (0%)	0/3 (0%)	0/1 (0%)	not tested
Candida albicans	2/2 (100%)	2/2 (100%)	1/1 (100%)	not tested
Chlamydophila pneumoniae	12/29 (41%)	12/25 (48%)	9/15 (60%)	0/4 (0%)
Chlamydia psittaci	0/1 (0%)	0/1 (0%)	not tested	not tested
Chlamydia trachomatis	2/9 (22%)	0/7 (0%)	0/5 (0%)	2/2 (100%)[c,d]
Cytomegalovirus	4/12 (33%)	2/9 (22%)	2/6 (33%)	2/3 (67%)
Coronavirus	18/32 (56%)	14/28 (50%)	9/16 (56%)	4/4 (100%)
Coxiella burnetii	0/7 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
Coxackievirus	0/1 (0%)	0/1 (0%)	not tested	not tested
Echovirus	1/4 (25%)	0/2 (0%)	0/1 (50%)	1/2 (50%)
E.coli	2/2 (100%)	2/2 (100%)	2/2 (100%)	not tested
Enterovirus	9/23 (39%)	8/19 (42%)	6/15 (40%)	1/4 (25%)
Haemophilus influenzae	3/4 (75%)	3/4 (75%)	3/3 (100%)	not tested
Haemolytic streptococ	2/2 (100%)	2/2 (100%)	1/1 (100%)	not tested
Herpes simplex virus	0/5 (0%)	0/4 (0%)	0/4 (0%)	0/1 (0%)
Klebsiella oxytoca	1/1 (100%)	not tested	not tested	1/1 (100%)
Klebsiella pneumoniae	2/2 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Legionella	3/7 (43%)	3/6 (50%)	3/5 (60%)	0/1 (0%)
Moraxella catarrhalis	5/5 (100%)	4/4 (100%)	3/3 (100%)	1/1 (100%)
Norovirus	1/2 (50%)	1/1 (100%)	1/1 (100%)	0/1 (0%)
Bordetella parapertussis	0/5 (0%)	0/3 (0%)	0/3 (0%)	0/2 (0%)
Parechovirus	0/3 (0%)	0/2 (0%)	0/2 (0%)	0/1 (0%)
Parvovirus	0/2 (0%)	0/2 (0%)	0/2 (0%)	not tested
Picornavirus	2/2 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Plesiomonas shigelloides	0/1 (0%)	0/1 (0%)	not tested	not tested
Pseudomonas aeruginosa	1/1 (100%)	not tested	not tested	1/1 (100%)
Rotavirus	7/22 (32%)	5/17 (29%)	4/11 (36%)	2/5 (40%)
Salmonella	1/3 (33%)	1/3 (33%)	0/1 (0%)	not tested
Streptococcus pneumoniae	3/3 (100%)	1/1 (100%)	1/1 (100%)	2/2 (100%)
Sapovirus	0/1 (0%)	0/1 (0%)	0/1 (0%)	not tested
Shigella	0/3 (0%)	0/3 (0%)	0/1 (0%)	not tested
Staphylococcus aureus	8/11 (72.7%)	7/10 (70%)	6/8 (75%)	1/1 (100%)

Toxoplasma	0/1 (0%)	0/1 (0%)	0/1 (0%)	not tested
Yersinia	0/1 (0%)	0/1 (0%)	not tested	not tested

Table 3. Multivariable logistic regression analyses of the association between premature delivery and clinical course and treatment of pertussis; crude and adjusted Odds Ratios (OR) and 95% Confidence intervals (95%CI). Term infants are set as reference. Significant results are in bold.

		Crude OR (95%CI)	Adjusted OR (95%CI)*
Symptoms at admission	Coughing attacks	0.8 (0.5-1.4)	0.8 (0.5-1.4)
	Apnea	1.6 (0.9-2.8)	**1.8 (1.0-3.3)**
	Whooping	0.3 (0.04-2.4)	0.3 (0.04-2.3)
	Vomiting	1.0 (0.6-1.6)	1.0 (0.6-1.6)
	Wheezing at inspiration	1.3 (0.5-2.9)	1.2 (0.5-2.7)
	Collapse	2.5 (0.5-12.7)	3.8 (0.7-19.7)
	Cyanosis	0.6 (0.4-1.0)	0.7 (0.4-1.1)
	Fever	1.2 (0.5-2.6)	0.9 (0.4-2.0)
	Feeding problems	1.1 (0.7-1.9)	1.1 (0.7-1.9)
Complications	Any complication	1.5 (0.7-3.0)	1.6 (0.8-3.4)
Treatment	Antibiotics before admission	1.1 (0.6-2.0)	1.1 (0.6-1.9)
	Antibiotics during admission	1.5 (0.7-3.2)	1.8 (0.9-3.9)
	Artificial respiration	**2.3 (1.1-4.8)**	**2.8 (1.3-6.0)**
	Additional oxygen	1.1 (0.7-1.9)	1.3 (0.8-2.2)
	Admission intensive care unit (ICU)	1.3 (0.6-2.7)	1.6 (0.8-3.6)
Discharge	Symptoms remaining	0.8 (0.5-1.3)	0.8 (0.5-1.4)

*: adjusted for coinfections and age in months ad admission.

Table 4. Multivariable logistic regression analysis of the association between vaccination against pertussis and clinical course and treatment of pertussis, stratified for term and preterm infants; crude and adjusted Odds Ratios (OR) and 95% Confidence intervals (95%CI). Unvaccinated infants are set as reference. Significant results are in bold.

		crude OR (95%CI) term infants	crude OR (95%CI) preterm infants	p-value[a]	Adjusted OR (95%CI) term infants[b]	Adjusted OR (95%CI) preterm infants[b]	p-value[a]
Symptoms at admission	Coughing attacks	0.9 (0.6-1.3)	0.8 (0.3-2.7)	0.9	0.8 (0.4-1.3)	0.8 (0.1-5.6)	0.9
	Apnea	**0.5 (0.3-0.9)**	**0.2 (0.05-0.7)**	0.1	0.6 (0.3-1.1)	0.2 (0.03-1.5)	0.1
	Whooping	2.6 (0.96-7.1)	<0.001 (<0.001->999.9)	0.9	1.8 (0.5-6.8)	0.4 (<0.001->999.9)	0.9
	Vomiting	1.1 (0.8-1.6)	1.0 (0.3-3.0)	0.9	0.9 (0.6-1.6)	0.6 (0.1-3.3)	0.9
	Wheezing at inspiration	1.7 (0.8-3.3)	2.7 (0.3-25.4)	0.7	1.0 (0.4-2.3)	1.6 (0.1-26.1)	0.7
	Collapse	1.3 (0.2-9.0)	0.6 (0.04-10.3)	0.7	7.2 (0.2-226.7)	0.6 (<0.001->999.9)	0.8
	Cyanosis	0.8 (0.6-1.1)	3.1 (0.9-10.0)	**0.03**	1.1 (0.7-1.8)	1.9 (0.3-11.6)	**0.02**
	Fever	1.6 (0.8-3.1)	1.3 (0.2-7.6)	0.8	0.7 (0.3-1.7)	>999.9 (<0.001->999.9)	0.8
	Feeding problems	0.9 (0.6-1.3)	0.6 (0.2-1.8)	0.6	0.9 (0.5-1.4)	0.8 (0.2-4.5)	0.6
Complications	Any complication	**0.4 (0.2-0.8)**	0.3 (0.07-1.5)	0.9	0.9 (0.4-2.5)	0.2 (0.01-4.6)	0.9
Treatment	Antibiotics before admission	**1.8 (1.2-2.8)**	2.7 (0.6-11.4)	0.7	1.2 (0.7-2.1)	12.3 (0.8-188.3)	0.7
	Antibiotics during admission	**0.4 (0.3-0.7)**	0.3 (0.03-2.8)	0.8	0.7 (0.4-1.3)	1.7 (0.1-23.7)	0.7
	Artificial respiration	**0.3 (0.1-0.7)**	**0.1 (0.02-0.7)**	0.4	0.8 (0.2-3.4)	0.4 (0.02-5.7)	0.5
	Additional oxygen	**0.2 (0.1-0.3)**	**0.2 (0.08-0.8)**	0.7	**0.3 (0.2-0.5)**	0.6 (0.09-4.0)	0.5
	Admission intensive care unit (ICU)	**0.1 (0.05-0.3)**	**0.2 (0.03-0.9)**	0.8	0.3 (0.1-1.1)	0.6 (0.04-7.6)	0.7
Discharge	Symptoms remaining	0.9 (0.6-1.3)	1.9 (0.7-5.1)	0.1	0.7 (0.5-1.2)	2.1 (0.7-6.7)	0.1

[a]: p-value for difference in OR between term and preterm infants

[b]: adjusted for coinfections and age in months at admission

Table 5. Number of infants vaccinated at admission, monthly cumulative coverage estimates and vaccine effectiveness against pertussis hospitalizations of 1st and 2nd infant dose for preterm and term infants, assessed with the screening method [10].

	Term infants			Preterm infants		
Age in months ↓	Vaccinated at admission n(%)	Coverage in general population	Vaccine effectiveness (95%CI)[a]	Vaccinated at admission n(%)	Coverage in general population	Vaccine effectiveness (95%CI)[a]
Main analysis						
0m	0/1 (0%)	na	na	0/1 (0%)	na	na
1m	2/144 (1.4%)	1.9%	na	0/14 (0%)	1.3%	na
2m	52/152 (34.2%)	90.9%	95%[b] (93%-96%)	9/15 (60%)	84.9%	73%[b] (20%-91%)
3m	67/78 (85.9%)	98.8%	93% (85%-96%)	13/15 (86.7%)	97.9%	86% (9%-96%)
4m	30/32 (93.8%)	99.4%	91%	4/4 (100%)	99.4%	na
Sensitivity analysis						
0m	0/1 (0%)	na	na	0/1 (0%)	na	na
1m	1/115 (0.9%)	1.9%	na	0/14 (0%)	1.3%	na
2m	33/98 (33.7%)	90.9%	95%[b] (92%-97%)	9/15 (60%)	84.9%	73%[b] (20%-91%)
3m	42/47 (89.4%)	98.8%	90% (71%-96%)	13/15 (86.7%)	97.9%	86% (9%-96%)
4m	14/14 (100%)	99.4%	na	4/4 (100%)	99.4%	na

[a]: according to the screening method

[b]: significant difference between term and preterm infants

Discussion

This medical record study on infant pertussis hospitalizations showed an overrepresentation of preterms hospitalized with pertussis, with 12% of all pertussis cases concerning preterm infants compared to 8% preterms on average in Dutch birth cohorts [12]. Furthermore, preterms were older at hospitalization and had more often received first vaccinations against pertussis. VE of the first dose of pertussis vaccination was lower for preterms than for terms. Furthermore, preterms tended to need more often intensive treatment and had a longer stay at the Intensive Care Unit. Likewise, preterms tended to be diagnosed more often with coinfections. Despite lower VE, the first vaccination against pertussis resulted in lower disease severity and less need for intensive treatment in both groups. Coinfections and age at admission influenced the need for intensive treatment and mitigated the beneficial effect of being vaccinated.

The overrepresentation of preterms is also reported in other studies. In Norway, 10% of infant pertussis hospitalizations concerned preterms, compared to 5.2% born prematurely nationwide [13]. More or less similar data are derived from England [7], Australia [14] and Canada [15]. Low birth weight, which is associated with preterm delivery, was increased among hospitalized pertussis cases in Jerusalem [16]. Likewise, Langkamp et al. showed that low birth weight infants were at increased risk of pertussis hospitalizations compared to normal birth weight infants [17].

The clinical picture in our observational study resembles findings in other retrospective studies. Marshall et al. showed that preterms had a higher pertussis disease severity score (defined by a longer hospital stay, ICU admittance, need for rehydration, respiratory support, coinfections and the presence of complications) than terms [14]. In England, a longer duration of hospitalization, higher frequencies of ICU admittance and coinfections were observed among preterms, although their frequency of coinfections was lower than ours (10% vs 37%) [7]. Langkamp et al. also reported a higher median age at hospitalization and a longer median length of stay among low birth weight infants than among normal birth weight infants [17].

In contrast, in case of more active and prospective study designs, higher frequencies of clinical characteristics were observed in infants (i.e. terms and preterms combined) hospitalized for pertussis, like higher frequencies of cyanosis/desaturation (72%) and apnea (33%) at admittance than in our study [16]. Australian researchers observed higher rates of ICU admittance (18%) and treatment with antibiotics (96%) but lower median length of ICU stay (6 days) [18]. In Switzerland, hospitalized infants <6m of age had higher frequencies of coughing attacks (93%), whooping (69%), vomiting (59%) and complications

(24%) [19, 20]. As active designs usually profit from more structured clinical observations and documentation in the medical record, the frequencies, found in the retrospective studies probably are an underestimation of the pertussis burden in terms and preterms [21].

The aim of vaccination against pertussis is to prevent severe disease. We confirmed that vaccination reduced disease severity and duration of hospitalization, comparable to other studies [18, 22-24], and in line with a previous study, performed in the Netherlands in 2006-2008 [5]. However, our data on vaccine effectiveness were higher than for example in studies in Germany (VE 68%; 95%CI 45.6-81.1) and New Zealand (VE 43%; 95%CI21-58) [25, 26]. Unfortunately, no data on GA were provided in these studies. In Norway (VE 60.7% in terms and 71.2% in preterms) and Denmark (VE 51% in terms vs 45% in preterms), no difference in effectiveness of the first pertussis vaccine dose against hospitalizations between terms and preterms was observed [13, 27]. Both Scandinavian countries start at age 3 months with their immunization schedule as compared to the Netherlands with a first dose between 6 weeks to 2 months. In 2 month olds, protective maternal antibodies may be higher as compared to 3 months of age and higher in terms than in preterms. [29]. Likewise, studies have showed a decreased immune response after immunization at 2 months in preterms compared with terms [30, 31] and an equal response in terms and preterms at 3 months [32]. The fact that the Scandinavian countries failed to see a difference in vaccine effectiveness between term and preterms might be explained by the interplay between maternal antibodies that reduce a first response and a less effective immune response in preterms at younger age that may have improved at age 3 months [28]We didn't find difference in VE of the second dose between terms and preterms.

Diagnosed coinfections influenced the effect vaccination had on the clinical course, similar to findings in other studies [7, 14]. Like in other studies, we observed coinfections with viral infections like RSV [33-38]. However, a recent systematic review concluded that the influence of coinfections on pertussis disease severity still is unclear [39].

Our study has several strengths. First, the study used nationwide data over a 10 year period. Participating hospitals were spread over the country and showed a good representation of tertiary, top clinical and local hospitals in the Netherlands. Collected data contained detailed information on clinical characteristics of pertussis, also including information on possible confounding factors, e.g. coinfections. Furthermore, linkage to the vaccination registry enabled us to use validated vaccination records. Finally, all pertussis cases were laboratory confirmed.

Limitations of our study are the retrospective design with differences in pertussis diagnostics, diagnostics for coinfections and registration of clinical and laboratory disease characteristics.
Secondly, the incomplete reporting of hospital diagnoses at discharge, assessed in a recent capture-recapture analysis [40] might have influenced our results. Although we could not stratify this underreporting by gestational age, the good representation of tertiary, top-clinical and local hospitals in our study probably led to inclusion of a representative variety in the spectrum of pertussis disease. The found overrepresentation of preterms, which is comparable to findings in other studies, underlines this conclusion.
Furthermore, the retrospective use of medical records led to missing data, e.g. on gestational age, birth weight, with possible impact on our results. For this reason our main analysis was based on all included records, assuming that records with unknown GA were born term. The performed sensitivity analysis showed no major impact of missing data on GA, thereby confirming our findings. Likewise, leukocytosis and CRP data were incomplete, also leading to less informative results.
Linking between medical records and vaccination data, based on pseudonymization, might have led to incorrect linkage. Medical records include the home address of the patient at time of the last visit, while the vaccination registry includes the current home address. Especially in case of frequent moving and a large interval between the last hospital visit and the current residence, linkage might be incorrect. In our study, 38% of infants did not move house. Furthermore, the use of additional pseudonyms based on previous home addresses, also stored in the vaccination registry, lowered the risk of incorrect linking.
In conclusion, we found an overrepresentation of preterms among pertussis hospitalizations with a slightly higher overall risk of complications, increased need for intensive treatment and lower effectiveness of the first infant pertussis vaccination. Recently, the Dutch Health Council advised to offer maternal pertussis vaccination in the 3rd trimester of pregnancy. While this strategy is overall very effective, preterms may benefit less due to less protective maternal antibody transfer before delivery [6, 7]. They probably will benefit more from 2nd trimester immunization. However, for infants born of unvaccinated mothers, a timely first dose remains important, as this prevents clinical pertussis and decreases disease severity. This study underlines the need for more in-depth surveillance of vaccine preventable diseases in relation to gestational age and more insights in optimizing the vaccination program for all children but in particular for preterm infants who are the most vulnerable group.

Acknowledgements

We thank J. Alblas for help in data management, P. Oomen for supplying vaccination data and all participating hospitals for their cooperation.

References

1. Versteegh FGA, Schellekens JFP, Fleer A, Roord JJ. Pertussis: a concise historical review including diagnosis, incidence, clinical manifestations and the role of treatment and vaccination in management. Reviews in Medical Microbiology **2005**; 16(3): 79-89.
2. Van Lier A, Oomen P, Giesbers H, et al. Immunisation coverage National Immunisation Programme in the Netherlands; year of report 2016. Bilthoven: National Institute for Public Health and the Environment, **2016**. Report No.: 2016-0064.
3. van der Maas NAT, Mooi FR, de Greeff SC, Berbers GAM, Conyn-Spaendonck MAE, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? Vaccine **2013**; 31(41): 4541-7.
4. de Melker HE, Schellekens JFP, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MAE. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. Emerg Infect Dis **2000**; 6(4): 348-57.
5. de Greeff SC, Mooi FR, Westerhof A, et al. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis **2010**; 50(10): 1339-45.
6. Amirthalingam G, Campbell H, Ribeiro S, et al. sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. CID **2016**.
7. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. Arch Dis Child **2017**.
8. DutchHospitalData. Gebruikershandleiding Landelijke Basisregistratie Ziekenhuiszorg (LBZ) 2014. Available at: https://www.dhd.nl/klanten/klantenservice/handleidingen_formulieren/Documents/Handleiding%20LBZ.pdf. Accessed 10-10-2016.
9. Wet op de beroepen in de individuele gezondheidszorg. Available at: http://wetten.overheid.nl/BWBR0006251/2016-08-01. Accessed 20 juni 2017.
10. Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol **1993**; 22(4): 742-6.
11. Woestenberg PJ, van Lier A, van der Maas NA, Drijfhout IH, Oomen PJ, de Melker HE. Delayed start of diphtheria, tetanus, acellular pertussis and inactivated polio vaccination in preterm and low birth weight infants in the Netherlands. Pediatr Infect Dis J **2014**; 33(2): 190-8.
12. van der Leeuw-Harmsen L, Rijninks-van Driel GC, Morshuis RHL, van Lith JMM, Tamminga P. Perinatale Registratie Nederland. Grote lijnen 1999-2012. Utrecht: Stichting Perinatale Registratie Nederland, **2013**.

13. Riise OR, Laake I, Vestrheim D, et al. Risk of Pertussis in Relation to Degree of Prematurity in Children Less Than 2 Years of Age. Pediatr Infect Dis J **2017**; 36(5): e151-e6.
14. Marshall H, Clarke M, Rasiah K, et al. Predictors of disease severity in children hospitalized for pertussis during an epidemic. Pediatr Infect Dis J **2015**; 34(4): 339-45.
15. Halperin SA, Wang EE, Law B, et al. Epidemiological features of pertussis in hospitalized patients in Canada, 1991-1997: report of the Immunization Monitoring Program--Active (IMPACT). Clin Infect Dis **1999**; 28(6): 1238-43.
16. Zamir CS, Dahan DB, Shoob H. Pertussis in infants under one year old: risk markers and vaccination status--a case-control study. Vaccine **2015**; 33(17): 2073-8.
17. Langkamp DL, Davis JP. Increased risk of reported pertussis and hospitalization associated with pertussis in low birth weight children. J Pediatr **1996**; 128(5 Pt 1): 654-9.
18. Elliott E, McIntyre P, Ridley G, et al. National study of infants hospitalized with pertussis in the acellular vaccine era. Pediatr Infect Dis J **2004**; 23(3): 246-52.
19. Heininger U, Klich K, Stehr K, Cherry JD. Clinical findings in Bordetella pertussis infections: results of a prospective multicenter surveillance study. Pediatrics **1997**; 100(6): E10.
20. Heininger U, Weibel D, Richard JL. Prospective Nationwide Surveillance of Hospitalizations due to Pertussis in Children, 2006-2010. Pediatr Infect Dis J **2013**.
21. Organization WH. Immunization surveillance, assessment and monitoring. Available at: http://www.who.int/immunization/monitoring_surveillance/en/. Accessed 28-02-2017.
22. Crespo Fernandez I, Soldevila N, Carmona G, et al. Surveillance of hospitalized and outpatient cases of pertussis in Catalonia from 2003 to 2009. Hum Vaccin Immunother **2013**; 9(3): 667-70.
23. Preziosi MP, Halloran ME. Effects of pertussis vaccination on disease: vaccine efficacy in reducing clinical severity. Clin Infect Dis **2003**; 37(6): 772-9.
24. Herzig P, Hartmann C, Fischer D, et al. Pertussis complications in Germany--3 years of hospital-based surveillance during the introduction of acellular vaccines. Infection **1998**; 26(4): 227-31.
25. Juretzko P, von Kries R, Hermann M, Wirsing von König CH, Weil J, Giani G. Effectiveness of acellular pertussis vaccine assessed by hospital-based active surveillance in Germany. Clin Infect Dis **2002**; 35(2): 162-7.
26. Radke S, Petousis-Harris H, Watson D, Gentles D, Turner N. Age-specific effectiveness following each dose of acellular pertussis vaccine among infants and children in New Zealand. Vaccine **2017**; 35(1): 177-83.
27. Hviid A. Effectiveness of two pertussis vaccines in preterm Danish children. Vaccine **2009**; 27(23): 3035-8.

28. Bonhoeffer J, Siegrist CA, Heath PT. Immunisation of premature infants. Arch Dis Child **2006**; 91(11): 929-35.
29. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. American journal of reproductive immunology **1996**; 36(5): 248-55.
30. Schloesser RL, Fischer D, Otto W, Rettwitz-Volk W, Herden P, Zielen S. Safety and immunogenicity of an acellular pertussis vaccine in premature infants. Pediatrics **1999**; 103(5): e60.
31. Slack MH, Schapira D, Thwaites RJ, et al. Acellular pertussis vaccine given by accelerated schedule: response of preterm infants. Archives of disease in childhood Fetal and neonatal edition **2004**; 89(1): F57-60.
32. Faldella G, Alessandroni R, Magini GM, et al. The preterm infant's antibody response to a combined diphtheria, tetanus, acellular pertussis and hepatitis B vaccine. Vaccine **1998**; 16(17): 1646-9.
33. Nuolivirta K, Koponen P, He Q, et al. Bordetella pertussis infection is common in nonvaccinated infants admitted for bronchiolitis. Pediatr Infect Dis J **2010**; 29(11): 1013-5.
34. Abu Raya B, Bamberger E, Kassis I, Kugelman A, Srugo I, Miron D. Bordetella pertussis infection attenuates clinical course of acute bronchiolitis. Pediatr Infect Dis J **2013**; 32(6): 619-21.
35. Korppi M, Hiltunen J. Pertussis is common in nonvaccinated infants hospitalized for respiratory syncytial virus infection. Pediatr Infect Dis J **2007**; 26(4): 316-8.
36. Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HK. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax **2006**; 61(7): 611-5.
37. Greenberg D, Bamberger E, Ben-Shimol S, Gershtein R, Golan D, Srugo I. Pertussis is under diagnosed in infants hospitalized with lower respiratory tract infection in the pediatric intensive care unit. Med Sci Monit **2007**; 13(11): CR475-80.
38. Cosnes-Lambe C, Raymond J, Chalumeau M, et al. Pertussis and respiratory syncytial virus infections. Eur J Pediatr **2008**; 167(9): 1017-9.
39. Goka EA, Vallely PJ, Mutton KJ, Klapper PE. Single and multiple respiratory virus infections and severity of respiratory disease: a systematic review. Paediatr Respir Rev **2014**; 15(4): 363-70.
40. van der Maas NAT, Hoes J, Sanders EAM, de Melker HE. Severe underestimation of pertussis related hospitalizations and deaths in the Netherlands: A capture-recapture analysis. Vaccine **2017**; 24(35): 4162-6.

Chapter 5

Effectiveness of Early Measles, Mumps, and Rubella Vaccination Among 6–14-Month-Old Infants During an Epidemic in the Netherlands: An Observational Cohort Study

Tom Woudenberg
Nicoline A.T. van der Maas
Mirjam J. Knol
Hester E. de Melker
Rob S. van Binnendijk
Susan J.M. Hahné

Published in:
J Infect Dis. 2017 Apr 15;215(8):1181-1187
(DOI: 10.1093/infdis/jiw586)

Abstract

Background

Routinely, the first measles, mumps, and rubella (MMR) vaccine dose is given at 14 months of age in the Netherlands. However, during a measles epidemic in 2013–2014, MMR vaccination was also offered to 6–14-month-olds in municipalities with <90% MMR vaccination coverage. We studied the effectiveness of the early MMR vaccination schedule.

Methods

Parents of all infants targeted for early MMR vaccination were asked to participate. When parent(s) suspected measles, their infant's saliva was tested for measles-specific antibodies. The vaccine effectiveness (VE) against laboratory-confirmed and self-reported measles was estimated using Cox regression, with VE calculated as 1 minus the hazard ratio.

Results

Three vaccinated and 10 unvaccinated laboratory-confirmed cases occurred over observation times of 106631 and 23 769 days, respectively. The unadjusted VE against laboratory-confirmed measles was 94% (95% confidence interval [CI], 79%–98%). After adjustment for religion and sibling's vaccination status, the VE decreased to 71% (−72%–95%). For self-reported measles, the unadjusted and adjusted VE was 67% (40%–82%) and 43% (−12%–71%), respectively.

Conclusions

Infants vaccinated between 6 and 14 months of age had a lower risk of measles than unvaccinated infants. However, part of the effect was caused by herd immunity, since vaccinated infants were more likely to be surrounded by other vaccinated individuals.

Background

Measles is a highly contagious viral disease. It can lead to severe illness and even death, with the greatest burden in the youngest children [1, 2]. Most deaths from acute measles are due to secondary infections resulting from measles-induced suppression of immune responses [3]. Measles vaccination programs have led to a large decline in global mortality, from an estimated 562 400 annual measles deaths in 2000 to 114 900 in 2014 [4].

Infants aged <1 year were at highest risk of measles in recent outbreaks in Europe [5, 6]. This is worrisome because the risk of measles-associated complications and case-fatality rates are highest among infants [2, 7]. Passively acquired maternal anti- bodies protect infants against measles during the first months of life. However, infants of vaccinated women have significantly lower concentrations of maternal antibodies than infants of naturally immune women [8], and protection is on average 2–3 months shorter [8, 9]. At the age of 6 months, most infants (95% born to naturally immune women and 99% born to vaccinated women) lack detectable maternal antibodies [8].

The World Health Organization advises delivering the first dose of measles, mumps, and rubella (MMR) vaccine to infants aged 9 months in measles-endemic countries and to infants aged 12 months in countries with low rates of measles transmission [10]. In the Netherlands, children are offered MMR vaccination at 14 months and 9 years of age. Infants who have lost their protection from maternal antibodies are susceptible until their first vaccination. Administering vaccinations at an earlier age than 9 months may be beneficial when the risk of measles ishigh.

However, measles vaccination of infants <9 months of age has been associated with lower proportions of children who develop protective antibody levels after measles vaccination. The median proportion of children who seroconverted after measles vaccination at 8–9 months of age was 90% (interquartile range [IQR], 82%–95%) among 44 studies, while the median was 99% (IQR, 93%–100%) among infants vaccinated at 11–12 months in 21 studies [11]. However, the majority of these studies were con- ducted in developing countries. Seroconversion results stratified by age may be different in industrialized countries. Reasons for this include lower levels of maternal antibodies, since most mothers have vaccine-induced immunity to measles only. In a study where infants were included without maternal antibodies, no differences were found in the seroconversion rates for infants vaccinated at 9 and 12 months of age [12].

In a systematic review of case-control and cohort studies, the effectiveness against laboratory-confirmed measles of a 1-dose measles-containing vaccine (MCV) administered at the age of 9–11 months was estimated to be 84%, while the vaccine

effectiveness (VE) for infants who were vaccinated at the age of ≥12 months was 93% [13]. VE estimates for infants vaccinated at <9 months of age are scarce. In a retrospective cohort study in Niger in 1995, a single dose of MCV administered to infants aged <9 months resulted in a VE of 87% (95% CI, 81%–91%) against self-reported clinical measles among children 6–59 months of age [14]. To date, no VE estimates against laboratory-confirmed measles have been reported in observational studies among infants vaccinated at <9 months of age. Estimates of VE against laboratory-confirmed measles are more accurate because they discriminate measles from other diseases with rash and fever.

Here we investigated VE against self-reported and laboratory-confirmed measles among infants who received an MMR vaccination between 6 and 14 months of age during a measles epidemic in the Netherlands. The epidemic started in May 2013 and lasted until March 2014, with 2700 reported cases [15]. Most cases were unvaccinated orthodox Protestant primary and secondary school-aged children. The epidemic peaked in July 2013, slowed down during the summer holiday, and progressed with a second, lower peak in October 2013. This study was possible because the Dutch Ministry of Health offered an MMR vaccination temporarily to all infants between 6 and 14 months of age who were living in municipalities with MMR vaccination coverage of <90% and to infants in orthodox Protestant families living elsewhere.

Methods

Study Procedures

We conducted a prospective observational cohort study during the measles epidemic in the Netherlands in 2013–2014. As part of the vaccination campaign, infants between 6 and 14 months of age living in municipalities where coverage with the first dose of MMR vaccine was <90% [16] were invited for an additional or an early MMR vaccination. Infants 6–11 months of age were offered an extra vaccination (and would thus still be eligible for their second MMR vaccination at the age of 14 months), while 12–14-month-old infants were offered an early MMR vaccination as an alternative for the regular time point at 14 months of age. All infants are eligible for another dose of MMR scheduled at 9 years of age. Approximately 4 weeks after the personal invitation for vaccination, all parents of infants targeted for the early MMR in the 29 municipalities received an invitation to enroll their infant(s) in the study. We could not invite parents of infants in orthodox Protestant families living outside of the 29 targeted municipalities to participate in the study, as religion is not registered in the vaccination registry of the Netherlands. Invitations to participate in the study were sent from week 35 of 2013 up to week 8 of 2014 [17]. Parents of invited infants were asked to register for the study by sending a reply form by regular mail, indicating their e-mail address. Subsequently,

they received a link to the online baseline questionnaire. Infants were followed until the end of the epidemic (14 March 2014). Along the follow-up period, parents were reminded monthly by e-mail to report suspected measles in their infant. When parents did so, they received a second questionnaire and a saliva sampling kit for detection of measles virus. The Central Committee on Research Involving Human Subjects of the Netherlands approved the study.

Data Collection

In the baseline questionnaire, vaccination status was asked, as well as permission to check vaccination status in the national vaccination register. Parents were also asked whether their infant(s) had had measles in the preceding 3 months. In the baseline questionnaire, measles was defined as having a fever (temperature, >38°C), exanthema, and at least 1 of the following symptoms: cough, runny nose, or sore eyes [18]. Other questions, among others, were about sex, day-care center attendance, vaccination status of the parent(s) and sibling(s), education level of the parent(s), religion, travel history, medication use, comorbidities, breastfeeding, birth weight, and duration of pregnancy. The second questionnaire, which parents received when they reported that their infant had measles, consisted of questions to ascertain symptoms to diagnose self-reported measles.

Laboratory Testing

When parents reported measles in their infant, they were sent a saliva sampling kit, consisting of a tube and a swab. Briefly, we used an immunoglobulin M (IgM) capture enzyme immuno- assay specifically designed for the detection of IgM antibodies in oral fluid specimens, according to procedures recommended by the manufacturer (MicroImmune, Hounslow, Middlesex, United Kingdom). The relative specificity and sensitivity of IgM antibody detection in oral fluid as compared to serum is near 100%, as reported by the manufacturer. An infant of whom the parents reported a suspected measles case and from whom the saliva sample tested IgM positive was regarded as a laboratory-confirmed measles case. Laboratory testing was only offered to suspected cases occurring after the baseline questionnaire was completed. Infants for whom it was indicated in the base- line questionnaire that they had had measles in the 3 months before filling out the baseline questionnaire were not offered saliva testing.

Outcomes

We estimated VE against laboratory-confirmed measles and self-reported measles. For VE estimation against laboratory-confirmed measles, the observation time

started at the date the baseline questionnaire was filled in and stopped at either the reported date of onset of disease, a second MMR vaccination or the end of the epidemic (14 March 2014), whichever came first. For self-reported measles, the baseline questionnaire included a question about the occurrence of measles in the preceding 3 months. Therefore, we included this 3-month period in the observation time for the outcome of self-reported measles. The start of the observation time for the outcome of self-reported measles was therefore 3 months before the baseline questionnaire, with a minimum at 6 months of age. The end of the observation time for self-reported measles was the date of onset of measles, a second MMR vaccination, or the end of the epidemic, whichever came first.

Statistical Analysis

Infants with a missing address or no permission to check their vaccination status were excluded. We also excluded self-reported cases before the start of the observation time, cases reported 5–12 days after vaccination, and infants who enrolled after their second MMR vaccination or after the epidemic.

VE was calculated as 1 minus the hazard ratio (HR) times 100 [19]. The HR is the ratio of the hazard among vaccinated infants versus the hazard among unvaccinated infants. Kaplan-Meier estimates were used to visualize empirical probabilities of laboratory-confirmed and self-reported measles in vaccinated and unvaccinated infants. A Cox proportional hazard model, which gives a HR as the outcome, assessed the association between vaccination status and the outcomes of laboratory-confirmed measles and self-reported measles. Owing to the varying exposure to measles during an epidemic, we used calendar time as the time scale [20]. Vaccination status was included as a time-varying exposure variable; infants could contribute person-time to both the unvaccinated and vaccinated group. The vaccinated person–time started 12 days after the MMR vaccination. Age was also included as a time-varying variable and was updated every quintile of the observation period.

The following covariates were considered a priori as potential confounders: age, breastfeeding, religion, sibling's vaccination status, day-care center attendance, and travel history. To test which covariates we had to include in our model, we first performed bivariable analyses. The covariate that gave the biggest relative change in the VE (with a minimum of 10%) was included in the model. Subsequently, we added the remaining covariates one by one to the model to check for another change of >10% in the VE. A final model was reached when none of the remaining covariates led to a >10% change. We tested the proportional hazards assumption by using scaled Schoenfeld residuals, where we considered the proportional hazards assumption to be valid with a *P* value of >.05 for the variables in the final model. Data analysis was conducted using R (version 3.2.0). Cox proportional hazards regression model and Kaplan-Meier estimates were conducted by using the package *survival*.

Vaccine

The vaccine administered during this vaccination campaign was the same as the live attenuated MMR vaccine used in the national immunization program (M-M-RVAXPRO; Sanofi Pasteur MSD). This vaccine contains at least 10^3 50% cell culture infectious doses of measles virus Enders' Edmonston strain [21].

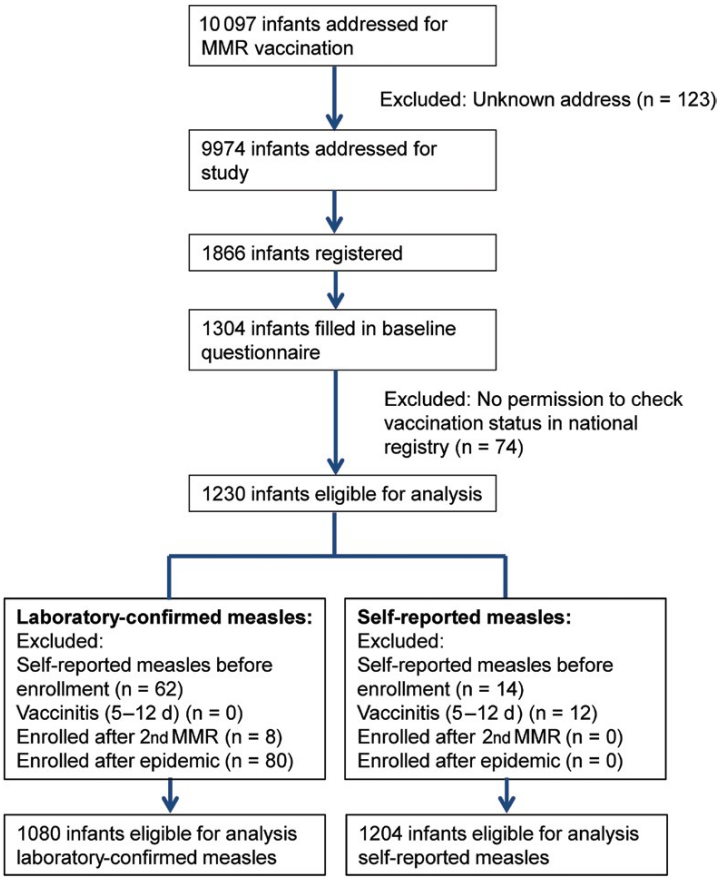


Figure 1. Flowchart of the study population. Abbreviation: MMR, measles, mumps, and rubella

Results

Between 13 July 2013 and 1 March 2014, 10097 infants in 29 municipalities were invited for an early MMR vaccination (Figure 1). For 123 infants, the address was not available or parents had indicated that they did not want to receive regular mail from the vaccination registry. We invited 9974 infants to participate in the study, of

whom 1866 (19%) agreed and 1304 (13%) filled in the baseline questionnaire. In total, 74 infants (6%) were excluded because parents did not give permission to check their infant's vaccination status, resulting in 1230 eligible infants (12%) for analysis.

Characteristics of the cohort are presented in Table 1. The vaccinated and unvaccinated groups differed considerably. Vaccinated infants were on average 31 days older at enrollment. Unvaccinated infants were more likely to have an unvaccinated sibling or parent and to go to a church with low vaccination coverage. Vaccinated and unvaccinated infants were similar with regard to sex, parents' education level, medication use, comorbidities and birth weight.

In total, 1080 infants were eligible for the analysis of the outcome of laboratory-confirmed measles, after the exclusion of 62 infants with self-reported measles before the start of the observation time, 8 infants who enrolled after their second MMR dose, and 80 infants who enrolled after the measles epidemic (Figure 1). During the observation period, 3 vaccinated and 10 unvaccinated laboratory-confirmed cases of measles were reported (Table 2). Two vaccinated infants were vaccinated at 6 months of age and 1 at 8 months of age. Most cases occurred between September and November 2013 (Figure 2). Using Cox proportional hazard modeling, we found an unadjusted HR of 0.06, which corresponds to a VE of 94% (95% confidence interval [CI], 79%–98%; Table 2). When we adjusted for confounding (sibling's vaccination status and religion), VE decreased to 71% (95% CI, –72%–95%).

For the analysis of the outcome of self-reported measles, we excluded 12 cases who reported measles 5–12 days following after the early MMR vaccination and 14 cases who reported measles before the start of the observation time. In total, there were 20 vaccinated and 37 unvaccinated self-reported cases of measles (Table 2), which were reported throughout the observation time (Figure 3). The unadjusted VE for self-reported measles was 67% (95% CI, 40%–82%), and the VE adjusted for religion and sibling vaccination status was 43% (95% CI, –12%–71%; Table 2).

Table 1. Characteristics of early vaccinated and unvaccinated infants (n = 1230) during an outbreak of measles in the Netherlands, 2013-2014.

Characteristic	Vaccinated	Unvaccinated	p-value[a]
Infants	919	311	
Gender (male)	460 (50%)	157 (51%)	0.90
Age at enrollment days median (IQR)	273 (232,357)	242 (226,301)	< 0.001
Day care center attendance	613 (67%)	150 (48%)	< 0.001
Unvaccinated mother	147 (16%)	128 (41%)	< 0.001
Unvaccinated father	313 (34%)	166 (53%)	< 0.001
Unvaccinated sibling	5 (1%)	55 (18%)	< 0.001
Sibling with a measles infection	3 (0%)	24 (8%)	< 0.001
Religion[b]			< 0.001
high coverage	818 (89%)	192 (62%)	
intermediate coverage	99 (11%)	89 (29%)	
low coverage	2 (0%)	30 (10%)	
Education mother			0.35
Low	25 (3%)	6 (2%)	
Medium	427 (47%)	158 (51%)	
High	467 (51%)	147 (47%)	
Education father			0.46
Low	85 (9%)	28 (9%)	
Medium	492 (54%)	155 (50%)	
High	342 (37%)	128 (41%)	
Medication usage	65 (7%)	18 (6%)	0.43
Breastfeeding			< 0.001
No	237 (26%)	54 (17%)	
Breastfed	535 (58%)	164 (53%)	
Breastfeeding	147 (16%)	93 (30%)	
Holiday in a foreign country	376 (41%)	92 (30%)	< 0.001
Co-morbidities	63 (7%)	13 (4%)	0.09
Birth weight in grams median (IQR)	3565 (3215, 3910)	3590 (3280, 3878)	0.75
Duration pregnancy in weeks median (IQR)	40 (39, 41)	40 (39, 41)	0.05

[a] Differences between groups were tested with Chi-square for categorical variables and Kruskal-Wallis test for continuous variables.

[b] Religion is grouped according to the vaccination coverage in infants' community. High coverage is comparable to the general population in the Netherlands (around 95%). Medium coverage is categorized by communities with vaccination coverage ranging between 50% and 70%. Low coverage churches have vaccination coverages ranging from 10% to 30 %

IQR: Interquartile range

Table 2. VE estimates of MMR vaccination among infants 6-14 months of age against laboratory confirmed measles and self-reported measles using Cox's proportional hazard model.

	Laboratory confirmed measles		Self-reported measles	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Cases	3	10	20	37
Observation time (days)	106,631	23,769	140,075	72,993
Unadjusted HR (95%CI)	0.06 (0.02 to 0.21)	Ref	0.33 (0.18 to 0.60)	Ref
Unadjusted VE (95%CI)	94% (79 to 98)		67% (40 to 82)	
Adjusted HR (95%CI)	0.292 (0.05 to 1.72)[a]	Ref	0.573 (0.29 to 1.12)[a]	Ref
Adjusted VE (95%CI)	71% (-72 to 95)		43% (-12 to 71)	

[a]: adjusted for sibling's vaccination status and religion

VE: vaccine effectiveness, MMR: measles mumps rubella, HR: hazard rate ratio, CI: Confidence interval

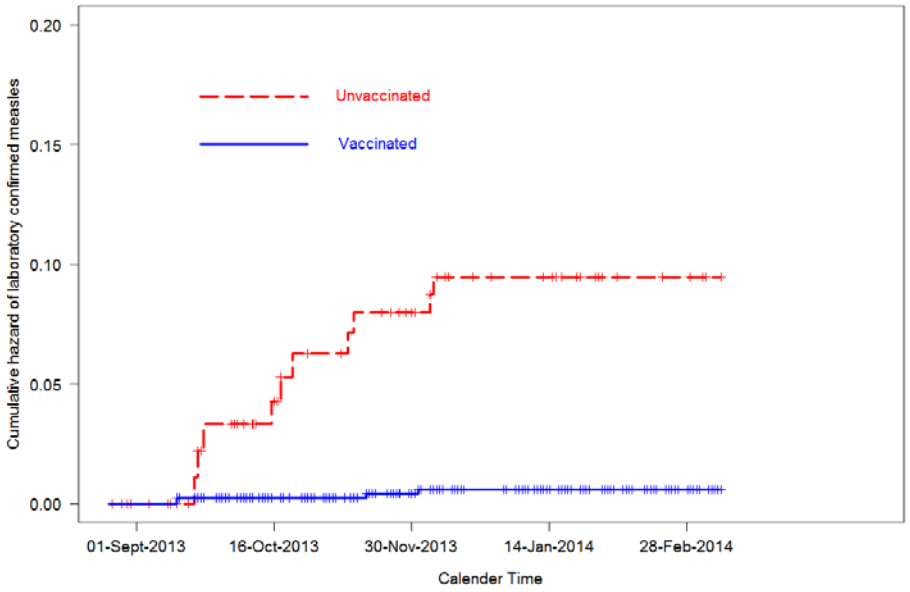


Figure 2. Kaplan–Meier curves of the cumulative hazard of laboratory-confirmed measles infection over time for vaccinated and unvaccinated infants.

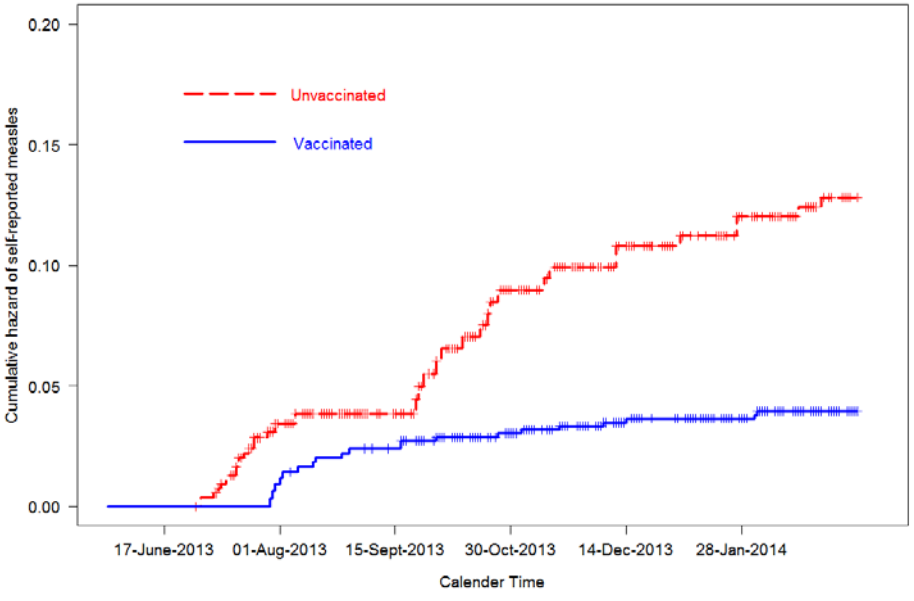


Figure 3. Kaplan–Meier curves of the cumulative hazard of self-reported measles infection over time for vaccinated and unvaccinated infants.

Discussion

We showed that infants vaccinated between 6 and 14 months of age had a reduced risk, compared with unvaccinated infants, of laboratory-confirmed measles during an epidemic in the Netherlands, with an unadjusted VE estimate of 94%. This reduction cannot be solely attributed to the effectiveness of the vaccine. Vaccinated infants were probably exposed to measles to a lesser extent than unvaccinated infants, as the latter were more frequently members of the orthodox Protestant community, in which the vaccination coverage is low, and more often had an unvaccinated sibling or parent. When we adjusted for these differences in exposure to measles, the VE against laboratory-confirmed measles decreased to 71%. Owing to low numbers, this estimate was no longer statistically significant.

Unadjusted and adjusted VE estimates against self-reported measles were 67% (95% CI, 40%–82%) and 43% (95% CI, −12%–71%), respectively. The lower VE estimates against self-reported measles, compared with laboratory-confirmed measles, most likely reflect misdiagnosis. First, with an effective vaccine, the presence of cases misdiagnosed as measles results in a lower VE, as relatively more of these cases are present in the vaccinated group [22]. Second, it could be that vaccinating parents may be more likely to erroneously interpret any rash appearance as measles, since they are probably less familiar with measles than parents who are opposed to vaccination. This could lead to a selective increase in false-positive cases among vaccinated infants as compared to unvaccinated infants and hence an underestimation of the VE. Furthermore, most laboratory-confirmed cases occurred from September to October, which coincided with a peak of reported cases during the measles epidemic in the Netherlands [15], while self-reported cases in our study population occurred constantly over time. Our estimate of VE against the outcome of laboratory-confirmed measles is more accurate, as the laboratory test excludes most rash cases that are not caused by the measles virus.

Our adjusted point estimate of the VE against laboratory-confirmed measles (71%) is adjacent to the lower end of the IQR of the VE (72%–95%) found in a systematic review [13]. This VE estimate was based on 44 MCV estimates, using laboratory confirmation of cases and studies with a cohort or case-control design. However, this estimate was limited to infants vaccinated at 9–11 months of age, while in our study infants 6–8 months old were also included.

A study more comparable in respect to age with our study was conducted during an outbreak in Canada [23]. Deserres et al estimated a VE of 96% (95% confidence interval [CI], 72%–99%) against clinical measles for infants 6–11 months of age. Our adjusted estimate against laboratory-confirmed measles borders the lower value of the 95% CI, despite the inclusion of infants vaccinated between 12–14 months of age in our study. However, the Canadian study assumed comparable levels of exposure to measles between the vaccinated and unvaccinated infants, whereas we tried to include

exposure to measles in our model through adjustment for surrogates of exposure to measles.

Our results indicate that exposure to measles as assessed through such proxies differed between vaccinated and unvaccinated infants and that it influenced the VE estimates. Adjustment of the VE with surrogates of measles exposure led to lower VE estimates for both self-reported and laboratory-confirmed measles. This was in line with our expectations, given that the measles epidemic in the Netherlands largely took place among unvaccinated orthodox Protestant children [15], who live in socio-geographic clusters [24]. Thus, we think that exposure to measles is an important factor to take into account in the estimation of VE in observational studies, especially given that parents' choice to vaccinate also depends on the choices of their social network [25] and that, if the networks of the parents' children overlap, clusters of unvaccinated children emerge [26]. To our knowledge, only one randomized clinical trial has been conducted to estimate the measles efficacy of MCV in children vaccinated at <9 months of age in an outbreak setting [27]. Because infants were randomly assigned to be vaccinated, different levels of exposure to measles can most likely be ruled out in this clinical trial. Martins et al followed 1333 infants aged 4.5 months, of whom 441 were vaccinated, for 5 months and found a VE of 94% (95% CI, 74%–98%) against laboratory-confirmed measles. In comparison with our estimate this is substantially higher, all the more since infants were vaccinated at 4.5 months of age. It is, however, important to note that in this trial the Edmonston Zagreb vaccine was used, which has been reported to have a higher immunogenicity in infants than other vaccines [27, 28].

The main limitation of our study is that infants were not randomly assigned to receive or not receive early MMR vaccination but self-selected whether to vaccinate, and therefore we studied different groups in respect to exposure to measles. We have addressed this difference in exposure to measles by correcting for surrogates, but residual confounding cannot be excluded. Another limitation of our study is the low response rate and small number of cases. As a result, we did not have sufficient statistical power to find precise VE estimates, which may account for some of the variance between our VE estimates and previous estimates in literature. In addition, the small number of cases limited us to study differences in the severity of disease between vaccinated and unvaccinated cases and to stratify the results by age at vaccination. In a subgroup analysis of infants vaccinated at <9 months of age and unvaccinated infants enrolling before 9 months of age, we found an unadjusted VE against laboratory-confirmed measles of 81% (95% CI, 7.6%–96%).

Since infants are at the greatest risk during recent outbreaks in Europe and as they are at the highest risk for complications, too, it is important to protect them during

outbreaks. Recently, a study by our group concluded that MMR vaccine is safe to protect infants aged 6–14 months of age [29]. The trade-off, however, is a lower VE, leaving relatively more vaccinated infants susceptible. This lower VE can be largely voided by the additional measles vaccination recommended in the World Health Organization schedule, given that the majority of children who did not develop sufficient antibodies after their first measles vaccination will develop protective antibody levels after their second measles vaccination [11].

However, a concern is that vaccinated infants who received their first MCV vaccination at 6 months of age—and despite subsequent secondary and tertiary doses—had lower levels of humoral responses at 7–10 years of age, compared with those who received the first dose of MMR at 12 months [30]. This blunting could be associated with the interference of maternal antibodies and an immature immunity. That this effect may be of clinical relevance is suggested by first results of an outbreak investigation among students in Canada [31]. Here relatively more twice-vaccinated cases were reported who received their first MMR dose at 12 months of age than twice-vaccinated cases who received their first MMR at 15 months of age.

In conclusion, MMR vaccinated infants between 6–14 months of age were at lower risk of measles than unvaccinated infants. However, part of the effect was caused by the herd immunity yielded by the regular national immunization program in the Netherlands; vaccinated infants were more likely to be surrounded by vaccinated individuals and were therefore to a lesser extent exposed to measles. Our VE estimates, adjusted for exposure to measles through the use of proxies, suggest that the early MMR vaccination campaign in the Netherlands was effective, but precise estimates are lacking, and further research on VE at a young age is required. In the meantime, given the high disease burden in infants <14 months of age and the early loss of maternal protection, early MMR vaccination is recommended when the risk of measles is high.

Acknowledgments

We thank the participating infants and their parents for their involvement in the study and Jeroen Kerkhof for measles laboratory diagnostic testing.

References

1. Duke T, Mgone CS. Measles: not just another viral exanthem. Lancet **2003**; 361:763–73.
2. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of mea- sles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol **2009**; 38:192–205.
3. de Vries RD, Mesman AW, Geijtenbeek TB, Duprex WP, de Swart RL. The patho- genesis of measles. Curr Opin Virol **2012**; 2:248–55.
4. Perry RT, Murray JS, Gacic-Dobo M, et al. Progress toward regional measles elimi- nation—worldwide, 2000–2014. MMWR Morb Mortal Wkly Rep **2015**; 64:1246–51.
5. Muscat M. Who gets measles in Europe? J Infect Dis **2011**; 204 Suppl 1:S353–65.
6. European Centre for Disease Prevention and Control (ECDC). Measles and rubella monitoring, January 2015—Reporting on January to December 2014 surveillance data and epidemic intelligence data to the end of January 2015. Stockholm, **2015**.
7. Moss WJ, Griffin DE. Measles. Lancet **2012**; 379:153–64.
8. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ **2010**; 340:c1626.
9. Waaijenborg S, Hahné SJ, Mollema L, et al. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccina- tion coverage. J Infect Dis **2013**; 208:10–6.
10. Measles vaccines: WHO position paper. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations **2009**; 84:349–60.
11. Moss WJ, Scott S. The immunological basis for immunization series: module 7: measles—Update 2009. Geneva: World Health Organization, **2009**.
12. Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. J Infect Dis **2001**; 184:817–26.
13. Uzicanin A, Zimmerman L. Field effectiveness of live attenuated measles-con- taining vaccines: a review of published literature. J Infect Dis **2011**; 204 Suppl 1:S133–48.
14. Kaninda AV, Legros D, Jataou IM, et al. Measles vaccine effectiveness in stan- dard and early immunization strategies, Niger, 1995. Pediatr Infect Dis J **1998**; 17:1034–9.
15. Woudenberg T, van Binnendijk RS, Sanders EAM, et al. Large measles epidemic in the Netherlands, May 2013 to March 2014: changing epidemiology. Euro Surveill 2017; 22(3):pii=30443.
16. van Lier EA, Oomen PJ, Mulder M, et al. Immunisation coverage National Immunisation Programme in the Netherlands. Available at: http://www.rivm.nl/dsresource?objectid=939f41ee-d178-4730-8308-92b91397e61d&type=org&disposition=inline.
17. National Institute for Public Health and the Environment (RIVM). Geen extra mazeleninenting meer voor kinderen van 6 maanden. Available at: http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Nieuwsberichten/2014/Geen_extra_mazeleninenting_meer_voor_kinderen_van_6_maanden. Accessed 10 october 2015.
18. European Centre for Disease Prevention and Control (ECDC). Measles. Available at: http://ecdc.europa.eu/en/healthtopics/vaccine-preventable-diseases/euvac/case_definition/Pages/measles.aspx. Accessed 25 September 2015.
19. Halloran ME, Longini IM Jr, Struchiner CJ. Design and interpretation of vaccine field studies. Epidemiol Rev **1999**; 21:73–88.
20. Clayton DH, M. Statistical models in epidemiology. Oxford: Oxford University Press, **2013**.
21. Summary of Product Characteristics of M-M-RVAXPRO. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000604/WC500030170.pdf.
22. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further observations. Epidemiol Rev **1988**; 10:212–41.
23. de Serres G, Boulianne N, Ratnam S, Corriveau A. Effectiveness of vaccination at 6

to 11 months of age during an outbreak of measles. Pediatrics **1996**; 97:232–5.

24. Ruijs WL, Hautvast JL, van der Velden K, de Vos S, Knippenberg H, Hulscher ME. Religious subgroups influencing vaccination coverage in the Dutch Bible belt: an ecological study. BMC Public Health **2011**; 11:102.
25. Brunson EK. The impact of social networks on parents' vaccination decisions. Pediatrics **2013**; 131:e1397–404.
26. Eames KT. Networks of influence and infection: parental choices and childhood disease. J R Soc Interface **2009**; 6:811–4.
27. Martins CL, Garly ML, Balé C, et al. Protective efficacy of standard Edmonston- Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a ran- domised clinical trial. BMJ **2008**; 337:a661.
28. Cutts FT, Grabowsky M, Markowitz LE. The effect of dose and strain of live attenu- ated measles vaccines on serological responses in young infants. Biologicals **1995**; 23:95–106.
29. van der Maas NA, Woudenberg T, Hahne SJ, de Melker HE. Tolerability of early measles-mumps-rubella vaccination in infants aged 6–14 months during a mea- sles outbreak in The Netherlands in 2013–2014. J Infect Dis **2015**.
30. Gans HA, Yasukawa LL, Sung P, et al. Measles humoral and cell-mediated immu- nity in children aged 5-10 years after primary measles immunization administered at 6 or 9 months of age. J Infect Dis **2013**; 207:574–82.
31. De Serres G, Boulianne N, Defay F, et al. Higher risk of measles when the first dose of a 2-dose schedule of measles vaccine is given at 12-14 months versus 15 months of age. Clin Infect Dis **2012**; 55:394–402.

Chapter 6

Tolerability of early measles-mumps-rubella vaccination in infants aged 6-14 months during a measles outbreak in the Netherlands in 2013-2014

Nicoline A.T. van der Maas
Tom Woudenberg
Susan J.M. Hahné
Hester E. de Melker

Published in:
J Infect Dis. 2015.
(DOI: 10.1093/infdis/jiv756*)*

Abstract

Background

In 2013-2014, a measles outbreak spread through the Netherlands. To protect young infants, measles-mumps-rubella (MMR) vaccination was offered to 6-14-month-olds in municipalities with MMR1 coverage below 90%. We assessed tolerability of this early MMR.

Methods

After study-entry, parents of eligible infants (n=10,097) filled in a questionnaire. In case the infant received an early MMR (n=962), we asked information on adverse events (AEs). AE-frequencies were compared between 6-8-, 9-11- and 12-14-month-olds. Using multivariable logistic regression, we assessed the association between the risk of AEs and age at early MMR.

Results

Parents of 59 (6.1%) and 350 (36.4%) infants receiving early MMR reported local and systemic AEs, respectively. Parents of infants vaccinated at 6-8 months reported less frequently systemic AEs (32%) than parents of children vaccinated at 9-11 (45%) and 12-14 (43%) months (p=<0.001). For local AEs there were no differences (5%, 7% and 10%, respectively; p=0.08). Compared to vaccination at 6 months, all older infants, except 14-month-olds, showed an increased risk for any AE and for systemic AEs starting 5-12 days after vaccination.

Conclusions

Early MMR is well tolerated with lowest AE-frequencies found in 6-8-month-olds. Thus, it is a safe intervention to protect young infants against measles.

Introduction

Measles is a highly contagious infectious disease, with most severe disease in young infants and adults (1). Measles vaccination was introduced in the National Immunisation Programme (NIP) in the Netherlands in 1976. Since 1987, measles vaccination is given in combined measles-mumps-rubella (MMR) vaccination at 14 months and 9 year of age with corresponding coverage amounting to 96% (first dose) and 93% (first and second dose) (2).

From May 2013 until March 2014, a measles outbreak spread across the Netherlands, mainly among orthodox Protestants living in socio-geographically clustered communities with a low acceptance of vaccination (3). A previous outbreak among the same group occurred in 1999-2000 with more than 3,200 registered cases (4).

To protect infants below the age of routine MMR vaccination in high-risk areas, all infants aged 6-14 months living in municipalities with MMR1 coverage below 90% were invited for an early MMR vaccination. Current vaccination guidelines in the Netherlands already advice to vaccinate infants from 6 months onwards when there is a real risk to contract measles, e.g. when travelling to a country where measles is endemic (5). This is similar to guidelines in the United States (6).

Worldwide licensed MMR vaccines are registered from 12 months of age, while in outbreak settings they can be used from 9 months onwards. In concordance with the Summary of Product Characteristics (SPC) information, infants receiving MMR vaccination before 12 months of age are offered a second MMR vaccination after the age of one year because of the beneficial effects on the cellular and humoral immune response against measles (7). Irrespective of early MMR vaccination, in the Netherlands all children are offered another dose of MMR at the age of nine years. The advice to vaccinate infants aged 6 months and older was based on Dutch population-based seroprevalence data from 1995-1996 and 2006-2007, combined with evidence on age-specific immunogenicity and effectiveness (8-11). The seroprevalence data suggested that most infants of 6 months or older lacked maternal antibodies, especially when they were born to vaccinated mothers.

MMR vaccination from 6 months old onwards is regarded safe based on studies mainly performed during vaccination campaigns in developing countries (12-15). Some studies also show beneficial effects due to a reduced overall mortality after early measles vaccination (16). In the light of continuing measles outbreaks in developed countries and the need to comply with WHO targets for eliminating measles and rubella, information on effectiveness, safety and impact of early MMR vaccination gives valuable input to policy makers responsible for outbreak control measures.

In this article we describe and discuss results of the tolerability monitoring of the early MMR vaccination campaign in the Netherlands.

Methods

Setting and participants

In response to the measles outbreak among orthodox Protestants, an outbreak management team decided on June 17th 2013 to offer early MMR vaccination to all infants between 6 and 14 months of age living in municipalities with MMR1 coverage below 90%. On July 13th 2013, parents of eligible infants received a personal invitation for early MMR through the routine vaccination programme register. The Netherlands has a very complete national vaccination registration, which allows direct targeting of additional vaccination to risk groups (17). Thereafter, all parents of infants turning 6 months in the previous week and resident in the eligible municipalities received an invitation for early MMR vaccination of their infant. Last invitations were distributed in week 8 of 2014. To avoid interference with the willingness to vaccinate, invitations to participate in our study were sent 4 weeks after the invitation for vaccination. Parents willing to participate could return an application form with their e-mail address. In return, they received a link to an online questionnaire.

Parents who indicated in the past that they do not want to receive regular mail from the vaccination registry were not invited to participate in our study.

For this study IRB-approval was not necessary, as checked with the Central Committee on Research Involving Human Subjects of the Netherlands.

Vaccine

The vaccine administered during this vaccination campaign was identical to the MMR vaccine used in the NIP at 14 months and 9 years of age at that time (MMRvaxpro®; Sanofi Pasteur MSD). This vaccine contains at least $1x10^3$ 50% cell culture infectious dose ($CCID_{50}$) measles virus Enders Edmonston strain, $12.5x10^3$ $CCID_{50}$ mumps virus Jeryl Lynn™ strain and $1x10^3$ $CCID_{50}$ rubella virus Wistar RA 27/3 strain. All strains are live attenuated. Measles and mumps strains are produced in chick embryo blasts, whereas the rubella strain is produced in WI-38 human diploid lung fibroblasts. The vaccination is given subcutaneously in the upper arm.

Data collection

The online questionnaire asked for demographics of the infant eligible for early MMR and of the entire household. Furthermore, past and present measles infections and vaccination status of all household members was ascertained. In case early MMR was administered, questions about local and systemic adverse events (AEs) were asked with details on severity, interval with vaccination and duration of symptoms. Tolerability data are only available for infants who received the early MMR vaccination before parents filled in the first questionnaire.

Outcome definitions

Local AEs were classified as mild, moderate or pronounced. Systemic AEs were dichotomized. We defined fever as a temperature ≥38.0°C., measured sublingual, intra-auricular or rectally, based on the Brighton Collaboration case definition (18). Very high fever was defined as a temperature ≥40.5°C. Time between early MMR and start of systemic AEs was divided in three periods, i.e. start on days 0-4, 5-12 or ≥13.

Covariates

All covariates were retrieved from the questionnaire. If parents permitted, their infant's vaccination status was checked in the national vaccination register. All other covariates were self-reported without validation.

Statistics

Frequencies and means of demographics, local and systemic AEs are presented overall and stratified by age, categorizing infants in 3 age groups; 6-8-, 9-11- and 12-14-month-olds. Differences were tested using Pearson's Chi Square or Fisher's exact test (for dichotomous and categorical variables) or student t-test (for continuous variables).

To assess whether age at time of the early MMR was associated with risk for any AE (i.e. local or systemic AE in any risk window) or with systemic AEs starting 5-12 days after early MMR vaccination only, we performed multivariable logistic regression. Hereby age was categorized per month. Covariates with a plausible or known effect on the outcome were part of the multivariable model as possible confounders, i.e. sex, underlying disease of the infant, ever being breastfed, gestational age, older siblings in the household, maternal age and educational level, measles vaccination status and past measles infection of the mother and reasons to refuse vaccination (see also Table 1). Using stepwise backward selection, all covariates with <10% influence on the estimate of the main determinant, i.e. age in months, were discarded from the model. We also assessed possible interactions. Risks are presented as odds ratios (ORs) with 95% confidence intervals (95%CI).

Analyses were performed using SAS version 9.3. In all analyses, a p-value <0.05 was considered statistically significant.

Results

Response

In total 10,097 infants in all (n=29) municipalities with MMR1 coverage below 90% in 2012 were invited for an early MMR. Of these, parents of 9,974 infants were invited to participate in the study (for 123 infants the address was not available or parents had indicated that they do not want to receive regular mail from the vaccination registry).

Parents of 1,866 infants (19%) responded. Finally, parents of 1,304 infants (13%) filled in the first questionnaire. By the time parents filled in the first questionnaire, 962 infants (74%) had already received an early MMR. We report tolerability data of these 962 infants.
The median interval between MMR0 and filling out the questionnaire was 49 days (mean 51.4d, range 1-211). For 6-8-month-olds, the median interval was 44d (mean 48.7d, range 1-211), while this was 57.2d (mean 55d, range 9-148) and 51d (mean 53.3d, range 8-144) for 9-11- and 12-14-month-olds, respectively. Differences in median interval between the groups were statistically significant ($p<0.0001$).

Demographics
Median age at early MMR vaccination was 7.0 months (range 5.7-14.9). In total 603 (62.7%) infants received their early MMR at the age of 6-8 months (median 6.3), whereas 239 (24.8%) and 120 (12.5%) infants received their early MMR at age 9-11 months (median 10.0) and 12-14 months (median 12.7), respectively. An equal number of boys and girls (n=481; 50%) received early MMR vaccination during this campaign. Sex distribution between the three age groups were equal ($p=0.3$; Table 1). Furthermore, we found no differences in day-care attendance; underlying disease of infant; duration of pregnancy; presence of older siblings; refusal of vaccination based on life philosophy or religion; maternal educational level; maternal vaccination status and maternal measles infection in the past between the three age groups. In contrast, 6-8-month-olds were less frequently ever being breastfed ($p=0.01$) and less frequently had a mother in the oldest age category, i.e. older than 38 years ($p=0.02$) than infants of older age groups.

Local AEs
Parents of 59 infants (6.1%) reported one or more local AEs following the early MMR (Table 2). There was a trend of an increasing frequency of local AEs with increasing age, but differences were not statistically significant ($p=0.08$). We found no difference in the frequency of any local AE between the early and the late responders, both in the overall study population ($p=0.09$) as well as in the three age groups ($p=0.2$, $p=0.5$ and $p=0.6$ for respectively 6-8m, 9-11m and 12-14m). Redness (n=53; 5.5%) was reported most often, followed by pain (n=40; 4.2%) and swelling (n=33; 3.4%). Redness, pain and swelling started within 24 hours after vaccination in 72%, 80% and 82% respectively, whereas symptoms lasted less than three days in 72%, 75% and 70%. Parents of 8 (0.1%), 6 (0.1%) and 4 (0.07%) infants reported that respectively redness, pain and swelling was pronounced.

Systemic AEs

Parents of 350 infants (36.4%) reported one or more systemic AEs (Table 2). Parents of infants who were 6-8 months old at the time of early MMR reported less frequently systemic AEs than older age groups (p<0.001). Overall frequencies were 31.7% (n=191), 45.5% (n=108) and 42.5% (n=51) for those aged 6-8, 9-11 and 12-14 month olds, respectively. We found no difference in the frequency of any systemic AE between the early and the late responders in the overall study population (p=0.1) and in the 12-14-month-olds (p=0.3). In the 6-8-month-olds the frequency of any systemic AE was higher in the early responders than in the late responders (52.8% vs 47.2%; p=0.05). Likewise, among the 9-11-month-olds early responders reported any systemic AE in 56.9% compared with 43.1% in late responders (p=0.04). No differences in the frequencies of specific systemic AEs were found between age groups, except for rash, which occurred less frequently in the group with the youngest age at vaccination (8%, 20% and 18%, respectively).

Listlessness (n=274; 28%) was reported most often, followed by fever (n=182; 19%), crying (n=185; 19%), rash (n=116; 12%) and sleeping problems (n=94; 10%). Parents of 2 infants reported fever with a temperature of 40.5°C or higher. For one of these fever started within the risk window 5-12 days after vaccination. Most systemic AEs started 5-12 days after the vaccination, with a range of 62% to 75% for specific systemic AEs. A minority of parents reported a start of symptoms within 4 days after vaccination (range of percentages regarding different systemic AEs 13%-26%) or more than 12 days after vaccination (range 5%-24%). In 30%-69% of specific systemic AEs, duration of symptoms was 2 days or less, whereas in 15%-26% and 16%-50% symptoms lasted 3 days or 4 days and more, respectively.

Influence of age on occurrence of local and systemic AEs

After entering all possible confounders in the multivariable logistic regression, for both outcomes stepwise backward selection led to removal of all covariates, i.e. no adjustment was necessary. With 6-month-olds set as reference, ORs for all older ages were above 1 (range 1.1-2.7 and 1.4-4.0 for any AE and systemic AEs 5-12d after vaccination, respectively) except for 14-month-olds (ORs 0.5 and 0.8) for local and systemic AEs (Table 3). For any AE, ORs were not statistically significant in 8- and 14-month-olds, whereas for systemic AEs occurring 5-12 days after vaccination ORs were non-significant in infants aged 7, 8, 12 or 14 months.

Table 1. Absolute number (%) of background characteristics per age group.

Background characteristics↓	Age at administration of first MMR->	6-8-months; N=603 n (%)	9-11-months; N=239 n (%)	12-14-months; N=120 n (%)	p-value
Day-care attendance	no	199 (33.0%)	81 (33.9%)	41 (34.2%)	0.9
	yes	404 (67.0%)	158 (66.1%)	79 (65.8%)	
Ever breastfed	no	176 (29.2%)	51 (21.3%)	23 (19.2%)	**0.01**
	yes	427 (70.8%)	188 (78.7%)	97 (80.8%)	
Underlying disease of infant	no	559 (92.7%)	230 (96.2%)	108 (90.0%)	0.06
	yes	44 (7.3%)	9 (3.8%)	12 (10.0%)	
Gender	male	301 (49.9%)	113 (47.3%)	67 (55.8%)	0.3
	female	302 (50.1%)	126 (52.7%)	53 (44.2%)	
Duration of pregnancy	37-44 wk	567 (94.0%)	228 (95.4%)	109 (90.8%)	0.6
	32-36 wk	28 (4.6%)	9 (3.8%)	9 (7.5%)	
	26-31 wk	6 (1.0%)	2 (0.8%)	2 (1.7%)	
	unknown	2 (0.3%)	0	0	
Older siblings in the household	no	273 (45.3%)	116 (48.5%)	47 (39.2%)	0.2
	yes	330 (54.7%)	123 (51.5%)	73 (60.8%)	
Refusing vaccination based on life philosophy	no	544 (90.2%)	212 (88.7%)	100 (83.3%)	0.2
	moderate	58 (9.6%)	26 (10.9%)	20 (16.7%)	

or religion	strong	1 (0.2%)	1 (0.4%)	0	
Maternal year of birth	1986-1995	113 (18.7%)	40 (16.7%)	17 (14.2%)	**0.02**
	1976-1985	444 (73.6%)	168 (70.3%)	86 (71.7%)	
	1966-1975	37 (6.1%)	26 (10.9%)	17 (14.2%)	
	unknown	9 (1.5%)	5 (2.1%)	0	
Maternal educational level	no education or only primary/secondary school	50 (8.3%)	24 (10.0%)	7 (5.8%)	0.5
	intermediate vocational education	230 (38.1%)	98 (41.0%)	51 (42.5%)	
	higher vocational education or university	316 (52.4%)	113 (47.3%)	62 (51.7%)	
	unknown	7 (1.2%)	4 (1.7%)	0	
Maternal vaccination status	unvaccinated	39 (6.5%)	23 (9.6%)	5 (4.2%)	0.3
	vaccinated	511 (84.7%)	194 (81.2%)	103 (85.8%)	
	unknown	53 (8.8%)	22 (9.2%)	12 (10.0%)	
Past maternal measles infection	no	405 (67.2%)	153 (64.0%)	69 (57.5%)	0.2
	yes	81 (13.4%)	32 (13.4%)	17 (14.2%)	
	unknown	117 (19.4%)	54 (22.6%)	34 (28.3%)	

Table 2. Absolute number and frequencies of local and systemic adverse events per age group and overall.

Age at administration of the early MMR	6-8-months; N=603 n (%)	9-11-months; N=239 n (%)	12-14-months; N=120 n (%)	Difference between age groups; p-value	Total; N=962
Any local AE	30 (5%)	17 (7%)	12 (10%)	0.08	59 (6%)
redness	26 (4%)	15 (6%)	12 (10%)	0.58	53 (6%)
pain	21 (3%)	13 (5%)	6 (5%)	0.15	40 (4%)
swelling	15 (2%)	11 (5%)	7 (6%)	0.67	31 (3%)
Any systemic AE	191 (32%)	108 (45%)	51 (43%)	0.0004	350 (36%)
listlessness	149 (25%)	87 (36%)	38 (32%)	0.68	274 (28%)
fever	106 (18%)	68 (28%)	25 (21%)	0.22	200 (21%)
crying	98 (16%)	59 (25%)	28 (23%)	0.82	185 (19%)
rash	46 (8%)	48 (20%)	22 (18%)	0.0004	116 (12%)
sleeping problems	52 (9%)	27 (11%)	15 (13%)	0.83	94 (10%)
diarrhoea	17 (3%)	10 (4%)	4 (3%)	0.96	31 (3%)
vomiting	12 (2%)	7 (3%)	2 (2%)	0.79	21 (2%)
paleness	11 (2%)	7 (3%)	2 (2%)	0.81	20 (2%)

Table 3. Logistic regression analysis of risk of any AE and of systemic AEs 5-12d after early MMR and age.

	Infants	Any AE			Systemic AEs 5-12d after vaccination		
age at time of MMR0		yes N (%)	OR	95%CI	yes N (%)	OR	95%CI
6 months	388	120 (31%)	ref		76 (20%)	ref	
7 months	123	51 (41%)	1.58	1.04-2.4	31 (25%)	1.38	0.86-2.23
8 months	81	27 (33%)	1.12	0.67-1.86	20 (25%)	1.35	0.77-2.37
9 months	72	31 (43%)	1.69	1.01-2.82	24 (33%)	2.05	1.18-3.56
10 months	81	39 (48%)	2.07	1.28-3.37	27 (33%)	2.05	1.21-3.47
11 months	66	30 (45%)	1.86	1.1-3.16	20 (30%)	1.79	1-3.19
12 months	68	31 (46%)	1.87	1.11-3.16	18 (26%)	1.48	0.82-2.68
13 months	55	30 (55%)	2.68	1.51-4.75	27 (49%)	3.96	2.21-7.11
14 months	12	2 (17%)	0.45	0.1-2.07	2 (17%)	0.82	0.18-3.83

Discussion

To our knowledge, this is the first study that assessed tolerability of MMR vaccination administered from 6 months of age onwards in a developed country. We showed that this early MMR was well tolerated and that AEs in infants receiving their first MMR dose at 6-8-month of age were less frequent compared to MMR administered at 14 months, the age when routine MMR1 vaccination is scheduled in the Netherlands.

We found that the occurrence of AEs is age dependent. Frequencies of all local and most systemic AEs were lower in the youngest age group of 6-8 month olds compared with older age groups. For both local as well as most systemic AE frequencies were lowest in the youngest age category. For fever and rash, we found respectively 15% and 7% (6m), 20% and 20% (9m), and 24% and 15% (12m). However, only the frequencies of rash and all systemic AEs combined differed statistically significant between the age groups. Studies performed in Uzbekistan and Malawi found no

influence of age on the occurrence of specific AEs with measles containing vaccines administered at 6 and 9 month of age (12, 13). Bolotovski et al. found frequencies of 6-14% for fever and rash after administration of several measles vaccines differing in strain and potency to 6 (n=1202) and 9 (n=1250) month old infants (13). AEs were collected via an interview during a home visit in the second week after vaccination. In the study of Helfand et al. proportions for fever and rash were somewhat lower than in our study (14% and 1%, 6m; n=512 and 11% and 1%, 9m; n=572), following measles vaccination of a HIV-unexposed control group (12). In the study of Helfand et al., parents recorded AEs in a daily log for 21 days after vaccination. The differences in the frequency of AEs between these studies and our study may be attributed to varying methods of AE ascertainment. Furthermore, Bolotovski and Helfand presented no case definition and cut-off for fever, possibly leading to different counting of cases with fever, which perhaps partly explains the differences.

In a study on German infants, receiving MMR, 70% of 9-11-month-olds (n=43) and 76% of 12-14-month-olds (n=29) reported fever (19). This is much higher than the frequencies we found (28% and 21%), but these differences are difficult to interpret giving the small sample size of the German study.

Another possible explanation for the lower frequencies of AEs in younger infants is the presence of maternal antibodies against measles virus that prohibit replication of vaccine virus and thereby prevent the occurrence of AEs. Dutch seroprevalence data showed that, in the general population, immunoglobulin G antibody levels were below the cutoff for protection in 54% of 3-month-old infants (95% confidence interval, 34%–74%) (9). Among children born to orthodox reformed Protestant mothers who in general were naturally infected, the duration of protection was approximately 2 months longer(10). Furthermore, breastfeeding, maternal vaccination status, and past measles virus infection of the mother were included in the multivariable regression analysis but did not influence the main estimate by >10% and were therefore not considered as confounders. Therefore, we think the influence of maternal antibodies is limited. However, we cannot exclude a possible influence of nondetectable, residual maternal antibodies. Furthermore, young infants are immunologically immature, which may also lead to less reactogenicity.

Two other Dutch surveys on the tolerability of MMR1, given at children aged 14 months, found different frequencies of local and systemic AEs than we assessed in our 12-14-month-olds (20, 21). Kroesbergen et al. (n=863) found 9% local reactions and 32%, 38% and 24% for fever, crying and rash, respectively (20), while Jongerius et al. (n=391) found 24%, 20% 17% and 17% for the respective AEs (21). In our study, frequencies were 10%, 14%, 18% and 13%. The lower frequencies we found may be explained by study logistics: study participation was asked 4 weeks after the invitation for vaccination and infants received the vaccination before parents filled in the survey and maybe they did not remember all AEs, in particular the less severe symptoms. Another possible explanation for the lower frequency of AEs found in our

study is that our primary aim was to assess vaccine effectiveness with additional questions on AEs, while both MMR1 surveys exclusively assessed tolerability. Therefore, frequencies found probably suffer less from over-reporting compared with the two tolerability surveys.

Apart from this survey, parents were asked to report AEs after vaccination to the Dutch Pharmacovigilance Center, Lareb. Lareb received 11 reports, of which 2 involved serious systemic AEs (1 infant had febrile convulsion and 1 experienced crying and dehydration).

Our study has several limitations. First, only 13% of the parents of eligible infants completed the questionnaire, which may hamper generalizability. However, the overall early MMR vaccination coverage in the 29 municipalities was 66%, while 74% of the infants in our study received early MMR vaccination. These percentages do not differ very much. Therefore, we think the risk of bias is low, despite the low response rate. Furthermore, the sex distribution in our study is comparable to the distribution in the general population.

The overall median interval between early MMR vaccination and questionnaire completion was >1.5months. This possibly influenced the reported AEs, resulting in an underestimation. However, because the age group in which this interval was shortest also had the lowest AE frequencies, recall bias may be limited.

Because this outbreak occurred in a high-income country, results may be less applicable to developing countries. The latter countries often have a less developed healthcare system and a greater prevalence of malnutrition, possibly (1) resulting in an impaired immune response and (2) influencing the occurrence of AEs.

Furthermore, all AEs were self-reported without additional validation. This may have led to an overestimation of AE frequencies. As known from the twin study by Peltola et al on MMR vaccine–associated AEs, the vast majority of AEs following MMR vaccination are temporally associated but not causally related (22). Therefore, most AEs reported in our study were probably not caused by MMR vaccination. Since we did not compare results with the occurrence of symptoms in age matched unvaccinated children, we could not assess causality. We also were unable create an internal control group by monitoring the occurrence of the AEs prior to vaccination, because we sent invitations to participate 4–5 weeks after the invitation for vaccination so that there would be no interference with parent's decision regarding the vaccination. However, the rates found are useful for monitoring variation in AE frequencies between groups and over time and an efficient and easy way to monitor tolerability.

To conclude, our results show that early MMR vaccine administration during an outbreak is safe to protect infants aged 6–14 months against measles. Frequencies of local and common systemic AEs were lowest in younger age classes.

References

1. Plotkin S, Orenstein WA, Offit PA. Vaccines. 6 ed2012.
2. Van Lier A. immunisation coverage National Immunisation Programme in the Netherlands; year of report 2014. Bilthoven: National Institute for Public Health and the Environment; 2014. Report No.: 150202003/2014.
3. Knol M, Urbanus A, Swart E, Mollema L, Ruijs W, van Binnendijk R, et al. Large ongoing measles outbreak in a religious community in the Netherlands since May 2013. Euro Surveill. 2013;18(36):pii=20580.
4. van den Hof S, Meffre CM, Conyn-van Spaendonck MA, Woonink F, de Melker HE, van Binnendijk RS. Measles outbreak in a community with very low vaccine coverage, the Netherlands. Emerg Infect Dis. 2001;7(3 Suppl):593-7.
5. National guideline on measles: National Institute for Public Health and the Environment-Centre for Infectious Disease Control; [updated 5-5-201124-06-2015]. Available from: http://www.rivm.nl/Bibliotheek/Professioneel_Praktisch/Richtlijnen/Infectieziekten/LCI_richtlijnen/LCI_richtlijn_Mazelen_morbilli.
6. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS, Centers for Disease C, Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(RR-04):1-34.
7. M-M-RVAXPRO: European Medicines Agency; 2015 [updated 22-01-201522-06-2015]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000604/human_med_000907.jsp&mid=WC0b01ac058001d124.
8. Effectiveness of early MMR on the short and long term: a comparative assessment Bilthoven: National Institute for Public Health and the Environment-Centre for Infectious Disease Control; 2013 [28-09-2015]. Available from: http://www.rivm.nl/dsresource?objectid=rivmp:210299&type=org&disposition=inline.
9. Mollema L, Smits GP, Berbers GA, Van Der Klis FR, Van Binnendijk RS, De Melker HE, et al. High risk of a large measles outbreak despite 30 years of measles vaccination in The Netherlands. Epidemiol Infect. 2014;142(5):1100-8.
10. Waaijenborg S, Hahne SJ, Mollema L, Smits GP, Berbers GA, van der Klis FR, et al. Waning of Maternal Antibodies Against Measles, Mumps, Rubella, and Varicella in Communities With Contrasting Vaccination Coverage. J Infect Dis. 2013.
11. van den Hof S, Berbers GA, de Melker HE, Conyn-van Spaendonck MA. Sero-epidemiology of measles antibodies in the Netherlands, a cross-sectional study in a national sample and in communities with low vaccine coverage. Vaccine. 1999;18(9-10):931-40.
12. Helfand RF, Witte D, Fowlkes A, Garcia P, Yang C, Fudzulani R, et al. Evaluation of the immune response to a 2-dose measles vaccination schedule administered at 6 and 9 months of age to HIV-infected and HIV-uninfected children in Malawi. J Infect Dis. 2008;198(10):1457-65.
13. Bolotovski VM, Grabowsky M, Clements CJ, Albrecht P, Brenner ER, Zargaryantzs AI, et al. Immunization of 6 and 9 month old infants with AIK-C, Edmonston-Zagreb, Leningrad-16 and Schwarz strains of measles vaccine. Int J Epidemiol. 1994;23(5):1069-77.
14. Chandwani S, Beeler J, Li H, Audet S, Smith B, Moye J, et al. Safety and immunogenicity of early measles vaccination in children born to HIV-infected mothers in the United States: results of Pediatric AIDS Clinical Trials Group (PACTG) protocol 225. J Infect Dis. 2011;204 Suppl 1:S179-89.
15. Whittle H, Hanlon P, O'Neill K, Hanlon L, Marsh V, Jupp E, et al. Trial of high-dose Edmonston-Zagreb measles vaccine in the Gambia: antibody response and side-effects. Lancet. 1988;2(8615):811-4.
16. Aaby P, Samb B, Simondon F, Seck AM, Knudsen K, Whittle H. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. BMJ. 1995;311(7003):481-5.
17. van Lier A, Oomen P, de Hoogh P, Drijfhout I, Elsinghorst B, Kemmeren J, et al. Praeventis, the immunisation register of the Netherlands: a tool to evaluate the National Immunisation Programme. Euro Surveill. 2012;17(17).
18. Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004;22(5-6):551-6.
19. Klinge J, Lugauer S, Korn K, Heininger U, Stehr K. Comparison of immunogenicity and reactogenicity of a measles, mumps and rubella (MMR) vaccine in German children vaccinated at 9-11, 12-14 or 15-17 months of age. Vaccine. 2000;18(27):3134-40.
20. Kroesbergen HT, Moret-Huffmeijer L, Vermeer-de Bondt PE. Tolerability of simultaneous administered MMR and MenC vaccination at 14 months of age. Tijdschrijft voor Sociale geneeskunde. 2005;83(7):425-31.
21. Jongerius MC, Rodermans I, van Boxtel RAJ. Post Marketing Study of the tolerability of Dt-IPV and MMR, 2008-2009. Nederlands Vaccin Instituut; 2010. Report No.: NVI-241.
22. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. A double-blind placebo-controlled trial in twins. Lancet. 1986;1(8487):939-42.

Chapter 7

Tolerability of two doses of pandemic Influenza vaccine (Focetria®) and of a prior dose of seasonal 2009-2010 Influenza vaccination in the Netherlands

Nicoline A.T. van der Maas
Sarah Godefrooij
Patricia E. Vermeer-de Bondt
Hester E. de Melker
Jeanet M. Kemmeren

Published in:
Hum Vaccin Immunother 2016 Apr 2;12(4):1027-32
(DOI: 10.1080/21645515.2015.1120394)

Abstract

In the Netherlands, people indicated for seasonal influenza vaccination are divided in three risk groups, i.e. those less than 60 years (y) with comorbidity and those 60y and over with and without comorbidity. Those risk groups were also eligible for pandemic vaccination during the 2009 influenza A(H1N1) pandemic.

We assessed tolerability of seasonal influenza vaccination and two doses of pandemic influenza A(H1N1) vaccine, adjuvanted with MF-59, administered 2 and 5 weeks after seasonal 2009-2010 vaccination among adults.

Vaccinees were asked to return questionnaires on local and systemic adverse events (AEs) after each of 3 consecutive vaccinations given at the office of their General Practitioner. Sex- and risk group-specific AE-frequencies were calculated. Generalized Linear Mixed Model with seasonal vaccination as reference was used to calculate odds ratios (ORs) for AEs of the two pandemic doses.

5553 questionnaires (3251 vaccinees) were returned. Vaccinees reported any local AE after seasonal vaccination and both pandemic doses in 34%, 23% and 18%, respectively. These percentages were 29%, 25% and 16% for any systemic AE. Men reported fewer local and systemic AEs then women ($p<0.0001$). The risk of local (OR range 0.34-0.63) and systemic (OR range 0.39-0.99) AEs (overall, stratified by risk group and by sex) was lower after both pandemic doses compared to seasonal vaccination. This decreased risk was more pronounced after the second pandemic dose than after the first.

Therefore, we conclude that MF59-adjuvanted pandemic vaccine given after seasonal vaccination was well tolerated.

Introduction

Annual influenza epidemics occur worldwide, resulting in considerable morbidity, mortality and economic burden.[1] Morbidity and mortality are generally associated with vulnerable populations at risk of complications of infection, like pneumonia.[2-5]
In 2009, the World Health Organization (WHO) declared a pandemic, caused by an Influenza A(H1N1) strain. In response, the Dutch Health Council advised that all people in the Netherlands, eligible for routine seasonal influenza vaccination should be offered vaccination against this pandemic strain.[6] Several additional groups were defined for vaccination by their General Practitioner (GP), e.g. pregnant women in their second and third trimester and household members of high-risk patients. Health care workers were offered vaccination by their employers whereas children between 6 months and 5 years of age and household members of infants below 6 months of age could get the vaccinations from the municipal health services.[6]
Given the urgency of availability, extensive information on tolerability of these new pandemic influenza vaccines lacked.[7] At the time the vaccines became available, a stern public debate about its safety started worldwide. In the Netherlands, safety of pandemic vaccinations was monitored by passive surveillance and by several active questionnaire surveys. Here we report on the tolerability of the pandemic vaccine administered after the seasonal vaccination in the Netherlands among adults vaccinated at GP office.

Results

Response and demographics

The overall response rate was an estimated 40% with approximately 14,000 questionnaires distributed. No exact numbers distributed per predefined risk group are available, precluding calculation of category specific response rates.
In total, 5553 questionnaires were returned by 3251 participants: 642 (19.7%) vaccinees returned all 3 questionnaires; 1018 (31.3%) and 1591 (48.9%) vaccinees returned 2 or just 1 questionnaire, respectively (Table 1). There was slight predominance (52.5-54.3%) of female respondents, which is comparable to the sex distribution for the adult population in the Utrecht province (52% females). Reported comorbidity varied by vaccination (69.7%-74.8%). In less than 3% of the respondents, sex and comorbidity were unknown. Participants mean age for the three vaccinations varied between 63.8y-65.2y. With respect to administered vaccine, women were statistically significantly younger than men (1.3y, 1.7y and 1.4y for the respective doses).

Table 1. Demographics of the study population

Vaccinees	*Seasonal 09/10*	*1st Focetria®*	*2nd Focetria®*
3 questionnaires	642	642	642
2 questionnaires	619	866	551
1 questionnaire	701	611	279
N	1962 (35.3%	2119 (38.2%)	1472 (26.5%)
Sex			
men	839 (42.8%)	951 (44.9%)	658 (44.7%)
women	1066 (54.3%)	1113 (52.5%)	775 (52.6%)
unknown	57 (2.9%)	55 (2.6%)	39 (2.6%)
Mean age in years (median; range)	65.0 (64.8; 18.4-101.5)	63.8 (63.8; 18.6-95.0)	65.2 (65.1; 18.1-100.8)
men	65.7 (65.1; 18.4-101.5)	64.6 (64.3; 18.7-89.5)	65.9 (65.2; 18.6-100.8)
women	64.4 (64.3; 18.4-94.7)	62.9 (63.5; 18.6-95.0)	64.5 (64.8; 18.1-93.4)
Comorbidity			
yes	1467 (74.8%)	1564 (73.8%)	1027 (69.8%)
no	440 (22.4%)	499 (23.5%)	402 (27.3%)
unknown	55 (2.8%)	56 (2.6%)	43 (2.9%)
Risk Groups			
<60y with comorbidity	392 (20.0%)	473 (22.3%)	255 (17.3%)
≥60y with comorbidity	1075 (54.8%)	1091 (51.5%)	772 (52.4%)
≥60y without comorbidity	440 (22.4%)	499 (23.5%)	402 (27.3%)
unknown	55 (2.8%)	56 (2.6%)	43 (2.9%)

Local Adverse Events

Participants reported a significant higher proportion of any local AE (redness, swelling and/or pain at the injection site) following the seasonal influenza vaccination compared with both pandemic vaccine doses (Table 2). For redness percentages were 17.9%, 4.9% and 3.6% for the respective doses, for swelling 17.3%, 5.1% and 3.9% and for pain at the injection site 28.9%, 20.9% and 17.2%. The majority concerned reports of mild or moderate events. Over the 3 doses together, for redness 20%-28% of the reports concerned pronounced local AEs. Likewise, 18%-19% and 12%-13% of reports on respectively swelling and pain were considered as pronounced.

For any local AE the reported frequency in women was statistically significant higher than in men.

Systemic Adverse Events

Vaccinees reported at least one systemic AE in 29.4% (n=576), 25.3% (n=535) and 16.4% (n=242) following the 3 respective vaccinations. Listlessness, fatigue, headache and myalgia were reported most frequently (Figure 1). After seasonal vaccination, 4.5% (n=88) of vaccinees reported fever, compared with 4.6% (n=98) and 1.9% (n=28) following the first and second pandemic doses, respectively. For fever following seasonal vaccination, 51 participants (2.6%) reported a 'the highest temperature measured'. Twenty-five Participants (1.3%) reported a temperature ≥38°C (median 38.5°C; range 38-39.6°C). For the first pandemic dose, 68 participants (3.2%) reported a highest temperature (41(1.9%) ≥38°C; median 38.0°C; range 38-40°C). For the second pandemic dose 11 (0.7%) out of 17 (1.2%) vaccinees reported a temperature ≥38°C (median 38.0°C; range 38-39°C). Proportions for all reported systemic AEs, except itch, were not statistically significantly different between the seasonal vaccination and the first pandemic dose. Proportions of reported fever, listlessness, fatigue, headache, dizziness and myalgia were all statistically significantly higher after the first pandemic dose than after de second pandemic dose.

Frequencies of reported systemic AEs in women were higher than in men, for all 3 vaccinations except for rash after both pandemic doses. These differences were statistically significant except for fever and fainting (all doses), dizziness (seasonal vaccination and second pandemic dose), listlessness (first pandemic dose) and arthralgia (second pandemic dose).

Risk Groups

For all 3 vaccine doses, the risk group <60y with comorbidity showed higher frequencies of local and systemic AEs compared with both other risk groups ≥60y (Table 3, Figure 2). This difference was statistically significant for any local AE, any

Table 2. Numbers and frequencies of severities of local adverse events by sex. Differences between men and women are tested. Significant p-values are in bold.

	Seasonal 09/10; N=1962 (%)[a]			1st pandemic dose; N=2119 (%)[b]			2nd pandemic dose; N=1472 (%)[c]		
	Men (n=839)	**Women (n=1066)**	**p-value**	**Men (n=951)**	**Women (n=1113)**	**p-value**	**Men (n=658)**	**Women (n=775)**	**p-value**
Any local AE	181 (21.6%)	463 (43.4%)	**<0.001**	1445 (15.3%)	328 (29.5%)	**<0.001**	85 (12.9%)	172 (22.2%)	**<0.001**
Any Redness	61 (7.3%)	278 (26.1%)	**<0.001**	9 (1.0%)	93 (8.4%)	**<0.001**	6 (0.9%)	47 (6.1%)	**<0.001**
mild	40 (65.6%)	80 (28.8%)	**<0.001**	4 (44.4%)	41 (44.1%)	0.7	3 (50.0%)	17 (36.2%)	0.4
moderate	13 (21.3%)	107 (38.5%)		4 (44.4%)	23 (24.7%)		1 (16.7%)	13 (27.7%)	
pronounced	5 (8.2%)	78 (28.1%)		1(11.1%)	20 (21.5%)		1 (16.7%)	14 (29.8%)	
unknown	3 (4.9%)	13 (4.7%)		0	9 (9.7%)		1 (16.7%)	3 (6.4%)	
Any Swelling	64 (7.6%)	265 (24.9%)	**<0.001**	25 (2.6%)	83 (7.5%)	**<0.001**	13 (2.0%)	42 (5.4%)	**<0.001**
mild	45 (70.3%)	103 (38.9%)	**<0.001**	13 (52.0%)	35 (42.2%)		7 (53.8%)	21 (50.0%)	0.17
moderate	11 (17.2%)	99 (37.4%)		8 (32.0%)	22 (26.5%)		5 (38.5%)	9 (21.4%)	
pronounced	5 (7.8%)	54 (20.4%)		2 (8.0%)	18 (21.7%)		1 (7.7%)	10 (23.8%)	
unknown	3 (4.7%)	3 (3.4%)		2 (8.0%)	8 (9.6%)		0	1(4.8%)	
Any Pain at injection site	159 (18.9%)	387 (36.3%)	**<0.001**	141 (14.8%)	293 (26.3%)	**<0.001**	79 (12.0%)	165 (21.3%)	**<0.001**
Mild	96 (60.4%)	162 (41.9%)	**<0.001**	92 (65.2%)	143 (48.8%)	**0.009**	45 (57.0%)	78 (47.3%)	**0.01**
Moderate	42 (26.4%)	143 (37.0%)		28 (19.9%)	83 (28.3%)		26 (32.9%)	45 (27.3%)	
pronounced	10 (6.3%)	59 (15.2%)		10 (7.1%)	41 (14.0%)		3 (3.8%)	30 (18.2%)	
unknown	11 (6.9%)	23 (5.9%)		11 (7.8%)	21 (8.9%)		5 (6.3%)	12 (7.3%)	

[a]: 57 participants with unknown sex
[b]: 55 participants with unknown sex
[c]: 39 participants with unknown sex

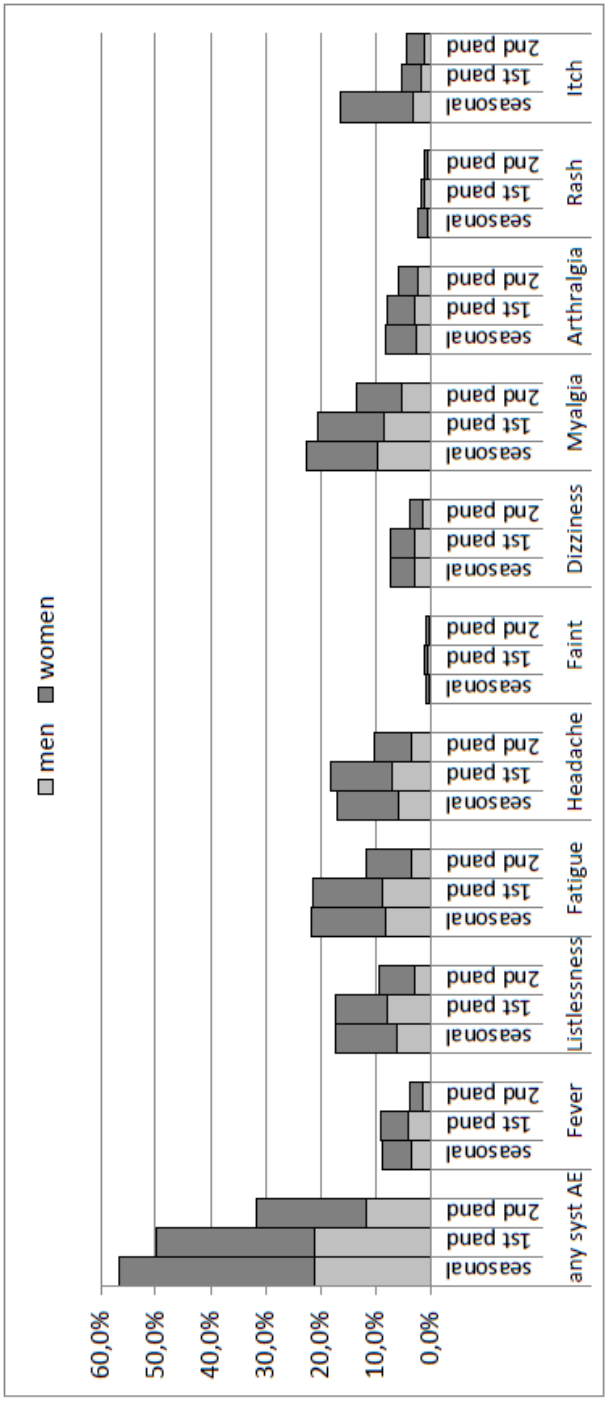


Figure 1. Sex specific proportions (%) of systemic adverse events' after seasonal Influenza vaccination and 2 doses of pandemic Influenza vaccine.

Table 3. Number and frequencies of local and systemic adverse events by risk group and vaccination. Differences between risk groups are tested. Statistical significant p-values are in bold.

	Seasonal 09/10; N=1962 (%)[a]				1st pandemic dose; N=2119 (%)[b]				2nd pandemic dose; N=1472 (%)[c]			
	<60y with comorbidity (n=392)	*≥60y with comorbidity (n=1075)*	*≥60y without comorbidity (n=440)*	**p-value**	*<60y with comorbidity (n=473)*	*≥60y with comorbidity (n=1091)*	*≥60y without comorbidity (n=499)*	**p-value**	*<60y with comorbidity (n=255)*	*≥60y with comorbidity (n=772)*	*≥60y without comorbidity (n=402)*	**p-value**
Any local AE	213 (54.3%)	308 (28.7%)	130 (29.6%)	**<0.001**	195 (41.2%)	194 (17.8%)	85 (17.0%)	**<0.001**	98 (38.4%)	105(13.6%)	59 (14.7%)	**<0.001**
Any Redness	113 (28.8%)	163 (15.2%)	66 (15.0%)	**<0.001**	49 (10.4%)	38 (3.5%)	15 (3.0%)	**<0.001**	21 (8.2%)	25 (3.2%)	7 (1.7%)	**<0.001**
Mild	30 (26.5%)	70 (42.9%)	21 (31.8%)	**<0.001**	17 (34.7%)	20 (52.6%)	8 (53.3%)	0.4	7 (33.3%)	9 (36.0%)	4 (57.1%)	0.6
Moderate	34 (30.1%)	55 (33.7%)	32 (48.5%)		15 (30.6%)	7 (18.4%)	5 (33.3%)		5 (23.8%)	7 (28.0%)	2 (28.6%)	
Pronounced	42 (37.2%)	34 (20.9%)	8 (12.1%)		13 (26.5%)	6 (15.8%)	2 (13.3%)		8 (38.1%)	7 (28.0%)	1 (14.3%)	
unknown	7 (6.2%)	4 (2.5%)	5 (7.6%)		4 (8.2%)	5 (13.2%)	0		1 (4.8%)	2 (8.0%)	1 (14.3%)	
Any Swelling	110 (28.1%)	162 (15.1%)	59 (13.4%)	**<0. 001**	52 (11.0%)	41 (3.8%)	15 (3.0%)	**<0.001**	28 (11.0%)	21 (2.7%)	8 (2.0%)	**<0.001**
Mild	38 (34.5%)	86 (53.1%)	23 (39.0%)	**0.01**	20 (38.5%)	19 (46.3%)	8 (53.3%)	0.3	13 (46.4%)	9 (42.9%)	6 (75.0%)	0.1
Moderate	37 (33.6%)	51 (31.5)	25 (42.4%)		15 (28.8%)	10 (24.4%)	6 (40.0%)		6 (21.4%)	8 (38.1%)	2 (25.0%)	
Pronounced	30 (27.3%)	23 (14.2%)	7 (11.9%)		13 (25.0%)	6 (14.6%)	1 (6.7%)		9 (32.1%)	2 (9.5%)	0	
unknown	5 (4.5%)	2 (1.2%)	4 (6.8%)		4 (7.7%)	6 (14.6%)	0		0	2 (9.5%)	0	
Any Pain at injection site	191 (48.7%)	256 (23.8%)	105 (23.9%)	**<0.001**	178 (37.6%)	179 (16.4%)	79 (15.8%)	**<0.001**	93 (36.5%)	99 (12.8%)	57 (14.2%)	**<0.001**
Mild	77 (40.3%)	123 (48.0%)	57 (54.3%)	0.06	83 (46.6%)	109 (60.9%)	47 (59.5%)	**0.006**	37 (39.8%)	55 (55.6%)	33 (57.9%)	**0.003**
Moderate	68 (35.6%)	90 (35.2%)	28 (26.7%)		45 (25.3%)	45 (25.1%)	20 (25.3%)		28 (30.1%)	25 (25.3%)	19 (33.3%)	
Pronounced	35 (18.3%)	26 (10.2%)	10 (9.5%)		33 (18.5%)	11 (6.1%)	8 (10.1%)		23 (24.7%)	10 (10.1%)	1 (1.8%)	
unknown	11 (5.8%)	17 (6.6%)	10 (9.5%)		17 (9.6%)	14 (7.8%)	4 (5.1%)		5 (5.4%)	9 (9.1%)	4 (7.0%)	

[a]: for 55 (2.8%) vaccinees information on comorbidity was missing.
[b]: for 56 (2.6%) vaccinees information on comorbidity was missing.
[c]: for 43 (2.9%) vaccinees information on comorbidity was missing.

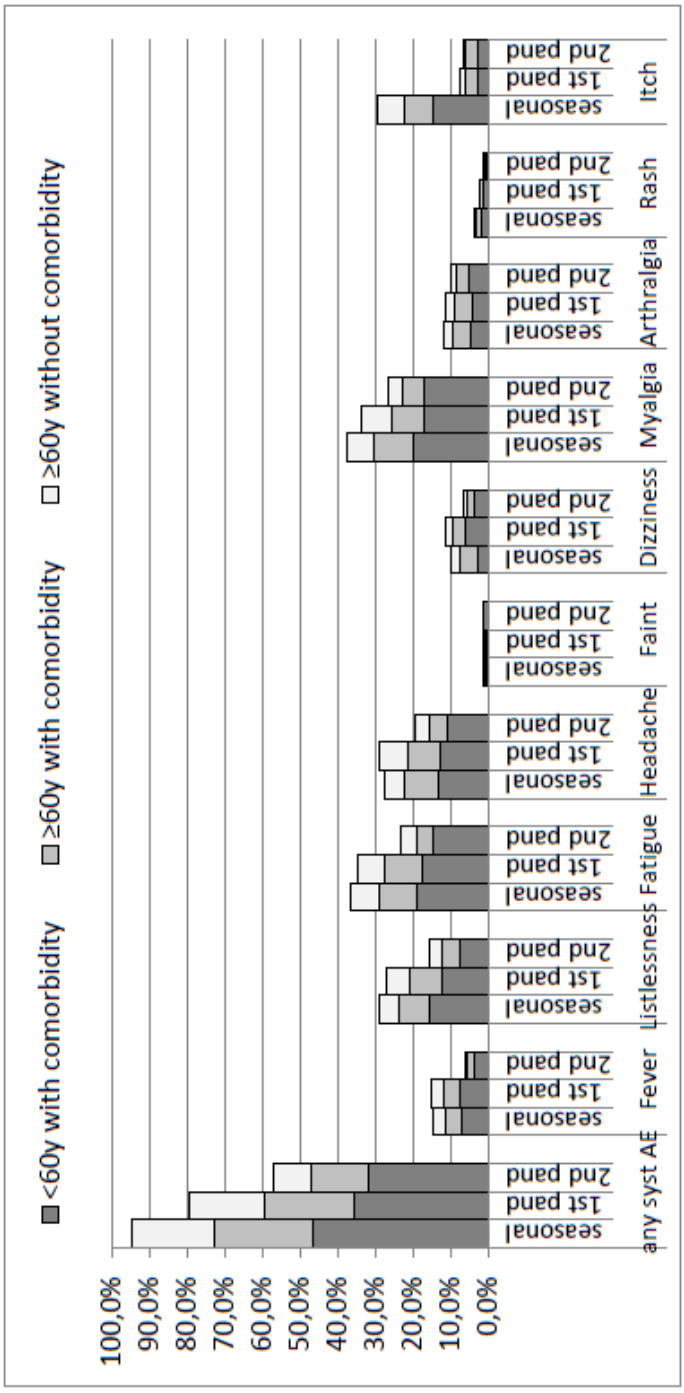


Figure 2. Risk group specific proportions (%) of systemic adverse events' after seasonal Influenza vaccination and 2 doses of pandemic Influenza vaccine.

redness, any swelling, any pain, any systemic AE, fever, fatigue, headache, myalgia (all doses), grades of redness and swelling (seasonal vaccination), listlessness (seasonal vaccination and first pandemic dose), grades of pain, dizziness (both pandemic doses), arthralgia, itch (seasonal vaccination and second pandemic dose) and for fainting (second pandemic dose).

Generalized Linear Mixed Model

GLMM, with seasonal influenza vaccine set as reference, showed a decreased risk for local and systemic AEs for both pandemic doses, overall (adjusted for age) and for separate risk groups (adjusted for sex) (Table 4). These differences were statistically significant, except for systemic AEs in both risk groups ≥60y and the male stratum in the overall analysis.

Table 4. Multivariable Generalized Linear Mixed Model analysis of the risk for local and systemic AEs after both pandemic doses with seasonal influenza vaccination set as reference, stratified by risk group

Risk Groups[a]	1st dose Focetria	2nd dose Focetria
	OR [95%CI]	OR [95%CI]
Local adverse events		
<60y with comorbidity	0.58 [0.43-0.75][b]	0.46 [0.33-0,63][b]
≥60y with comorbidity	0.54 [0.43-0.67][b]	0.41 [0.31-0.52][b]
≥60y without comorbidity	0.46 [0.32-0.63][b]	0.38 [0.26-0.55][b]
Overall	♂0.63 [0.48-0.81][c]	♂0.53 [0.38-0.70][c]
	♀0.47 [0.38-0.57][c]	♀0.34 [0.27-0.42][c]
Systemic adverse events		
<60y with comorbidity	0.64 [0.48-0.84][b]	0.52 [0.37-0.72][b]
≥60y with comorbidity	0.92 [0.73-1.14][b]	0.49 [0.38-0.65][b]
≥60y without comorbidity	0.94 [0.67-1.30][b]	0.39 [0.26-0.60][b]
Overall	♂0.99 [0.77-1.26][c]	♂0.48 [0.35-0.65][c]
	♀0.69 [0.57-0.84][c]	♀0.45 [0.35-0.56][c]

[a]: 154 vaccinees had no information on comorbidity

[b]: adjusted for sex

[c]: adjusted for age

AEs in respondents with three vs less than three questionnaires (data not shown)

We found no statistically significant differences for any of the reported local AEs between the participants who returned all three or fewer questionnaires (all p-values ≥ 0.1).

However, vaccinees who returned all 3 questionnaires, reported statistically significantly lower frequencies of any systemic AE after seasonal vaccination and the

second pandemic dose compared with those who filled in fewer questionnaires. Likewise, this holds for some specific systemic AEs.
Regarding reported local and systemic AEs, in general no statistically significant differences were observed between risk groups with participants returning all three questionnaires and risk groups returning fewer questionnaires.
GLMM, for participants returning three questionnaires, also showed decreased risks after both pandemic doses, but with the smaller numbers, more ORs were statistically non-significant (data not shown).

Discussion

We compared and presented observational tolerability data of seasonal and pandemic influenza vaccination, consecutively administered in late 2009. Data are partly cross-sectional, but 20% of participants provided tolerability data on all three vaccinations, offering the possibility of a cohort-based analysis.
In general, results show lower frequencies of both local and systemic AEs following the two-dose pandemic vaccine compared with the seasonal influenza vaccine, although not all differences are statistically significant. In addition, women reported higher frequencies of AEs than men did and people <60y with comorbidity reported the highest frequencies of AEs compared to vaccinees ≥60y with and without comorbidity.
We found higher proportions for pain at the injection site as well as for systemic AEs compared with findings of Harmark et al. who also studied the tolerability of Focetria® [8] in the Netherlands. Harmark et al. used Dutch inhabitants in their survey who received their pandemic vaccinations through GPs. However, they did not restrict inclusion to people who were eligible for seasonal vaccination, as we did. However, coverage data show that most Dutch people eligible for the pandemic vaccination were also vaccinated with seasonal influenza vaccine.[9] This implies that most participants in Harmarks study probably also received seasonal influenza vaccine prior to the pandemic doses but they only assessed AEs after pandemic vaccinations. The differences found may be caused by inclusion of other groups, e.g. pregnant women and household members of high-risk patients, and by recall bias. Harmark et al. collected data between November 16, 2009 and March 3, 2010 and participants could register online within this entire period. However, nearly all GPs finished their pandemic vaccination campaigns before Christmas 2009. In our study, questionnaires were handed out directly after immunization and we requested to send them back after one week. We did find equal frequencies of local redness and swelling, possibly indicating that the source population in both surveys shows much resemblance.

Within the different risk groups, the proportion AEs was statistically significant higher in the <60y with comorbidity group compared with the other older age risk groups. A similar result was found in two other studies on tolerability of influenza vaccination and in a study on tolerability of Q-fever, all showing that the odds of AEs decrease with increasing age. [8, 10, 11] This decreasing risk for AEs with increasing age may be caused by immunosenescence and/or comorbidity or medication.[12]
Furthermore, the sex dependency of AEs we found is also found in the Q-fever study [11] and similar to the findings of Harmark et al..[8]
Several studies comparing MF59 adjuvanted vaccines with non-adjuvanted vaccines, have found that adjuvanted vaccines resulted in slightly more AEs [2, 13] as is also known for other adjuvants. Interestingly however, we found lower rates of AEs after the pandemic doses compared with the non-adjuvanted seasonal influenza vaccines. Several explanations for these findings may be possible. First, the seasonal 2009-2010 influenza vaccine did contain a H1N1 strain, although it differed from the circulating pandemic H1N1 strain. Perhaps this influenced the reactions to the subsequent pandemic doses, because of some cross-immunity.
A second explanation for our results could be that although an adjuvant was added to the pandemic vaccine, the lower amount of virus antigen may have resulted in fewer AEs. One pandemic dose contained 7.5 mcg virus antigen compared with in total 45 mcg virus in the seasonal influenza vaccines.
Furthermore, the seasonal vaccines contained three different influenza strains, which could trigger a stronger and broader response of the immune system by multiple epitopes and by interaction, resulting in more AEs.
Finally, there is the possibility of assessment bias due to the decreasing attention for experienced AEs in booster doses.

Strengths and Limitations
Through our study we gained insight in the occurrence of adverse events following immunization (AEFI) after subsequent doses of different influenza vaccines. This resembles real life, because people eligible for seasonal influenza vaccination often also are eligible for pandemic vaccines. Data as in our study provide important information on within and between variance of the participants regarding the occurrence of AEFI. However, our study also has several limitations. We found lower frequencies of some systemic AEs between participants returning three questionnaires and participants, returning fewer, although most of the differences were non-significant. Therefore, we think this influence will be limited. However, questionnaire surveys on AEs are prone to selection bias, as participants tend to return the questionnaire only in case of AE-occurrence, usually resulting in an overestimation of frequencies.
We also had to rely on self-reported comorbidity and AEs. Our classification was not validated by the GP, which could have led to misclassification. For comorbidity this is

probably non-differential, because coding was performed independent of the knowledge on AEs. Therefore, we think the influence of misclassification regarding risk groups will be limited. However, differences in interpretation of solicited AEs could have influenced the frequencies found. Furthermore, the respective risk groups could have different reply attitudes, influencing the results found.
In addition, information on date and time of onset and duration of each AE contained a lot of missing values. Therefore, no analysis could be performed on these variables and likelihood of causality could not be assessed. For local AEs a causal relation with the vaccination is highly likely. However, for systemic AE other coincidental influences could be the cause. Furthermore, we did not include an unvaccinated control group and therefore, even reported systemic AE frequencies with a short lag time include the background rate.
Our data could also be influenced by the so called 'healthy vaccinee' effect, i.e. people who are willing or able to come to the GPs office for a vaccination may be healthier than people who are not able to come.[14] This might influence the generalizability of our results. However, we believe these frequencies are useful for monitoring variations in AE rates in the general population under real life circumstances and our questionnaire surveys are an appropriate method for surveillance purposes in view of costs and efficiency.

Conclusion
The MF59-adjuvanted pandemic influenza vaccine was well tolerated with lower reported frequencies of local and systemic AEs compared with the prior seasonal influenza vaccination, administered two to five weeks earlier. A possible 'prime-boost' relation with the seasonal influenza vaccine may explain the lower frequencies both of the first and second pandemic dose. As is seen in other vaccination campaigns women had higher rates of reported AE compared with men, as have younger people than the elder. Further research is necessary in understanding AEs after consecutive doses of influenza vaccine. Effective vaccination strategies and education are required to combat forthcoming influenza pandemics.

Materials and methods

Setting
GPs located in the Utrecht province (n = 15) were approached by telephone to ask for cooperation. Five GP practices consented and participated, located in different districts and villages to address variation in degree of urbanization and socio-economic status. GPs organized the vaccinations mainly in mass vaccination sessions at their office. Seasonal vaccination was given first, after 2 weeks followed by 2

consecutive doses of pandemic vaccine, 3 weeks apart as stipulated in the guidelines.[6] At each of these mass vaccination sessions, staff of the Dutch Centre for Infectious Disease Control (Cib) of the National Institute for Public Health and the Environment (RIVM) asked all vaccinees to participate in this tolerability survey when leaving the GP office. After consent, vaccinees were handed a questionnaire to fill in and return to CIb in a pre-stamped envelope. Thus, a participant could fill in 3 questionnaires, one for each vaccination. Besides an oral reminder at the next vaccination rounds to send in all questionnaires, no reminders were sent. People vaccinated on occasions other than at mass sessions were not recruited. Medical ethical approval of this study was not necessary because only questionnaire data were used and participants were not subjected to imposed rules or acts.

Inclusion criteria

Adults of 18 years (y) and older who received any of the influenza vaccinations at the GP could participate. The returned questionnaires were categorized in three study groups: people <60 y with comorbidity, those aged ≥60y with comorbidity and people aged ≥60y without comorbidity. These three categories are in line with the Dutch General Practitioners Association (NHG) criteria for eligibility for seasonal influenza vaccination, based on the annual HC advice.

Vaccines

The two seasonal influenza vaccines, used in the Netherlands in 2009, i.e. Vaxigrip® (split virion; Sanofi Pasteur MSD) and Influvac® (subunit surface antigens; Abbott), are both trivalent inactivated vaccines without adjuvants or thiomersal, given intramuscularly or subcutaneously. The composition of the vaccines for the season 2009/2010 was: A/Brisbane/59/2007 (H1N1)-like virus (15mcg); A/Brisbane/10/2007 (H3N2)-like virus(15mcg); and B/Brisbane/60/2008-like virus (15mcg). Seasonal vaccines were supplied in single-dose syringes.

The pandemic vaccine, used by all GPs was Focetria® (Novartis) and had 7.5 mcg influenza virus surface antigens of A/California/7/2009 (H1N1) like virus per dose. The vaccine contained MF59C.1 as adjuvant. It was presented in multi-dose containers with thiomersal as preservative. The two-dose pandemic vaccination campaign started on November 2, 2009. The seasonal vaccination campaign started in the month before. The 2009 vaccination campaign ended before Christmas. All questionnaires were received before the end of January 2010.

Data Collection

With the questionnaires information on age, sex, comorbidity, medication, vaccine type and dose number was acquired. In addition, information was collected on local adverse events (AEs) like redness, swelling and/or pain at the injection site (4 categories to tick by the respondent: none, mild, moderate or pronounced) and

systemic AEs, including fever, lethargy, fatigue, headache, fainting, dizziness, myalgia, arthralgia, rash and itch (yes/no). In case of fever, we asked for the highest temperature measured and calculated the median temperature. For each local or systemic AE, additional information on the date and time of onset and the duration of each AE was asked, until one week after immunization.
We computed 2 dichotomous (yes/no) variables for any reported local AE and any reported systemic AE, respectively.

Statistics

The proportions of reported local and systemic AEs were calculated with 95% confidence intervals (95%CI), for each risk group and sex. For fever the mean, median and range of the 'highest temperature measured' was determined.
To check for selection bias, we used chi square test to assess differences in AE frequencies between groups who returned all three questionnaires and fewer than three questionnaires, stratified for the three vaccinations and risk groups.
Data were also analyzed by means of a Generalized Linear Mixed Model (GLMM), to address dependency of data. Possible confounders studied were age, sex and comorbidity. Variables with statistically significant influence on the outcome were left in the multivariable model. To address possible selection bias, we performed the GLMM on participants, who returned all three questionnaires, similar to the above mentioned chi square test.
P-values <0.05 were considered statistically significant. Data were analyzed using SPSS version 22 and SAS 9.3.

References

1. Simonsen L. The global impact of influenza on morbidity and mortality. Vaccine 1999; 17 Suppl 1:S3-10.
2. Fukase H, Furuie H, Yasuda Y, Komatsu R, Matsushita K, Minami T, et al. Assessment of the immunogenicity and safety of varying doses of an MF59(R)-adjuvanted cell culture-derived A/H1N1 pandemic influenza vaccine in Japanese paediatric, adult and elderly subjects. Vaccine 2012; 30:5030-7.
3. Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010; 59:1-62.
4. Gasparini R, Lai P, Panatto D. Today's influenza vaccines-why an adjuvant is needed and how it works. European Infectious Disease 2010; 4:36-40.
5. WHO. Influenza vaccines-WHO position paper. 2005.
6. Stein ML, Van Vliet H, Timen A. Chronological overview of the 2009 H1N1 pandemic and the response of the Centre for Infectious Disease Control (Cib) of the National Institute for Public Health and the Environment (RIVM). Bilthoven: National Institute for Public Health and the Environment, 2010.
7. van Puijenbroek EP, van Grootheest AC. Monitoring adverse events of vaccines against Mexican flu. The International journal of risk & safety in medicine 2011; 23:81-7.
8. Harmark L, van Hunsel F, Hak E, van Grootheest K. Monitoring the safety of influenza A (H1N1) vaccine using web-based intensive monitoring. Vaccine 2011; 29:1941-7.
9. Tacken M, Mulder J, Visscher S, Tiersma W, Donkers J, Verheij R, et al. Monitoring vaccinatiegraad Nationaal Programma Grieppreventie 2009. Nijmegen: LINH, 2010.
10. Gasparini R, Schioppa F, Lattanzi M, Barone M, Casula D, Pellegrini M, et al. Impact of prior or concomitant seasonal influenza vaccination on MF59-adjuvanted H1N1v vaccine (Focetria) in adult and elderly subjects. International journal of clinical practice 2010; 64:432-8.
11. Schoffelen T, Wong A, Rumke HC, Netea MG, Timen A, van Deuren M, et al. Adverse events and association with age, sex and immunological parameters of Q fever vaccination in patients at risk for chronic Q fever in the Netherlands 2011. Vaccine 2014; 32:6622-30.
12. McElhaney JE, Effros RB. Immunosenescence: what does it mean to health outcomes in older adults? Current opinion in immunology 2009; 21:418-24.
13. Pellegrini M, Nicolay U, Lindert K, Groth N, Della Cioppa G. MF59-adjuvanted versus non-adjuvanted influenza vaccines: integrated analysis from a large safety database. Vaccine 2009; 27:6959-65.
14. Simonsen L, Viboud C, Taylor RJ, Miller MA, Jackson L. Influenza vaccination and mortality benefits: new insights, new opportunities. Vaccine 2009; 27:6300-4.

Chapter 8

Safety of vaccination against Influenza A(H1N1) during pregnancy in the Netherlands: results on pregnancy outcomes and infant's health: cross sectional linkage study

Nicoline A.T. van der Maas

Joyce Dijs-Elsinga

Jeanet M. Kemmeren

Alies van Lier

Mirjam J. Knol

Hester E. de Melker

Published in:
BJOG 2015
(DOI: 10.1111/1471-0528.13329)

Abstract

Objective

This study aims to assess the safety of H1N1-vaccination, administered during the second and third trimester and containing MF59 and thiomersal (Focetria®), measured by pregnancy outcomes and infant's health.

Design: Cross sectional linkage study.

Setting and sample: A sample of pregnant women, eligible for prenatal screening, were invited to participate.

Methods

Questionnaire data were linked with *the Netherlands* Perinatal Registry (n=1920). Information on infant's growth, development (n=1739) and infection-related contacts with the general practitioner (GP) during the first year of life (n=1671) was obtained.

Main outcome measures: Multivariate logistic regression was used to assess the association between H1N1-vaccination and small-for-gestational age, preterm delivery and a composite adverse outcome, i.e. low Apgar-score, NICU-admission, neonatal resuscitation or perinatal death. Influence of maternal vaccination on growth, development and GP infection-related contact-rates were assessed using multivariate linear mixed modelling and multivariate negative binomial regression, respectively.

Results

Response rate was 21%. Though we found differences in characteristics between unvaccinated and vaccinated women, in the multivariate analyses no association was found between H1N1-vaccination and small-for-gestational age (OR 0.84; 95%CI 0.50 to1.43), preterm delivery (OR 0.98; 95%CI 0.59 to1.62) and the composite adverse outcome (OR 0.84; 95%CI 0.44 to1.60). We found no differences in weight-for-age (-0.05; 95%CI -0.13 to +0.04), length-for-age (-0.01; 95%CI -0.09 to +0.06), head circumference-for-age (-0.05; 95%CI -0.13 to +0.03), developmental-scores (-0.06; 95%CI -0.28 to +0.17) and infection-related GP contact-rates (incidence rate ratio 1.07; 95%CI 0.91 to 1.28) between infants of unvaccinated and vaccinated mothers.

Conclusion

Pregnancy outcomes did not differ between H1N1-vaccinated and unvaccinated women. Furthermore, growth, development and GP infection-related contact-rates, assessed after the first year of life, were similar in offspring of vaccinated and unvaccinated mothers.

Introduction

In spring 2009 an Influenza A(H1N1) pandemic occurred. Influenza during pregnancy increases the risk of hospitalization due to respiratory complications, especially for women with comorbidity (1-3). Furthermore, during the 2009 pandemic, an increased risk of adverse pregnancy outcomes after infection was reported (4-6). Therefore, the Dutch Health Council advised all pregnant women in the second and third trimester to be vaccinated (7). A thiomersal-containing vaccine, adjuvanted with MF59 (Focetria®, Sanofi Pasteur MSD, Lyon, France) was used. Until that moment, there were no universal vaccination programmes for healthy pregnant women in the Netherlands.

In 2009, information on the safety of influenza vaccination during pregnancy was scarce and merely based on non-adjuvanted seasonal influenza vaccines. No safety signals were acknowledged in these studies, i.e. no serious adverse events, no differences in adverse pregnancy outcomes or infant hospital admissions, no excess of malformations or childhood malignancies (8-11).

To date, several studies on the safety of adjuvanted influenza vaccines during pregnancy have been published. None showed an increased risk on adverse pregnancy outcomes (12-19). The majority of the studies concerned the effect of Pandemrix®, adjuvanted with ASO3. None of the studies included follow up of the offspring up to one year of age.

The Centre for Infectious Disease Control of the Netherlands, part of the Dutch National Institute for Public Health and the Environment (RIVM) monitored the determinants of acceptance, coverage and safety of the H1N1-vaccination campaign among pregnant women. Data on acceptance and coverage have been reported previously (20). The current paper describes and discusses the safety of vaccination with Focetria® during the second and third trimester of pregnancy. To assess the possible impact of the vaccination, data on pregnancy outcomes and growth, development and infection-related contacts with the general practitioner (GP) of the infants up to 1 year of age were retrieved from three different sources and linked to data of a questionnaire survey.

Methods and materials

Study population and setting

All pregnant women in the Netherlands are offered screening on infectious diseases, i.e. hepatitis B, syphilis and HIV, around the 12th week of pregnancy (in any case before the 15th week). The Centre for National population screening of RIVM is responsible for this screening programme. Department for Vaccine Supply and Prevention Programmes of RIVM is responsible for data management. Data are

registered in a nationwide database. A random sample of nearly 15,000 pregnant women, eligible for vaccination against Influenza A(H1N1) in November and December 2009 and known to the Department for Vaccine Supply and Prevention Programmes were asked to participate in a questionnaire study on determinants of acceptance and vaccine coverage (20). Women who were willing to participate in further research on safety were asked to fill out an additional questionnaire, to give permission to link to *the Netherlands* Perinatal Registry (PRN) (21) , to obtain information on growth and development of the infant from the child health care and to ask for infection-related contacts with the general practitioner (GP) during the first year of life. Due to higher risks on low birth weight and short gestational age, women with multiple births were excluded.
Medical ethical approval of this study was not necessary because only routinely collected data were used and participants were not subjected to imposed rules or acts. All participants signed written informed consent for the respective study parts. Furthermore, the Board of the PRN approved the study. The latter included approval obtained upon assessment by a privacy commission.

Data collection
The Netherlands Perinatal Registry (PRN) is a joint effort of four professional organizations that provide perinatal care in the Netherlands: Royal Organization of Midwives in the Netherlands, National Organization of General Practitioners, Dutch Association of Obstetrics & Gynaecology and Paediatric Association of the Netherlands. PRN covers about 95% of all deliveries. Only pregnancies from 16 weeks onwards are registered in PRN, so information on early abortions is not available. Participating midwifes, obstetricians and GPs performing deliveries fill in predefined forms concerning a large number of variables for each birth. Data processing and -cleaning is performed in a systematic way to enhance comparability and enable trend analysis.
Questionnaire data were linked to the database of midwifes, obstetricians and paediatricians from PRN based on date of birth of mother and child and four digits of postal code. In this way, forms were combined when multiple obstetric professionals were involved in the care process during pregnancy, delivery or the postpartum period. No other personal data were accessible to the researchers.
Three dichotomous pregnancy outcomes were defined:
1. Small-for-gestational age, defined as a birth weight below the tenth percentile, adjusted for gestational age (GA) and based on Dutch averages (22).
2. Preterm delivery, i.e. birth before 37 weeks GA.
3. A composite indicator for other severe adverse outcomes, including at least one of the following: low Apgar-score (score < 7 at 5 minutes after delivery), admission to Neonatal Intensive Care Unit (NICU), resuscitation of the new-born or perinatal death.

Growth and development of infants is monitored by Dutch child health care centres, for which attendance amounts to 99% (23). Growth is subdivided in length, weight and head circumference and recorded according to standardized graphs for Dutch children (24, 25). Development is measured by "van Wiechen schedule" with age specific milestones according to the 90th percentile for Dutch children (26). Hereby five aspects are scored, i.e. fine and gross motor function, speech, language and psychosocial aspects. The scores on the developmental instrument were quantified using a developmental score (D-score), based on the Rasch model. A D-score enables a comparison of scores between persons and an evaluation of the developmental velocity within a child (27).
Data about infection-related contacts of the children within their first year of life were collected through medical records of GPs. Nearly all people living in the Netherlands are registered with a GP. The medical records from GPs contain all relevant medical history, including prescriptions, laboratory results and secondary care information. For each child, we asked the GP for an excerpt including all contacts, i.e. telephone calls, consults at the office and house visits, during as well as outside working hours, related to temperature or fever, symptoms of an infection of one or more organ systems or prescriptions to treat infectious symptoms. The number of contacts were counted.

Vaccine and vaccination

Pregnant women eligible for vaccination could receive their vaccination at the GP practice. GPs offered these H1N1-vaccinations free of charge from 9 November 2009 onwards. The H1N1-vaccination campaign was finished before Christmas, with only a few people vaccinated in 2010. A two-dose schedule was used with an interval of 3 weeks between the doses. The only vaccine used was Focetria®, delivered as multi-dose containers with thiomersal as a preservative, MF59C.1 as adjuvant and 7.5 micrograms influenza virus surface antigens of A/California/7/2009 (H1N1) like virus per dose. In this study, vaccination status was self-reported.

Covariates

All but three covariates were retrieved from the self-reported questionnaires (see Table 1). Maternal problems (defined as abnormalities in general medical, gynaecological and obstetric history and obstetric problems during current pregnancy), birth weight and small-for-gestational age were retrieved from PRN-data. All covariates were chosen based on a plausible or known possible influence on the outcomes.

Statistical analysis

Differences in characteristics of vaccinated and unvaccinated women were tested using Pearson's Chi Square or Fisher's exact test (for dichotomous and categorical variables) or student t-test (for continuous variables).

Multivariate logistic regression analysis was used to assess the association between H1N1-vaccination and the three defined adverse pregnancy outcomes. To improve comparison of the models for the three outcomes, all models included the same set of possible confounders, i.e. year of birth, country of birth, educational level, self-reported use of alcohol, tobacco and drugs during pregnancy, parity, underlying medical condition as reason for vaccination, maternal problems, H1N1-infection and philosophy of life, e.g. religion, anthroposophy. Associations are presented as odds ratios (ORs) with 95% confidence interval (95%CI).

The z-scores, i.e. standard deviation scores, for head circumference-for-age, length-for-age and weight-for-age were calculated using Dutch references (22). A z-score is computed to determine the outcome of an individual in relation to reference measurements of a comparable population with the same age and sex. Z-scores were analysed using a linear mixed effect model, with random intercept and random slope for age. We compared z-scores between infants of vaccinated and unvaccinated mothers, and adjusted for birth weight, sex and number of previous pregnancies.

Differences in D-scores between infants of vaccinated and unvaccinated mothers were assessed using a linear mixed effect model with random intercept and random slope for age, adjusted for educational level of the mother and whether or not the mother was born in the Netherlands.

Counts of the total number of infection-related contacts in the first year of life, registered in the medical record of the GP, were analysed using negative binomial regression, adjusted for educational level, country of birth of the mother and small-for-gestational age. Differences in contact rates were expressed as an incidence rate ratio (IRR).

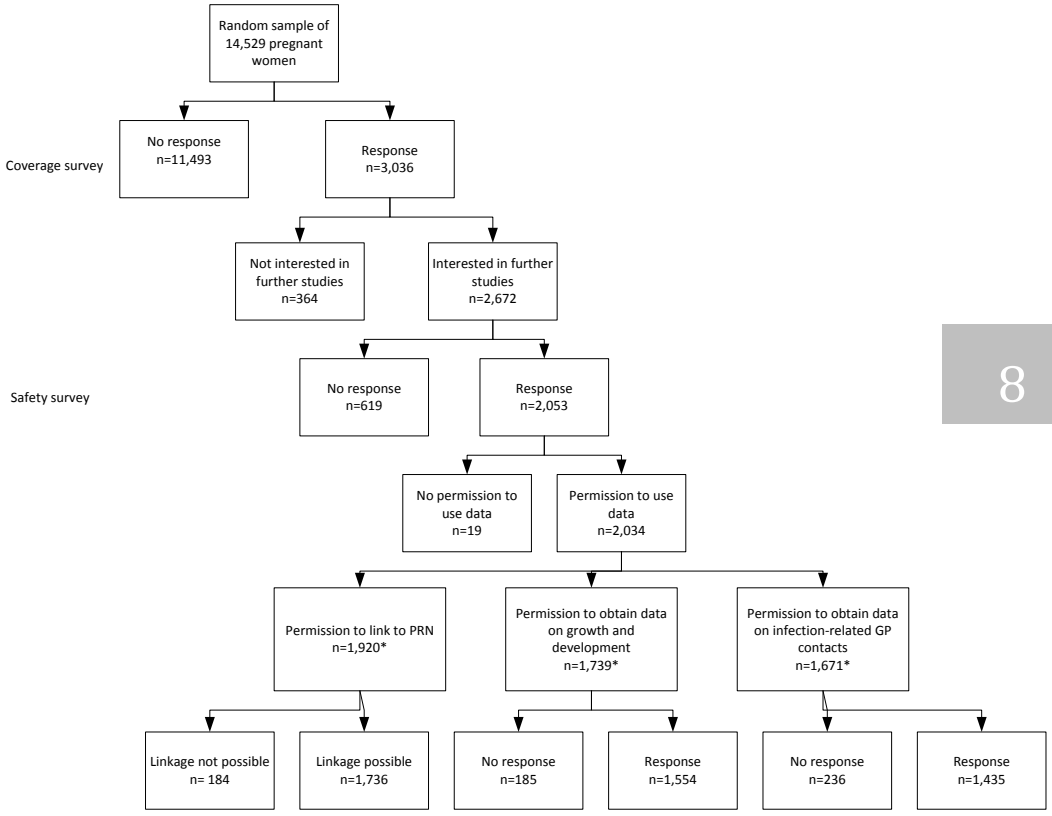
Before the study, we estimated that about 2,200 pregnant women had to be included to detect an increase in the prevalence of abnormal postnatal growth from 2.5% to 5%, measured through length and weight ($\alpha = 0.05$, $\beta=0.20$), based on an expected vaccination coverage of 33%-50%. Hereby, abnormal growth is defined as length or weight below the 2.5^{th} percentile or above the 97.5^{th} percentile compared to a reference group of Dutch infants of the same sex and age.

Analyses were performed using SAS version 9.3, z-scores for growth were computed using R. In all analyses, a p-value <0.05 was considered statistically significant. Furthermore, unvaccinated mothers and their offspring were set as reference in all analyses.

Results

Study population

Twenty-one percent of the 14,529 invited women participated in the coverage study, of whom 88% (n=2,672) were interested in further studies (20). In figure 1, the number of women in each step of the study is presented. Finally, we could link data of 1,736 women (85.3% of the 2,034 who participated in this study) to the *Netherlands* Perinatal Registry (PRN), we obtained data on growth and development of 1,554 children (76.4%) and information on infection-related GP contacts of 1,435 children (70.6%).



*: 1,656 women gave permission to retrieve data from all three sources.

Figure 1: flow chart of identification of the study population.

Of the women who gave permission to use questionnaire data, 66.7% (n=1,357) were vaccinated, 32.9% (n=669) received no vaccination and 0.4% (n=8) had an unknown vaccination status.

Vaccinated women were older than unvaccinated women, had a higher educational level, were more often multipara, more frequently had an underlying medical condition as reason for vaccination and less often reported a religious background or a specific life philosophy such as anthroposophy compared to unvaccinated women. (Table 1) There was no difference in country of birth, self-reported use of alcohol or drugs and self-reported smoking during pregnancy.

Table 1. Background characteristics of H1N1-vaccinated and unvaccinated pregnant women.

Background characteristics	Vaccinated [a] (N=1,357); n(%)	Not vaccinated (N=669); n(%)	p-value[b]
Year of birth			
before 1970	37 (2.7%)	18 (2.7%)	**p<0.0001**
1970-1974	278 (20.5%)	138 (20.6%)	
1975-1979	618 (45.5%)	249 (37.2%)	
1980-1984	377 (27.8%)	216 (32.3%)	
1985 or later	47 (3.5%)	48 (7.2%)	
Country of birth			
the Netherlands	1289 (95.1%)	641 (95.8%)	p=0.45
other country	67 (4.9%)	28 (4.2%)	
Educational level			
no education or only primary/secondary school	54 (4.0%)	39 (5.8%)	**p=0.03**
intermediate vocational education	405 (29.9%)	222 (33.2%)	
higher vocational education or university	898 (66.2%)	408 (61.0%)	
First pregnancy			
yes	545 (40.3%)	338 (50.6%)	**p<0.0001**
no	809 (59.7%)	330 (49.4%)	
Underlying medical condition			
yes	89 (6.6%)	22 (3.3%)	**p=0.002**
no	1268 (93.4%)	647 (96.7%)	
Self-reported use of alcohol during pregnancy			
yes	97 (7.2%)	35 (5.3%)	p=0.11
no	1250 (92.8%)	625 (94.7%)	
Self-reported use of drugs during pregnancy			
yes	2 (0.2%)	3 (0.5%)	p=0.16
no	1347 (99.8%)	658 (99.5%)	
Self-reported smoking during pregnancy			
yes	57 (4.2%)	27 (4.1%)	p=0.87
no	1286 (95.8%)	633 (95.9%)	
Philosophy of life			
no specific philosophy of life	1152 (90.2%)	505 (78.5%)	**p<0.0001**
religious	71 (5.6%)	74 (11.5%)	
anthroposophy/homeopathy/alternative medicine/other	54 (4.2%)	64 (10.0%)	

[a] = reported to have received at least one vaccination against Influenza A (H1N1)

[b] = Pearson's χ^2 or Fisher's exact test; p-values in bold indicate significant results

Pregnancy outcomes

Of the 1,736 women with data linked to PRN, 1,184 women (68%) were vaccinated and 552 (32%) were not. They gave birth to 902 boys and 819 girls. Of 15 infants, the sex was unknown. No maternal deaths were reported.

Logistic regression showed no association between H1N1-vaccination and small for gestational age (SGA) (crude OR 0.81, adjusted OR 0.84; 95%CI 0.50 to 1.43). (Table 2) Likewise, no increased risk for preterm birth (crude OR 0.95, adjusted OR 0.98; 95%CI 0.59 to 1.62) nor for the composite outcome (crude OR 1.01, adjusted OR 0.86; 95%CI 0.46 to 1.64) was found.

Growth and development

We found no statistically significant difference in the z-score for weight-for-age between infants of unvaccinated and vaccinated mothers (-0.05; 95%CI -0.13 to +0.04), adjusted for sex, number of infants in the household and birth weight. This indicates that the weight of infants of vaccinated mothers and unvaccinated mothers is distributed similarly compared to a reference group of Dutch infants of the same age and sex. Similar results were found for length-for-age and head circumference-for-age (z-score -0.01 (95%CI -0.09 to +0.06 and -0.05 (95%CI -0.13 to +0.03, respectively).

Furthermore, we found no statistically significant differences in developmental-scores between infants of vaccinated and unvaccinated mothers (-0.06; 95%CI -0.28 to +0.17), adjusted for educational level and country of birth of the mother.

Infection related GP contacts

Total number of GP contacts per infant in the first year of life ranged from 0-29 (mean 3.4, median 3.0). (Figure 2) In total, 1336 and 3438 GP-contacts were reported for infants of unvaccinated women and vaccinated women, respectively. Acute (upper) airway infections were mentioned as reason for the GP-contact in 28% and 27% of the contacts of infants of unvaccinated and vaccinated mothers, respectively, followed by acute otitis media (9% and 10%), gastro-intestinal complaints (7% and 6%) and fever (7% and 5%). For other diseases, the percentages were lower. Sixty-two hospitalizations were documented.

We found no significant difference in the proportion of infants having contact with their GP for infection-related symptoms between vaccinated and unvaccinated mothers. The incidence rate ratio was 1.07 (95%CI 0.91 to 1.28), adjusted for SGA and educational level and country of birth of the mother.

Table 2. Logistic regression analysis of vaccination against Influenza A(H1N1) and small for gestational age, preterm birth and a composite adverse outcome (including at least one of the following: Apgar score < 7, NICU-admission, neonatal resuscitation, perinatal death).

		Small for gestational age (SGA)				Preterm birth (gestational age <37 weeks)				Composite adverse outcome			
		total N	% SGA	crude OR (95%CI)	adjusted[a] OR	total N	% preterm	crude OR (95%CI)	adjusted[a] OR	total N	% composite	crude OR (95%CI)	adjusted[a] OR
Vaccinated	no	528	5.1%	Ref	Ref	523	5.0%	Ref	Ref	528	6.1%	Ref	Ref
	yes	1123	4.1%	0.81 (0.50-1.33)	0.84 (0.50-1.43)	1104	4.9%	0.95 (0.59-1.54)	0.98 (0.59-1.62)	1123	4.1%	1.01 (0.54-1.88)	0.84 (0.44-1.60)

[a] Adjusted for year of birth, country of birth, educational level, use of alcohol, tobacco and drugs during pregnancy, parity, underlying medical condition as reason for vaccination, maternal problems, H1N1-infection and life philosophy

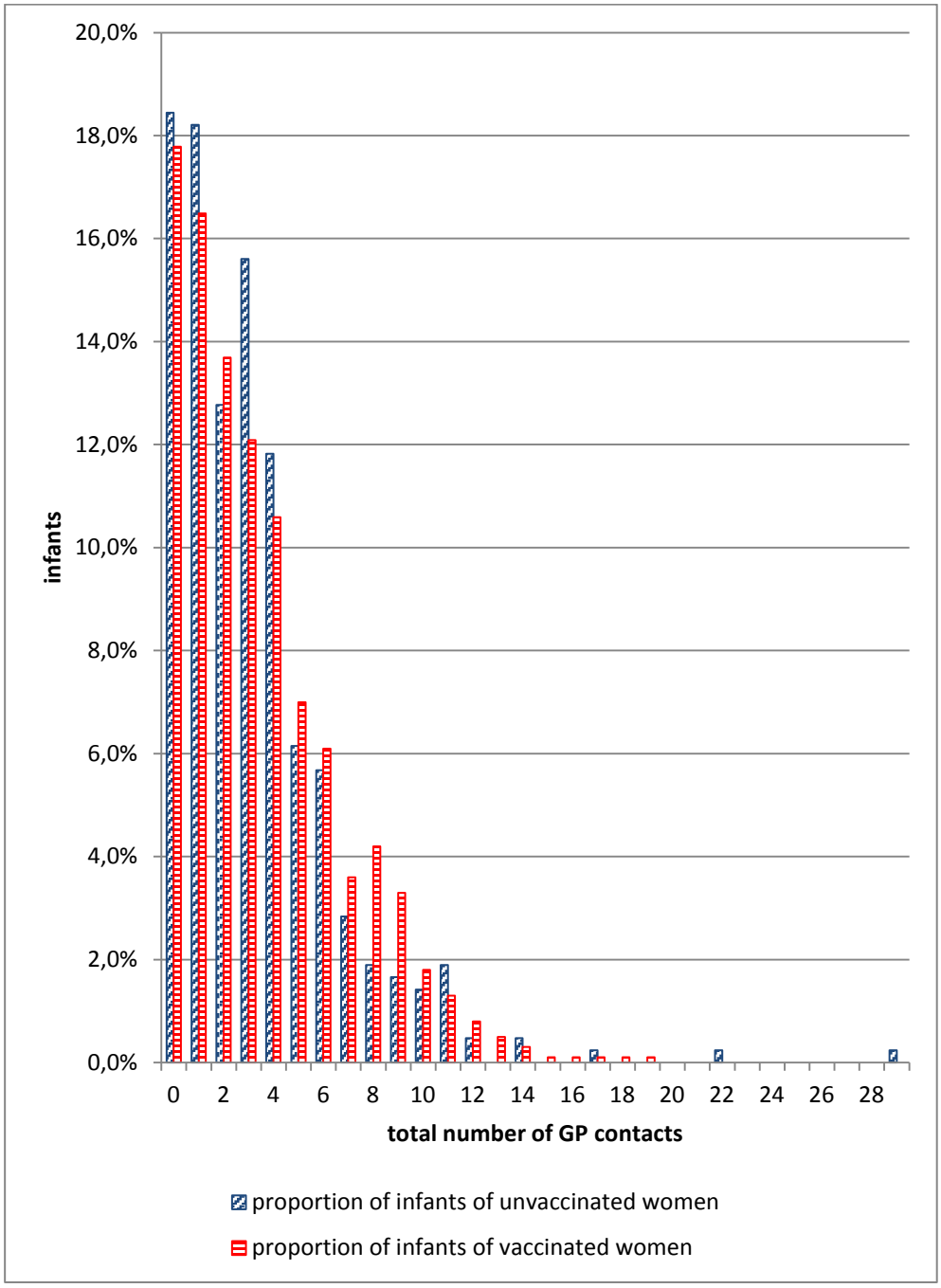


Figure 2. Frequencies of infant GP contacts of unvaccinated and vaccinated mothers during the first year of life.

Discussion

Main findings.

To our knowledge this is the first study about the safety of MF59-adjuvanted H1N1-vaccination, not only assessing pregnancy outcomes, but also the possible impact on the infant's health during the first year of life. We found no increased risk of MF59-adjuvanted H1N1-vaccination in the second and third trimester of pregnancy on adverse pregnancy outcomes measured by preterm birth, small-for-gestational age and a composite outcome including rare but severe adverse outcomes. Furthermore, we found no negative impact on growth (i.e. head circumference, length and weight), development and GP contacts for infection-related reasons during the first year of life.

Strengths and limitations.

This study has several strengths. Data collection and –entry were performed independent of the vaccination status. Data were merged with the original questionnaire data after data entry in the respective study databases and only the original questionnaire contained information on self-reported maternal vaccination status.

Furthermore, vaccinated and unvaccinated mothers were recruited simultaneously, so they were exposed to the same environmental influences, e.g. influenza infection.

Due to the extensive questionnaire survey, we were able to adjust for several well-known confounders, e.g. smoking. Finally, PRN-data are cleaned and coded using standardized methods, resulting in good comparability of pregnancy outcomes.

Several limitations must be acknowledged. The participants of this study were not fully representative of all Dutch pregnant women. In the first questionnaire survey on coverage and acceptance there was a low and selective response (20). Respondents were slightly older and less likely to have a due date in November 2009 compared to non-respondents. Furthermore, respondents were more frequently born in the Netherlands and had a higher educational level than assessed in nationwide surveys. Although we cannot exclude this may have affected our results, it is unlikely that any selective response would have had large impact on the association between H1N1-vaccination during pregnancy and the studied outcomes, because our results are comparable with results of other studies, including a non-selective, nationwide cohort study, performed in Denmark (14-16, 19, 28, 29). Furthermore, our analysis of adverse pregnancy outcomes showed significant effects of several well-known risk factors with the outcome measures, e.g. smoking (data not shown). Finally, frequencies of preterm birth, support of pregnancy and delivery by midwife or gynaecologist in our study were comparable with results of the PRN-data in general, enclosing 95% of the pregnancies in the Netherlands (30).

Likewise, the number of participants did not amount to the number, assessed in the sample size calculation, but we think a higher number of participants will not change

our conclusion, because our results are in line with results of other studies and frequencies of important variables are comparable with frequencies, found in other databases, as already mentioned above.

Timing of vaccination could not be included as a possible confounder, because of the presence of unvaccinated women in our study. Stratifying vaccinated women by trimester of vaccination and comparing each subset with the group of unvaccinated women would reduce the power of the study, so we decided not to do this.

Our results are not generalizable to women, vaccinated in their first trimester, because in the Netherlands, only women in their second and third trimester were eligible for vaccination.

The estimated coverage among pregnant women was 63% (20). In the subset of women, participating in the follow-up study on safety, 67% of the women reported to be vaccinated, i.e. an overrepresentation of vaccinated mothers. This might have influenced our results. However, we were able to adjust for a large number of possible confounders, so we think this influence will be limited.

Misclassification due to mistakes in data entry can have influenced our results. However, this misclassification is probably non-differential, because during data collection and -entry the vaccination status of the participant was unknown.

Furthermore, in the Netherlands, registries do not include a personal unique identifier. Therefore, linking of PRN- and questionnaire data was only possible based on date of birth of the mother and child, and postal code. This might have led to inaccurate linking in case of identical linking variables in two or more records. This misclassification is probably non-differential, because information on vaccination status was unknown during linkage. Furthermore, we tried to prevent these inaccuracies by manually reviewing overlapping records and by also using infants' birth weight as a linking variable in these records, if the exact weight was available in the questionnaire data.

The H1N1-vaccination campaign was implemented during the pandemic. In fact, 66 pregnant women in our study reported to have had pandemic flu. In most cases, the exact date of onset was unknown and no laboratory confirmation was performed. Forty-eight of these women also reported H1N1-vaccination. Analysis without the inclusion of these 66 women did not change our results (data not shown). Therefore, we think the influence of this was limited.

Finally, the vaccination status was self-reported. The occurrence of recall bias is possible when pregnant women were unaware of their vaccination status. However, we believe this risk is small, because there was strong debate about vaccination during pregnancy in our country.

Interpretation.

Our results are in line with previous studies on the safety of adjuvanted H1N1-vaccines, administered during pregnancy (14-16, 19, 28, 29). All these studies included at least low birth weight, preterm birth or small-for-gestational age in their analysis, and in none of these studies, an increased risk on these outcomes following vaccination was found.

Our results on infant's growth fit well to the findings of normal birth weight and normal duration of pregnancy after H1N1-vaccination during pregnancy, because following intrauterine noxious exposure, abnormal postnatal growth may not occur without fetal growth impairment (31, 32). Furthermore, the similar development of infants of vaccinated and unvaccinated mothers we found is consistent with the fact that no excess of congenital anomalies was found in any study (14, 19, 28, 29). Frequent or long-term hospitalization due to congenital anomalies may result in impaired (motor) development (33, 34). In these cases, often a catch up in development is seen after discharge. Furthermore, some congenital anomalies and impaired development have a common aetiology, e.g. genetic syndromes, exposure to noxious agents, congenital brain anomalies (35-38). However, a normal development in the first year of life does not imply a normal development later in life (39).

Conclusion

Our study showed no increased risk for several adverse pregnancy outcomes and infant's health during the first year of life following administration of an influenza A(H1N1) vaccine, adjuvanted with MF59 and preserved with thiomersal, during the second and third trimester of pregnancy. These findings are reassuring for public and professionals and may help the decision making process on maternal immunization in case of a new pandemic and possible other infectious diseases, which can be prevented by maternal vaccination. Further research regarding the safety, effectiveness and acceptability of maternal immunization is needed to further cover gaps in knowledge.

Acknowledgments

We thank:
-G.A. van Essen (Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands), A.J. van Loon (Martini hospital, Groningen, the Netherlands) and N. van Holthe (Erasmus Medical Centre, Rotterdam, the Netherlands) for their contribution to the study proposal.
-E.M.L. Düsseldorp (Netherlands Organization for Applied Scientific Research "TNO", Leiden, the Netherlands) for calculation of the developmental scores.
-W. van der Hoek (RIVM), F.G.A. Versteegh (Groene Hart hospital, Gouda, the Netherlands) and N.E Verbeek (University Medical Centre Utrecht, Utrecht, the Netherlands) for critically reviewing the first draft of the manuscript
-Royal Organization of Midwives in the Netherlands for informing their members
-all pregnant women, who participated in this study.

References

1. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis. 2008;14(1):95-100.
2. Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? Vaccine. 2009;27(35):4754-70.
3. Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis. 2008;8(1):44-52.
4. Kelly H, Mercer G, Cheng A. Quantifying the risk of pandemic influenza in pregnancy and indigenous people in Australia in 2009. Euro Surveill. 2009;14(50).
5. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009;374(9688):451-8.
6. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517-25.
7. advice vaccination against pandemic influenza A(H1N1)2009: target groups and priotizing. den Haag: Health Council of the Netherlands, 2009 2009/16.
8. Heinonen OP, Shapiro S, Monson RR, Hartz SC, Rosenberg L, Slone D. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. Int J Epidemiol. 1973;2(3):229-35.
9. Heinonen OP, Slone D, Shapiro S. immunizing agents. In: Kaufman DW, editor. Birth defects and drugs in pregnancy. Littleton: Publishing Sciences Group; 1977. p. 314-21.
10. Munoz FM, Greisinger AJ, Wehmanen OA, Mouzoon ME, Hoyle JC, Smith FA, et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol. 2005;192(4):1098-106.
11. immunisation safety review: thiomersal-containing vaccines and neurodevelopmental disorders. Washington, DC: Institute of Medicine, 2001.
12. Huang WT, Chen WC, Teng HJ, Huang WI, Huang YW, Hsu CW, et al. Adverse events following pandemic A (H1N1) 2009 monovalent vaccines in pregnant women--Taiwan, November 2009-August 2010. PLoS One. 2011;6(8):e23049.
13. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ. 2012;344:e2794.
14. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. JAMA. 2012;308(2):165-74.

15. Ludvigsson JF, Zugna D, Cnattingius S, Richiardi L, Ekbom A, Ortqvist A, et al. Influenza H1N1 vaccination and adverse pregnancy outcome. European journal of epidemiology. 2013;28(7):579-88.
16. Rubinstein F, Micone P, Bonotti A, Wainer V, Schwarcz A, Augustovski F, et al. Influenza A/H1N1 MF59 adjuvanted vaccine in pregnant women and adverse perinatal outcomes: multicentre study. BMJ. 2013;346:f393.
17. Sammon CJ, Snowball J, McGrogan A, de Vries CS. Evaluating the hazard of foetal death following H1N1 influenza vaccination; a population based cohort study in the UK GPRD. PLoS One. 2012;7(12):e51734.
18. Haberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med. 2013;368(4):333-40.
19. Heikkinen T, Young J, van Beek E, Franke H, Verstraeten T, Weil JG, et al. Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study. Am J Obstet Gynecol. 2012;207(3):177 e1-8.
20. van Lier A, Steens A, Ferreira JA, van der Maas NA, de Melker HE. Acceptance of vaccination during pregnancy: Experience with 2009 influenza A (H1N1) in the Netherlands. Vaccine. 2012;30(18):2892-9.
21. PRN-foundation. http://www.perinatreg.nl.
22. TNO. https://www.tno.nl/downloads/20100608%20Factsheet%20Resultaten%20Vijfde%20Landelijke%20Groeistudie1.pdf.
23. Verbrugge HP. Youth health care in The Netherlands: a bird's eye view. Pediatrics. 1990;86(6 Pt 2):1044-7.
24. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res. 2000;47(3):316-23.
25. Talma HY, Bakker B, Hirasing RA, Van Buuren S. Handleiding bij het meten en wegen van kinderen en het invullen van groeidiagrammen. Leiden: TNO Quality of Life; 2010.
26. Laurent de Angulo MS, Brouwers-deJong EA, Bulk A. Ontwikkelingsonderzoek in de jeugdgezondheidszorg: het van Wiechenonderzoek: de Baecke-Fassaert motoriektest. fourth edition ed: Van Gorcum; 2008.
27. Jacobusse G, van Buuren S, Verkerk PH. An interval scale for development of children aged 0-2 years. Stat Med. 2006;25(13):2272-83.
28. Kallen B, Olausson P. Vaccination against H1N1 influenza with Pandemrix((R)) during pregnancy and delivery outcome: a Swedish register study. BJOG. 2012.
29. Oppermann M, Fritzsche J, Weber-Schoendorfer C, Keller-Stanislawski B, Allignol A, Meister R, et al. A(H1N1)v2009: a controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine. 2012;30(30):4445-52.
30. PRN. http://www.perinatreg.nl/uploads/150/136/Jaarboek Zorg in Nederland 2009 Tabellen.pdf.
31. Engelberts AC, Koerts B, Waelkens JJ, Wit JM, Burger BJ. [Measuring the length of newborn infants]. Ned Tijdschr Geneeskd. 2005;149(12):632-6.
32. Villar J, Belizan JM. The timing factor in the pathophysiology of the intrauterine growth retardation syndrome. Obstet Gynecol Surv. 1982;37(8):499-506.
33. Symington A, Pinelli J. Developmental care for promoting development and preventing morbidity in preterm infants. Cochrane Database Syst Rev. 2006(2):CD001814.
34. Santo CC, Goncalves MT, Piccolo MM, Lima S, Rosa GJ, Paulin E, et al. [Physical therapy performance in respiratory and motor involvement during postoperative in children submitted to abdominal surgeries]. Acta medica portuguesa. 2011;24(6):1013-8.
35. Dereymaeker AM, Fryns JP, Haegeman J, Deroover J, Van den Berghe H. A genetic-diagnostic survey in an institutionalized population of 158 mentally retarded patients. The Viaene experience. Clinical genetics. 1988;34(2):126-34.
36. Fryns JP, Kleczkowska A, Dereymaeker A, Hoefnagels M, Heremans G, Marien J, et al. A genetic-diagnostic survey in an institutionalized population of 173 severely mentally retarded patients. Clinical genetics. 1986;30(4):315-23.
37. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009;360(16):1597-605.
38. Samren EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia. 1997;38(9):981-90.
39. Prins SA, von Lindern JS, van Dijk S, Versteegh FG. Motor Development of Premature Infants Born between 32 and 34 Weeks. International journal of pediatrics. 2010;2010.

Chapter 9

Guillain-Barré syndrome: background incidence rates in the Netherlands

Nicoline A.T. van der Maas
Merlijn A. Kramer
Bart C. Jacobs
Eva M. van Soest
Jeanne P. Dieleman
Jeanet M. Kemmeren
Hester E. de Melker
Miriam C.J.M. Sturkenboom

Published in:
Journal of the Peripheral Nervous System 16:243–249 (2011)
(DOI: 10.1111/j.1529-8027.2011.00356.x)

Abstract

Guillain-Barré syndrome (GBS) is a (sub)acute polyradiculoneuropathy, which may occur following immunisation. To interpret the occurrence of GBS after introduction of large scale immunization programmes, it is important to define recent background incidence rates (IRs) of GBS.

We used a general practitioner electronic medical record database to assess age specific GBS IRs between 1996 and 2008 in the Netherlands. All possible GBS cases were manually reviewed. Validated incident cases were reviewed by a neurologist (BJ) for diagnostic certainty using the GBS case definition of the Brighton Collaboration (BC).

In a population of 638,891 persons, we identified 23 validated incident GBS cases (mean age 46 year). IR was 1.14 per 100,000 person years (95%CI 0.67-1.61) and was lower for people under 50 years (0.76; 95%CI 0.41-1.32) compared with elderly of 50 years or older (1.80; 95%CI 0.98-3.05). Only 6 cases fulfilled level 1 or 2 of diagnostic certainty of the BC case definition.

IR of GBS increases with age. Since vaccinations are often targeted at specific age groups, age specific rates should be used to monitor GBS observed versus expected rates after introduction of large scale vaccination programmes..

Introduction.

Guillain-Barré Syndrome (GBS) is a (sub)acute polyradiculoneuropathy.(1, 2)
Already in 1978, diagnostic criteria for GBS were developed.(3) More recently, it became clear that the clinical spectrum of GBS was pathophysiologically diverse.(4) Nowadays, we know that the kind of preceding event and specific host factors seem to determine the form and severity of GBS.(5)
Worldwide, the reported GBS incidence rates (IR) vary between 0.4 to 4 per 100,000, depending on age, sex, region, study methodologies and case ascertainment.(1, 2, 6-8)
Besides a known association with infections (9), vaccinations also have been suggested to increase the risk of GBS, although biological mechanisms remain to be elucidated. A sudden increase in cases was seen following a vaccination campaign against swine flu in 1976 in the USA.(10) More recently, an association between the quadrivalent Meningococcal vaccine and GBS was postulated.(11)
As in other countries, in the Netherlands, vaccination campaigns recently have been expanded, such as vaccination against human papillomavirus (HPV) for girls, broader age range for seasonal Influenza vaccination and vaccination against pandemic influenza virus.(12-14)
Background incidence rates are important in signal detection, using observed versus expected analysis during a mass vaccination campaign.(15, 16) Here we present age specific incidence rates of GBS in the Netherlands between 1996 and 2008. Furthermore, we classified the certainty of diagnosis by using the new GBS Brighton Collaboration case definition, which was developed to facilitate international comparison of GBS data in vaccinovigilance.(17)

Methods and Materials.

Setting

The Integrated Primary Care Information (IPCI) database is a longitudinal general practitioner (GP) research database, presently containing more than 1 million patient records from more than 400 GPs in the Netherlands. The patient population is representative of the Dutch population regarding sex and age, except for a slight under representation of the elderly population who move to nursing homes.(18-20) Nearly all people in the Netherlands are registered with a GP from their date of birth onwards. The medical records from GPs contain all relevant medical history, including secondary care information. The electronic records of the patients in the IPCI database store anonymized information on demographics, signs and symptoms (using the International Classification for Primary Care (ICPC) codes and narratives), diagnosis (ICPC and narratives), clinical findings, specialist referrals, laboratory results,

hospitalizations, and drug prescriptions.(18) Summaries of hospital discharge letters and letters from specialists are entered as free text and hard copies of original letters can be provided upon request.(19) Each patient in the database has a unique code, containing specific patient information, encrypted in a standardized way. Therefore, double counting of cases can be checked and corrected for.
The IPCI database complies with the European Union guidelines on the use of medical data for medical research and has been proven valid for (pharmaco)-epidemiological studies.(20) The Scientific and Ethical Advisory Group of the IPCI database approved the study.

Study population
The total study population comprised all persons in the IPCI database between January 1996 and April 2008. To have sufficient background morbidity information on all subjects, the GP practice had to be contributing data to the IPCI database for at least 1 year and the patient had to be registered with the GP for at least 1 year. Follow-up started on January 1996 or on the date that 1 year of valid history was available. Follow-up ended on the date the person transferred out of the practice, on the date of last data supply by the GP, death, diagnosis of GBS, or April 2008.

Case ascertainment
Cases of GBS were identified in the IPCI database using an extensive computerized database search including a list of disorders regarded as GBS variants or with similar symptoms as GBS. See Table 1 for a complete list of search criteria and Fig. 1 for an overview of the case identification process.

Table 1: search criteria for Guillain Barré syndrome

Guillain Barré syndrome, "GBS"
acute inflammatory demyelinating polyradiculopathy, AIDP
chronic inflammatory demyelinating polyradiculopathy, CIDP
Miller Fisher syndrome, Miller Fischer syndrome, MFS, MF
Landry
(Poly)neuropathy
(Poly)radiculopathy
acute motor-axonal neuropathy, AMAN
acute motor-sensory axonal neuropathy, AMSAN

We first carried out a broad electronic narrative search, using GBS search criteria, to find potential cases (step 1).
In a first validation (step 2 fig. 1), the full electronic medical record of all records with one or more GBS search criteria was manually reviewed in order to eliminate obvious non-cases and to classify cases as either incident or prevalent case. If the first

diagnosis occurred after the start of follow-up time of that person, this case was defined as incident. Patients with a diagnosis of GBS prior to study entry were classified as prevalent. Furthermore, incident cases were divided in true and possible cases. Cases were considered as true cases if the electronic medical record stated that GBS was confirmed by a neurologist. Cases were defined as possible if a differential diagnosis of GBS was made by the GP or a neurologist, but no final diagnosis had been made.

A second validation (step 3 fig. 1) was carried out on all true and possible incident cases. A short questionnaire was sent to the GPs together with a request to supply copies of specialist letters. The questionnaire was used to confirm the diagnosis of GBS and the date of onset of weakness or other neurological deficits as a first manifestation of GBS. Furthermore, information on infections, vaccinations or drug prescriptions within 6 weeks prior to GBS was requested. Information from discharge letters was used to establish the nadir severity of disease, using the frequently used GBS disability score (legend Table 2).(21)

Brighton Collaboration (BC) case definitions.

In 2009 the Brighton Collaboration (BC) GBS Working Group developed a standardized case definition for (variants of) GBS as an adverse event following immunization (AEFI).(17) The case definition contains three levels of diagnostic certainty. Ideally, information is collected during hospitalization. Information regarding the onset of muscle weakness, deep tendon reflexes, nadir of symptoms, illness pattern, electrophysiological findings and cerebrospinal fluid analysis is required to fully classify the level of diagnostic certainty for GBS cases. For classification of Miller-Fisher syndrome (MFS), additional information on the presence of ophthalmoparesis and ataxia is required. In epidemiological studies case classification is often done retrospectively. In this study we used information in the electronic medical record, the GP-questionnaire and the specialist letter to assess the BC classification retrospectively, acknowledging the fact that the information for appropriate assessment (e.g. test results of specialist) may not be available in medical records or discharge letters. This classification was performed by an expert neurologist (BJ) to ensure the most reliable interpretation of all available medical information.

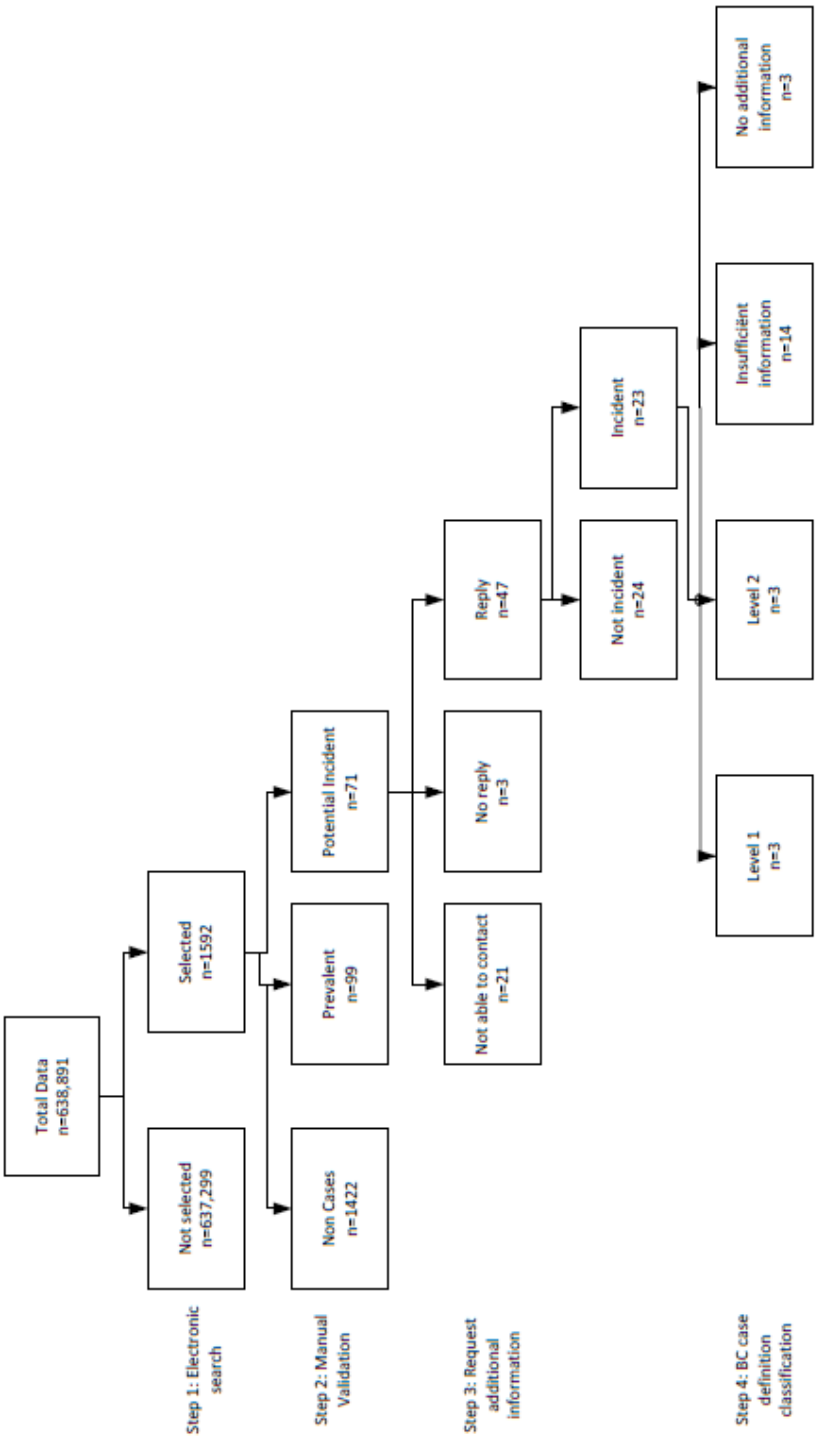


Figure 1: The identification of incident cases from the total study population.

Statistical analysis

Incidence rates (IR) of GBS were calculated by dividing the total number of incident cases by the total number of person years (py) at risk of the study population. Rates were calculated per calendar year and calendar month, by sex and age. To better study seasonality we grouped months into seasons: winter including December-February, spring including March-May, summer including June-August and fall including September-November. The 95% confidence intervals (CI) were based on the Poisson distribution. Some GPs could not retrieve the decoded patient identifier anymore because they had changed practice software system. Both the cases and the source population of the GPs that could not provide additional information were excluded from the primary analysis. A secondary sensitivity analysis was done in the total population by including possible and true incident GBS cases and the source population of the GPs that could not provide data for a maximum scenario. The expected absolute number of GBS cases in the Dutch population was calculated using age specific rates and the age distribution of the Dutch population (www.statline.nl).

Results

Study population

The source population for the study comprised 191 GP practices, including 638,891 patients, contributing a total follow up time of 2,328,655 py (mean 3.65 py, range 0.003-11.0 py). Within this population, the broad narrative search revealed 1592 records with a match in the GBS search criteria. After the first manual review of the full electronic medical record of all the potential patients, using symptoms, diagnoses and specialist referrals, we retained 170 potential GBS cases. Of those cases, 99 were prevalent and 71 were classified as true (n=41) or possible (n=30) incident cases. For 21 out of these 71 cases, i.e. 14 true and 7 possible cases, the GPs could not be contacted as they switched GP information system or stopped their practice. For the remaining 50 cases (70%) the GP could be contacted, covering a source population of 578,117 patients. For 47 of the 50 cases additional information was received.

For 23 of the 47 documented cases the GP confirmed the diagnosis of GBS (n=21) or MFS (n=2) in nearly all cases supported by neurologist letters (true incident cases). This implies a positive predictive value (PPV) of 49% (95%CI 35%-63%) for GBS identification based on the manual review of the electronic medical record only. For the 24 other cases, GBS was not confirmed since symptoms were very mild and disappeared spontaneously (n=3), GBS diagnosis was rejected or alternative diagnosis was made (n=9) based on additional laboratory investigation or consultancy of a neurologist. In 10 cases information on the correct diagnosis was missing, but it was definitely no GBS, in one case the GP used the GBS code inadvertently and one case was lost to follow up (Fig. 1).

The mean age of the 23 true incident cases was 46 years (median 51; range 3-75 years) and 30% was male. A preceding infection or vaccination was recorded in 70% and 6%, respectively. The mean duration of hospitalization was 19.3 days (median 17; range 7-36 days) and the mean time of follow up after diagnosis was 280 days (median 106, range 7-1,026 days). Intravenous immunoglobulins were administered to 88% of the patients. No patient underwent plasmapheresis. Four patients needed mechanical ventilation during hospitalization. Minor sequelae or signs of neuropathy were present in 76%. One patient died. Two patients (9%) had a second episode of GBS, with the second episode following 8 months and 3 years after the first onset-date, respectively (Table 2)

Table 2: Characteristics of 23 true incident cases with Guillain-Barré Syndrome

Characteristic	absolute numbers (%) or mean (median; range)	N[a]
Mean age in years	46 (51; 3-75)	23
Male (%)	7 (30%)	23
Mean hospital stay in days	19.3 (17; 7-36)	14
Receiving intravenous gamma globulins	14 (88%)	16
Treated with plasmapheresis	0 (0%)	19
Need of mechanical ventilation during hospitalization	4 (21%)	19
Mean time of follow up in days	280 (106; 7-1026)	17
GBS disability score[b] =0	1 (5.9%)	17
GBS disability score[b] = 1	13 (76.5%)	17
GBS disability score[b] = 3	2 (11.8%)	17
GBS disability score[b] = 6	1 (5.9%)	17
GBS relapse	2 (9%)	23
infection within 6 wk prior to GBS	16 (70%)	23
vaccination within 6 wk prior to GBS	1 (6%)	17

[a] = number of patients for whom information was available

[b] = GBS disability score: 0= healthy state; 1= minor symptoms or signs of neuropathy but capable of manual work/running; 2= able to walk without support of a stick (5 m across an open space) but incapable of manual work / running; 3= able to walk with a stick, appliance or support (5 m across an open space); 4= confined to bed or chair bound; 5= requiring assisted ventilation for at least part of the day; 6=dead.

Applying the GBS Brighton Collaboration case definition rules on information from the GP medical records, questionnaire and discharge letters showed that only three cases fulfilled criteria for level 1 of diagnostic certainty, three cases were classified as level

2. For the remaining 17 true incident cases, the electronic medical record, specialist letter and questionnaire contained insufficient information to score the BC level appropriately or meet the minimal criteria for GBS according to the BC classification scheme (Fig 1).

Incidence rates

The incidence rate (IR) based on the 23 true incident cases in the primary study population was 1.14 per 100,000 py (95%CI 0.67-1.61). The IR based only on the first validation step in the electronic medical record, containing 71 possible and true incident cases (i.e. not considering additional information from the GP) was 3.05 per 100,000 py (95%CI 2.34-3.41). Taking into account the positive predictive value of 49% the IR in the entire population would be 1.49 per 100,000 py (Table 3).

Table 3: Incidence rates per 100,000 person years of Guillain-Barré Syndrome by calendar year and age.

	Total				
	possible + true incident cases		true incident cases only		X[b]
	N[a]	IR(95%CI)	N[a]	IR(95%CI)	IR
Overall	71	3.05 (2.34-3.41)	23	1.14 (0.67-1.61)	1.4
Calendar year					
1996	3	4.72 (0-7.44)	0	-	2.31
1997	6	5.19 (1.04-7.31)	2	2.23 (0-5.32)	2.54
1998	2	1.25 (0-2.14)	0	-	0.61
1999	8	3.66 (1.12-4.96)	1	0.57 (0-1.70)	1.80
2000	8	3.48 (1.07-4.71)	2	1.07 (0-2.56)	1.70
2001	9	4.12 (1.43-5.49)	3	1.66 (0-3.55)	2.02
2002	7	3.07 (0.80-4.23)	2	1.03 (0-2.45)	1.50
2003	1	0.43 (0-0.87)	0	-	0.21
2004	4	1.60 (0.03-2.41)	3	1.32 (0-2.81)	0.79
2005	11	4.27 (1.75-5.55)	4	1.68 (0.03-3.32)	2.09
2006	7	3.44 (0.89-4.74)	4	2.02 (0.04-4.00)	1.68

2007	4	2.99 (0.06-4.49)	2	1.50 (0-3.57)	1.47
2008	1	5.07 (0-10.13)	0	-	2.04
Age at diagnosis					
< 10	4	1.50 (0.03-2.97)	3	1.25 (0-2.66)	0.74
10-19	5	1.79 (0.22-3.37)	1	0.40 (0-1.18)	0.88
20-29	7	2.26 (0.59-3.94)	2	0.73 (0-1.73)	1.11
30-39	8	2.11 (0.65-3.57)	2	0.59 (0-1.40)	1.03
40-49	15	4.13 (2.04-6.22)	3	0.91 (0-1.95)	2.02
50-59	10	3.27 (1.24-5.30)	4	1.43 (0.03-2.84)	1.60
60-69	10	4.89 (1.86-7.93)	4	2.15 (0.04-4.25)	2.40
≥ 70	12	5.44 (2.36-8.52)	4	1.99 (0.04-3.93)	2.67

[a] = number of cases

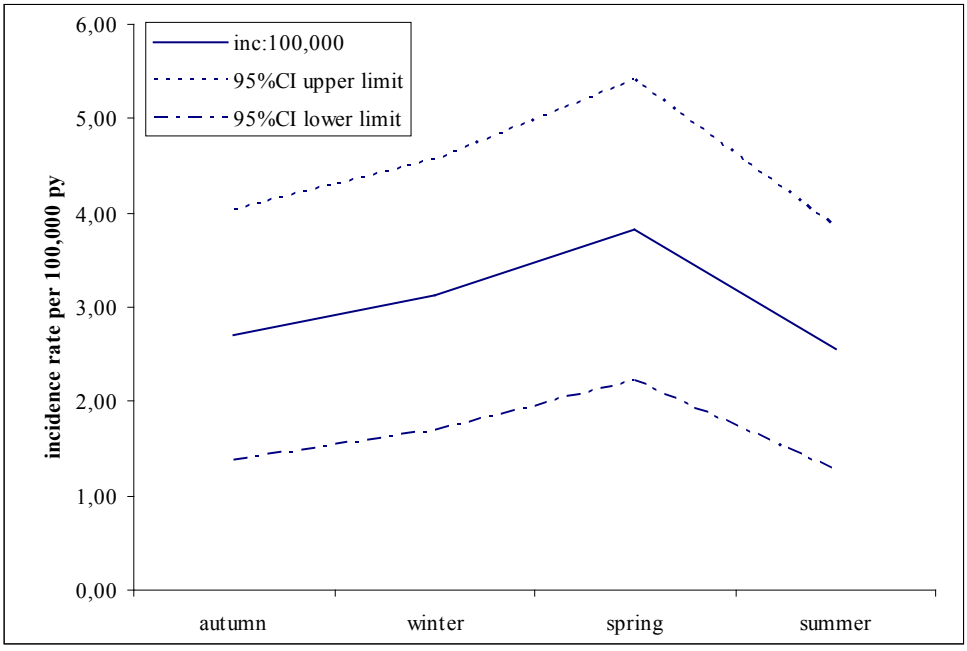
[b] = total number of possible and true incident cases * positive predictive value (=0.49)

In the primary study population, the IR was lowest for 10-19 year olds (0.40 per 100,000 py; 95%CI 0-1.18) and highest for 60-69 year old people (2.15 per 100,000 py; 95%CI 0.04-4.25). The IR for people < 50 years of age was significantly lower (0.76; 95%CI 0.41-1.32) compared with elderly of 50 years or older (1.80; 95%CI 0.98-3.05) (Table 3).
We found no significant differences in age- and calendar year specific IR between men and women. No trend was found in IRs over the different calendar years in the primary and total study population (considering 71 possible and true incident cases). Seasonal changes could only be studied in the total population: rates seemed highest in spring (IR: 3.8; 95%CI 2.2-5.4) and lowest in summer (IR: 2.6; 95%CI 1.3-3.8) (Fig. 2).

Extrapolation to absolute number of cases in the Netherlands

Based on the age specific GBS rates in the primary study population translated to that of the Dutch population, the absolute number of GBS cases, expected in one year, would be 166-186 (95%CI 0-394) in the Netherlands.(www.statline.nl).

Figure 2: seasonal incidence rates of Guillain-Barré Syndrome (autumn containing September-November, winter December-February, spring March-May, summer June-August)



Discussion

The main finding of this study is that the incidence rate of GBS did not change over the years in the Netherlands: in our study the incidence rates based on validated cases was estimated at 1.14 per 100,000 py (95%CI 0.67-1.61) during 1996-2008, which is very similar to the rate from a previous Dutch study, covering the 10 years prior to our study (1987-1996) and based on hospitalization records (IR 1.18 per 100,000; 95%CI 1.08-1.29).(3, 8) Neither of the studies found a change in IR over the calendar years within their study period, further strengthening the suggestion that the rate is rather constant over the past 20 years in the Netherlands. This finding is important as

it allows historic rates to be used for calculations of the expected number of cases. For the Netherlands it means that we could expect around 190 cases of GBS yearly. Furthermore, these age-specific rates can be used to calculate the expected rates of GBS cases if mass vaccination is targeted at predefined age groups.

A secondary finding of this study is the low positive predictive value (49%) in recorded diagnoses of GBS in electronic medical records. Electronic health care databases are frequently used to estimate background rates of disease and cross reference with GPs and treating physicians cannot always be done.(15) Our low positive predictive value, based on review of electronic medical records from GPs shows that for trustworthy background rates, additional information needs to be collected either through specialist letters or preferably by chart review in the hospital. Rates based on non-validated cases may lead to overestimations (21, 22) and reduce the usefulness of these rates for observed vs. expected analysis.

The rate we found is comparable with the results of other international studies. Hughes et al. (1997) found a mean IR of 1.3 per 100,000 persons, based on 35 identified series of GBS patients, published before 1997.(2) A recent review (2009) of the epidemiology of GBS, comprising 63 studies, performed in Europe and North America, most of which covering time periods between 1980 and 2000, reported rates between 0.84 and 1.91 per 100,000py.(22)

The clinical characteristics of the GBS patients included in our study were also comparable with those reported in previous studies, as reviewed by Hughes and McGrogan.(2, 22) The Dutch study on GBS during 1987-1996 was part of both reviews.(8) In our study, 73% of the cases had a preceding infection, whereas McGrogan reports 40%-70%. In line with McGrogan (22), we found no strong seasonal pattern of GBS rate in the total study population. In contrast, Koningsveld et al. found a more pronounced seasonal preponderance over 1987-1999 in Curaçao, possibly related to an increase in Campylobacter jejuni infections.(23) Furthermore, nearly 90% of our cases received intravenous immunoglobulins, implicating that especially severe cases were included in our study.

A third important finding of the current study is that the validated cases were all diagnosed as GBS or MFS by a neurologist, but in 70% of the cases the additional information (often discharge letter) was insufficient to meet at least level 3 classification of diagnostic certainty of the BC case definition. This is mostly explained by insufficient detail in the discharge letter. To meet the BC case definition level 3 or better it is necessary to value changing symptoms during the course of the disease, which is usually not fully recorded in medical files and letters. This means that the BC criteria which are meant to allow for international harmonization of case definitions are less suitable for retrospective validation and classification of cases obtained from healthcare databases even if additional validation information is obtained.(24) Given the usefulness of healthcare databases to rapidly estimate background rates of events of potential interest and the importance of standardizing case classification such as

the one for GBS, the BC might want to consider creating a separate classification for this type of research.
The incidence rate distribution increases with age. Some age categories are also considered to have a higher risk for infectious diseases and are often vaccinated according to a population based immunization programme. Just recently, Centers for Disease Control and Prevention reported a rate ratio of 1.77 (95%CI 1.12-2.56) for

GBS following Influenza A(H1N1) vaccination compared with non-vaccinees.(25) Furthermore, in the years 2006-2009, analysis of data from the Vaccine Adverse Event Reporting System (VAERS) showed a higher reporting rate of GBS after the administration of quadrivalent HPV vaccine than that of the general population.(26) Assessing GBS age specific baseline incidence rates is important to address an increase in GBS reports following immunizations properly. Low incidence rates stress the importance for international collaboration in order to detect a much smaller increase timely.
Being retrospective and observational in nature, our study has certain limitations. The incidence rate of elderly people living in nursery homes might be underestimated due to a slightly under representation in the medical record database used in this study. However, the incidence rate for people older than 70 years found in our study is comparable with corresponding age specific incidence rates of several studies, as shown in the review of McGrogan et al..(22) Using predefined search criteria, true cases may be missed, resulting in underestimation. To prevent this, we applied a broad search algorithm to capture all potential cases. Since our incidence estimate is well in range with other, much larger studies, we believe that false negatives are of minor importance in this study. Validation through additional information requested to the GP, decreased the influence of false positives. However, for a large number of cases we were unable to obtain further information anymore since the GP had changed medical record keeping software and could not decrypt our patient identifier anymore. To avoid underestimation of the rates both the cases as well as the source population of these GPs were not considered.
In conclusion, our study showed a stable GBS incidence rate of 1.14 per 100,00 py (95%CI 0.67-1.16) in the Netherlands for the period 1996-2008, increasing with age, using validated data of a GP medical record database. Assessing GBS age specific baseline IRs is important to address an increase in GBS reports following immunization properly, especially if the targeted population has age restrictions. In view of the low background rate of GBS international collaboration is essential to detect a small risk increase following vaccination timely.

References

1. Hughes RA, Cornblath DR. Guillain-Barre syndrome. Lancet. 2005;366(9497):1653-66.
2. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. J Infect Dis. 1997;176 Suppl 2:S92-8.
3. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre syndrome. Ann Neurol. 1990;27 Suppl:S21-4.
4. Griffin JW, Li CY, Ho TW, Tian M, Gao CY, Xue P, et al. Pathology of the motor-sensory axonal Guillain-Barre syndrome. Ann Neurol. 1996;39(1):17-28.
5. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barre syndrome. The Lancet Neurology. 2008;7(10):939-50.
6. Rantala H, Uhari M, Niemela M. Occurrence, clinical manifestations, and prognosis of Guillain-Barre syndrome. Arch Dis Child. 1991;66(6):706-8; discussion 8-9.
7. Hart DE, Rojas LA, Rosario JA, Recalde H, Roman GC. Childhood Guillain-Barre syndrome in Paraguay, 1990 to 1991. Ann Neurol. 1994;36(6):859-63.
8. Van Koningsveld R, Van Doorn PA, Schmitz PI, Ang CW, Van der Meche FG. Mild forms of Guillain-Barre syndrome in an epidemiologic survey in The Netherlands. Neurology. 2000;54(3):620-5.
9. Jacobs BC, Rothbarth PH, van der Meche FG, Herbrink P, Schmitz PI, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barre syndrome: a case-control study. Neurology. 1998;51(4):1110-5.
10. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barre syndrome reported in association with the administration of swine influenza vaccines. Am J Epidemiol. 1984;119(6):841-79.
11. Guillain-Barre syndrome among recipients of Menactra meningococcal conjugate vaccine--United States, June-July 2005. MMWR Morb Mortal Wkly Rep. 2005;54(40):1023-5.
12. Gezondheidsraad. Vaccinatie tegen baarmoederhalskanker. Den Haag: Gezondheidsraad; 2008. Contract No.: 2008/08. ISBN 978-90-5549-702-7
13. Gezondheidsraad. Griepvaccinatie: herziening van de indicatiestelling. . den Haag: Gezondheidsraad; 2007. Report No.: 2007/09; ISBN978-90-5549-638-9.
14. Gezondheidsraad. Vaccinatie tegen pandemische influenza A/H1N1 2009: doelgroepen en prioritering. . den Haag: Gezondheidsraad; 2009. Report No.: 2009/10; ISBN978-90-5549-765-2.
15. 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 immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009;374(9707):2115-22.
16. Callreus T, Svanstrom H, Nielsen NM, Poulsen S, Valentiner-Branth P, Hviid A. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. Vaccine. 2009;27(22):2954-8.
17. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.
18. Lamberts H, Wood M, Hofmans-Okkes IM. International primary care classifications: the effect of fifteen years of evolution. Fam Pract. 1992;9(3):330-9.
19. van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM, et al. The introduction of computer-based patient records in The Netherlands. Ann Intern Med. 1993;119(10):1036-41.
20. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med. 1999;38(4-5):339-44.
21. Bogliun G, Beghi E. Validity of hospital discharge diagnoses for public health surveillance of the Guillain-Barre syndrome. Neurol Sci. 2002;23(3):113-7.
22. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barre syndrome worldwide. A systematic literature review. Neuroepidemiology. 2009;32(2):150-63.
23. van Koningsveld R, Rico R, Gerstenbluth I, Schmitz PI, Ang CW, Merkies IS, et al. Gastroenteritis-associated Guillain-Barre syndrome on the Caribbean island Curacao. Neurology. 2001;56(11):1467-72.
24. Bonhoeffer J, Heininger U, Kohl K, Chen RT, Duclos P, Heijbel H, et al. Standardized case definitions of adverse events following immunization (AEFI). Vaccine. 2004;22(5-6):547-50.
25. Preliminary results: surveillance for Guillain-Barre syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine - United States, 2009-2010. MMWR Morb Mortal Wkly Rep. 2010;59(21):657-61.
26. Souayah N, Michas-Martin PA, Nasar A, Krivitskaya N, Yacoub HA, Khan H, et al. Guillain-Barre syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006-2009. Vaccine. 2011;29(5):886-9.

Chapter 10

Incidence of multiple sclerosis in the general population in The Netherlands, 1996-2008

Merlijn A. Kramer

Nicoline A.T van der Maas

Eva M. van Soest

Jeanet M. Kemmeren

Hester E. de Melker

Miriam C.J.M. Sturkenboom

Published in:
Neuroepidemiology 2012;39:96-102
(DOI: 10.1159/000338678)

Abstract

Background

We estimated the Multiple Sclerosis (MS) incidence in The Netherlands for better active monitoring of potential vaccine safety signals.

Methods

A retrospective cohort study (1996-2008) was conducted using a population-based general practice research database containing electronic medical records. Additional information was collected to validate incident probable cases.

Results

In the source population (648,656 persons), 146 incident probable MS cases were identified. Overall incidence rate was 6.3/100,000 person years (py; 95%CI 5.2-7.2). In the sub-group in which MS could be fully validated, the incidence increased from 4/100,000 py (95%CI 3-5) in 1996-2004 to 9/100,000 py in 2007/8 (95%CI 6-16). This increase was highest among women, but not statistical significant different by gender. The median lag time between first recorded symptoms and MS diagnosis decreased from 32 months (<1998) to 2 months (> 2005).

Conclusions

MS is rare in The Netherlands. In recent years, there was a slight increase in the incidence especially among women during the fertile age. This increase coincided with a decrease in lag time between symptoms and diagnosis, both for men and women. This trend should be taken into account in the interpretation of MS cases occurring in a population where new vaccinations will be introduced shortly.

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system manifesting with signs of multiple neurological dysfunctions, e.g. loss of vision, tingling/numbness, and limb weakness [1]. The onset of disease is mostly between 20-45 years of age [2,3].
The European incidence rate (IR) of MS was estimated at 4.3 cases per 100,000 per year [4] and 20 years ago (1995-1990) at 3.0 per 100.000 for The Netherlands [5].
There is a heavy debate in the literature about the potential association between vaccinations and occurrence of autoimmune diseases, amongst which MS [6-10]. One of the suspected links which have been claimed is between MS and hepatitis B (HBV) vaccination. In one study, increased onset of MS symptoms within 3 years of HBV vaccination was observed compared to unvaccinated controls [11]. Earlier and subsequent studies as well as a systematic review failed to support this association, although some studies had methodological and power issues [12-18].
To be able to conduct observed/expected analysis and to judge possible changes in MS incidence over time in particular in association with changes in vaccination programmes (i.e. universal HBV vaccination [18], vaccination against human papillomavirus [19] and pandemic Influenza A(H1N1)) we aimed to re-estimate the incidence of MS.

Methods

The Integrated Primary Care Information (IPCI) database is a longitudinal general practitioner research database. Data collection started in 1996 and presently contains more than 800,000 patient lives originating from more than 400 general practitioners (GPs) in The Netherlands [20,21]. The patient population is representative of the Dutch population regarding age and sex. In the Dutch health care system, almost all citizens are registered in a GP practice. A GP acts as a gatekeeper to, and as a central receiver of information from secondary care. Therefore, patients' medical records at the GP are likely to contain all relevant medical information. Electronic records of the patients in IPCI database comprise anonymized information on demographics, signs and symptoms (using the International Classification for Primary Care (ICPC) codes and narratives), diagnoses (ICPC and narratives), clinical findings, specialist referrals, laboratory results, hospitalizations, and drug prescriptions. Summaries of letters from specialists are entered as free text and hard copies of original letters can be provided upon request [20]. The IPCI database complies with the European Union guidelines on the use of medical data for medical research and has been proven valid for (pharmaco)-epidemiological studies [22]. The Scientific and Ethical Advisory Group of the IPCI project approved the study.

Study population

The total study population comprised of all persons with a patient record in the IPCI database between January 1996 and April 2008, who had at least one year of valid database history (i.e. GP practice contributed data to IPCI database for at least 1 year and the patient was registered with the GP for at least 1 year). This history was required to have sufficient background information on all subjects. Follow-up started on January 1996 or on the date that 1 year of valid history was available, whichever date was latest. Follow-up was terminated at the earliest of the following dates: when the person transferred out of the practice, the date of last data supply by the GP, death or MS diagnosis.

Case definition

MS cases were identified through multiple steps. The first step was an extensive computerized database search for codes and narratives pointing to MS, including a list of disorders with similar symptoms as MS (i.e. encephalomyelitis, systemic lupus erythematosus, optic neuritis, myelitis transversa).(available on request)

In the second step, complete electronic medical records of potential cases were manually reviewed in order to eliminate obvious non-cases and to pre-classify patients as prevalent or incident and as probable or possible. A patient with a MS diagnosis prior to study entry was classified as a prevalent MS case and was excluded from further analyses. When the first symptoms started after start of follow-up time of that person, this was defined as an incident case. Incident cases were considered as probable if the record stated that the patient had MS and this diagnosis was confirmed by a neurologist. A case was defined as possible if a differential MS diagnosis was made by the GP or neurologist, but no final diagnosis had been made yet. Possible cases were not included in final analysis.

In the third step a short questionnaire was administered to GPs that could still be contacted in order to assess whether a probable incident case was truly an incident case. The questionnaire was used to confirm the MS diagnosis and to obtain the (date of) first symptoms of MS. To assess the latter, GPs could choose between the symptoms 'change of sensation', 'weakness of the limbs', 'visual disturbance' or 'unknown'. GPs could fill in other symptoms as free text also. When a symptom was mentioned, the date of onset was requested. Additionally copies of all specialist letters related to MS were requested. These letters provided information about the medical history of the patient, the date of MS diagnosis and physical examination.

Statistical analysis

The MS incidence was calculated by dividing the total number of probable MS cases by the total number of person years at risk (py) in the source population. Incidence rates were calculated by calendar year, sex and age. Ninety-five percent confidence intervals (95%CI) were based on a Poisson distribution. The incidence was calculated in the total study population (maximum estimate of MS incidence) as well as in the sub-population of patients registered at practices from which additional information could be obtained. Moreover, we standardized rates by sex and age using the 2002 population for The Netherlands. We tested for a trend in the incidence ratio for males and females separately by fitting a piecewise Poisson regression model. Next, a piecewise Poisson regression model that included both sex and trend was fitted and another model that additionally included an interaction between both. Trend and age analyses were all conducted in the restricted (validated) population only.

Results

Study population

The dynamic study population consisted of 648,656 patients who contributed a total of 2,344,724 py of follow up during the study period (mean 3.6 years per person). Within this study population, 796 potential MS cases were identified. After review of the electronic medical records (i.e. the second validation step), 547 cases were classified as prevalent cases, 146 as incident probable cases and 103 as incident possible cases (Figure 1). In 159 practices (source population 511265 patients) with a total of 92 probable incident MS cases, additional information on the (date of onset of) first symptoms and specialist letters could be requested from the GP. Of the 92 probable incident cases, 84 (91%, i.e. positive predictive value) were confirmed as definite incident MS cases, i.e. 'restricted' population. Eight cases were not confirmed by the GPs as incident MS cases, 1 case was found to be a prevalent case, 4 cases were eventually not diagnosed with MS and 3 were classified as possible MS case. The median age at diagnosis for incident cases in both the total (n=146) and the restricted population (n=84) was 39 years (interquartile range (IQR) 33-49 years). Respectively 73% and 79% of cases in the total and the restricted population were females. According to the additional information provided by GPs, patients were diagnosed with MS by a specialist with a median of 6 months (range 0 months – 18 years) after they consulted their GP with MS symptoms. The median lag time between the first visit to the GP with MS symptoms and MS diagnosis decreased over time from 32 months (0 months -18 years) in the period before 1998 to 2 months (0-20 months) in the period after 2005 both for males and females. Changes in sensation (39%), weakness of the limbs (30%) and visual disturbance (22%) are symptoms related to MS for which most patients visited their GP the first time.

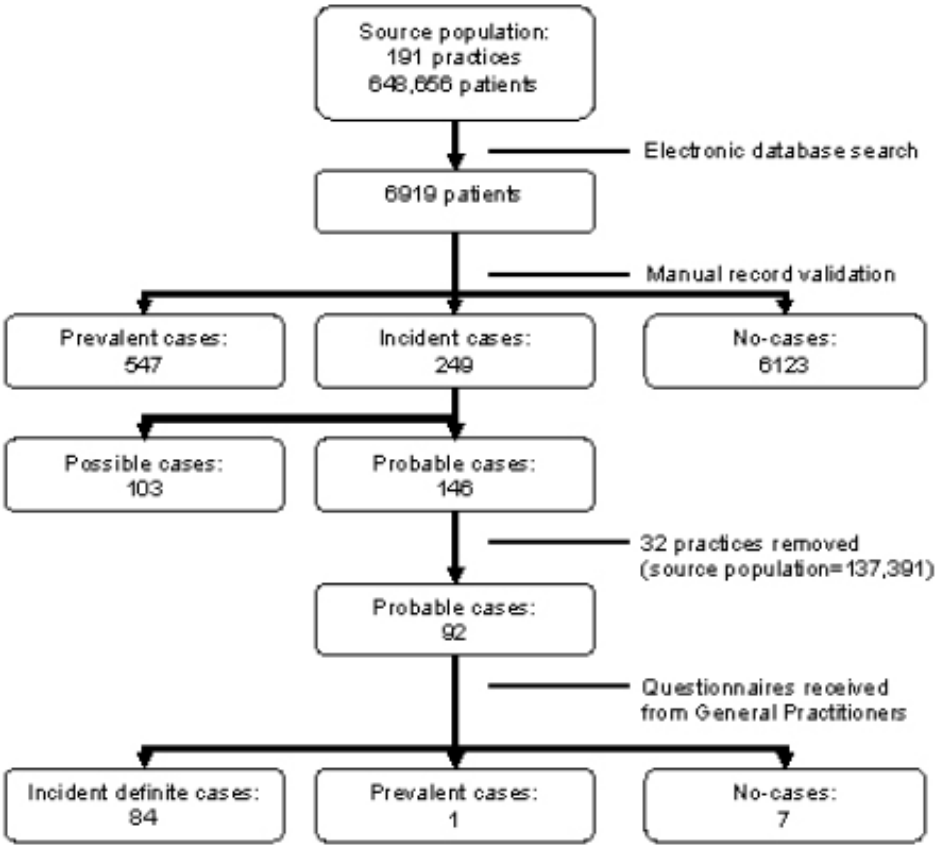


Figure 1 Flowchart of case validation

Incidence

In the total study population, which includes probable incident cases for whom no additional information was available, the incidence rate (IR) was 6.3 per 100,000 py (95%CI 5.2-7.2; Table 1 - Total population). The overall age-sex standardized IR of MS based on confirmed cases by the GP and specialist letters was 4.8 per 100,000 py (95%CI 3.9-6.0; Table 1 - Restricted population).

The IR of MS in the restricted population was around 4 per 100,000 py between 1996 and 2005 (Figure 2). After 2005, the IR of MS slowly increased to 9 per 100,000 py in 2007/8. We found a statistically significant increase in the MS incidence over the period 2005-2008 (6.4 per 100,00 py, 95%CI 4.7-8.9) compared to the preceding study period (4.0 per 100,000 py, 95%CI 3.0-5.3).

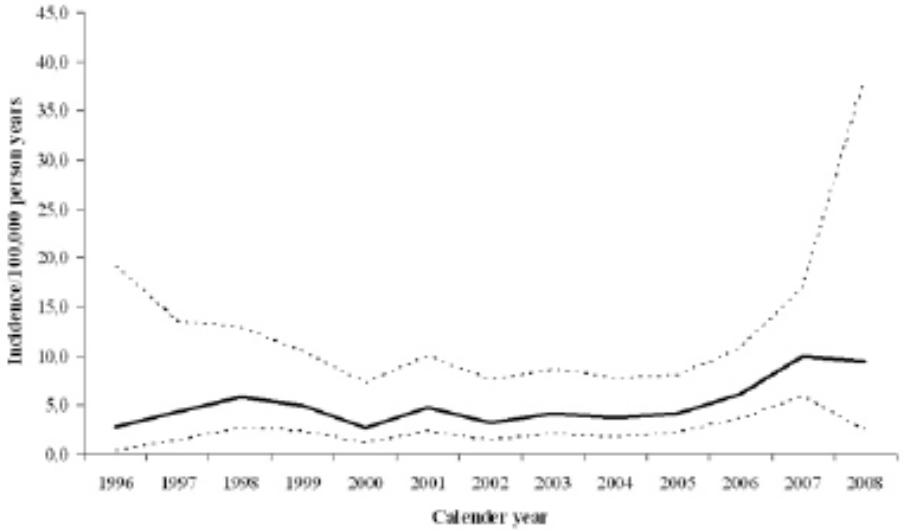


Figure 2 Overall incidence rate of multiple sclerosis for the restricted population, 1996-2008, with upper and lower 95%-confidence intervals.

The incidence rate was higher among women (7.5 per 100,000 py, 95%CI 5.9-9.6) than men (2.1 per 100,000 py, 95%CI 1.3-3.3) (Figure 3). For males no significant increasing trend after 2005 was found (p-value= 0.62), while for females a significant increase in the trend of the incidence was present (p-value = 0.0026). However, a likelihood ratio test showed that there was no significant difference in trends between males and females (p-value = 0.38). Differences between sexes were observed for the age at diagnosis. For women, a peak in the MS incidence was shown in the age group 30-39 years. For men, only a small peak could be observed for those aged 50-59 years (Figure 4, Table 1).

Table 1 Sex-specific incidence rates of multiple sclerosis by age at diagnosis for the period 1996-2008

	Overall						Men		Women	
	Total			Restricted*			Total (39 cases)	Restricted* (18 cases)	Total (107 cases)	Restricted* (66 cases)
	N	PY	IR (95%CI)	N	PY	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
Overall	146	2344724	6.3(5.2-7.2)	84	1747715	4.8(3.9-6.0)	3.3(2.4-4.6)	2.1(1.3-3.3)	9.1(7.5-11.0)	7.5(5.9-9.6)
Age										
<10	0	269073	-	0	201027	-	-	-	-	-
10-19	2	281742	0.7(0-1.7)	1	207514	0.5(0.1-3.4)	1.4(0.3-5.6)	0.9(0.1-6.7)	-	-
20-29	19	313021	6.1(3.3-8.8)	13	231372	5.6(3.3-9.7)	2.5(0.9-6.7)	3.4(1.3-9.0)	9.8(5.9-16.2)	8.0(4.1-15.3)
30-39	49	382530	12.8(9.2-16.4)	32	281124	11.4(8.0-16.1)	5.1(2.7-9.5)	3.5(1.4-8.3)	20.9(15.3-28.7)	19.8(13.6-28.8)
40-49	40	365499	10.9(7.6-14.3)	20	269229	7.4(4.8-11.5)	4.3(2.2-8.7)	1.5(0.4-5.9)	17.7(12.5-25.0)	13.5(8.5-21.5)
50-59	27	307079	8.8(5.5-12.1)	16	233152	6.9(4.2-11.2)	9.0(5.3-15.2)	5.1(2.3-11.3)	8.6(5.0-14.7)	8.7(4.7-16.1)
60-69	8	204874	3.9(1.2-6.6)	2	156884	1.3(0.3-5.1)	1.0(0.1-7.1)	-	6.7(3.2-14.0)	2.5(0.6-10.0)
>=70	1	220906	0.5(0-1.3)	0	167413	-	-	-	0.7(0.1-5.3)	-

Note: IR=incidence rate, PY=person years, CI=confidence interval

*Restricted group: those cases of whom additional information on the diagnosis and copies of specialist letters were received from the GP

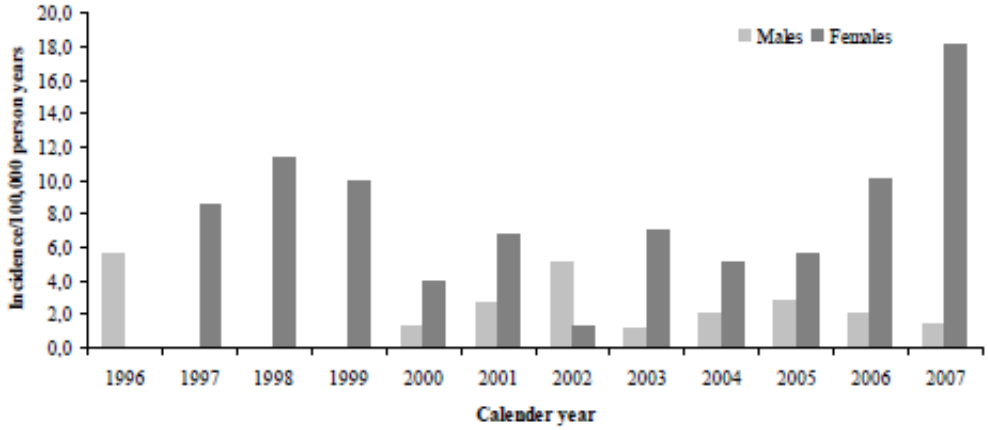


Figure 3 Incidence rate of multiple sclerosis by sex in the restricted population over calendar time. No female cases and no male cases were found in 1996 and 1997-1999, respectively.

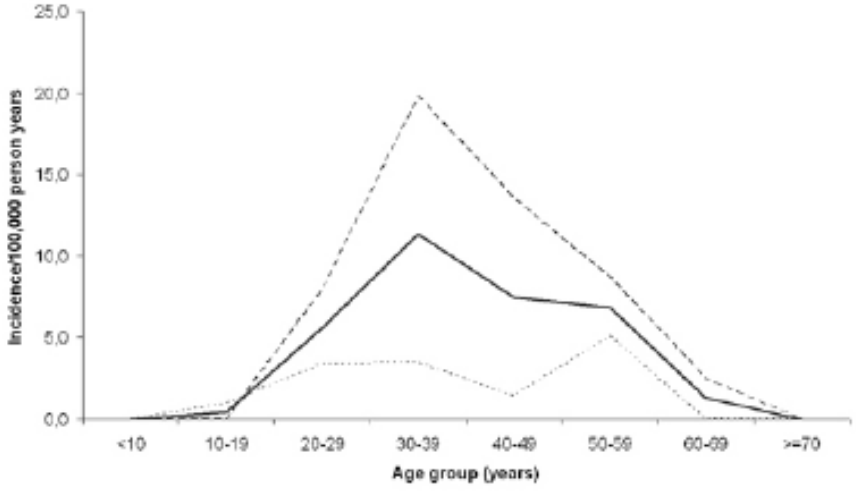


Figure 4 Incidence rates of multiple sclerosis per age category by sex in the restricted population, 1996-2008.

Males Females Overall

Discussion

This paper shows that during 1996-2005, the MS incidence in our study population was approximately 4 per 100,000 py. From 2005 onwards, the incidence has gradually increased to 9 per 100,000 py in 2007/8. The incidence rate was three times higher for women than for men, but there was no significant difference by gender in the overall incidence trend. The results of our study show a higher MS incidence (4.8 per 100,000 py, 95%CI 3.9-6.0) than previously reported in The Netherlands (3.0 per 100,000).[5] However, the earlier estimate was based on the period 1985-1990 and was conducted in a small region of The Netherlands.

As MS incidence changes by latitudes, the incidence rate for The Netherlands should only be compared with rates of surrounding regions with comparable latitudes (52^0N), e.g. the United Kingdom (UK) and Germany. Alonso et al. found a crude incidence rate of 5.5 cases per 100,000 py (95%CI 5.1-5.9) for the entire population in the UK (1993-2000) [23]. For Germany, an annual incidence of 8.0 per 100,000 py (95%CI 6.4-10.0) was reported for the period 1998-2002 [24]. Other study results from surrounding regions are limited to Nordic countries [25-27], whereby the study of Grytten et al [25] showed an increasing incidence (1953-1997) to 6 per 100,000 py (95%CI 5.0-7.2) in 1993 to 1997.

An explanation for the increasing MS incidence may be changes in diagnostic criteria (availability of MRI and CSF analysis), diagnostic awareness in the public health service system and an increasing proportion of people with only minor symptoms and signs diagnosed with MS. More rapid diagnosis due to the availability of MRI and changing criteria for MS diagnosis was reflected by a steady decline in the delay between onset of symptoms and actual diagnosis for both men and women. The median interval between date of first symptoms and assessment by a neurologist declined from 32 months in the period before 1998 to only 2 months for the period after 2005. The range in diagnostic delay also decreased over time, although the broad range in diagnostic delay (0-20 months in the period 2005-2008) is still indicative of the often insidious onset and slow progression of several cases. If MRI availability and/or diagnostic awareness caused the observed increase, then the incidence rate would stabilize or might decrease in the coming years. Other explanatory factors for an increasing MS incidence are largely unknown but changes in environmental factors have been suggested [28,29]. In line with our study, several other studies reported that the increasing MS incidence was mostly attributable to an increase among women [23,25,27,30-34]. Solid evidence for the shift in F:M sex ratio is yet unknown but perhaps changing lifestyle factors among women, e.g. increased smoking, use of oral contraceptives, changing roles of women in workforce, dietary habits and timing in childbearing years may play a role [32]. In some countries the increase started several decades ago or has already stabilized. In our study, which covered a 13-year period, an increasing difference in MS incidence for men and women was only visible over the

past five years, but the difference in trends between males and females was not statistically significant. For women, the highest incidence was observed in the age group 30-39 years, while for men no well-defined peak in the incidence was shown. Almost identical patterns in MS incidences by age were observed for both men and women in the UK and France [23,30]. In the UK however, the incidence for women peaked in the 40-44 age group [23]. A Canadian and US study found similar patterns in women, but not in men (peak incidence in 25-34 and 45-54 age group respectively) [35,36]. A Norwegian study found a peak incidence for both men and women in the age group 50-59 years [25].

The relatively smaller size of the population under 10 years of age and the slow progression of disease might explain why we did not observe any young MS cases. It seems rather difficult to diagnose children with MS. Vague symptoms such as fatigue, tinglings, blurred vision with one eye and clumsy locomotion are not well understood by parents and not mentioned by children [37].

As this is a retrospective and observational study, certain limitations should be mentioned. Misclassification can be introduced by using computerized medical records. Since MS is often difficult to diagnose, cases who are not (yet) diagnosed with MS by a specialist will not be identified as potential cases. Our estimates may be an underestimation of the true MS incidence. The reliability of our observed rates is however supported by similar results from other studies and there is no reason to believe that the degree of underestimation has changed over time. To decrease the inclusion of false positives, additional information was requested from the GP; however this was not available for all patients, since some GPs had changed information system and could not de-crypt the patient code anymore. Restricting the analyses to only those for whom additional information was received from their GP did not change the observed trend of MS over the past years. Our MS incidence estimates were based on small numbers resulting in broad confidence intervals. The relatively wide confidence intervals for the years 1996 and 2008 were due to the low number of person-years by left censoring in 1996 (early stage of the IPCI database) and a high degree of right censoring in 2008 (data available until April 2008).

Conclusions

Insight into the background incidence rates of autoimmune diseases prior to vaccine introduction is a crucial part of the assessment of possible vaccine safety concerns. Background rates provide information about the expected number of events in the absence of vaccination. In our study the upper confidence limit of the observed incidence rate by age could be used to calculate the expected number of cases per age group. If vaccination of a particular (age) group is more likely to be perceived as a

trigger (i.e. exacerbation of an underlying silent autoimmune process) or a cause, this will be reflected by an increase in the MS incidence in this (age) group. Signal detection may be done based on observed and expected ratios.[38]
The assessment in this study of the age and gender specific background MS incidence will improve safety monitoring after recently or new introduction of vaccines.

Acknowledgments

The authors thank Prof. dr. C.H. Polman for critically reading the manuscript.

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG: Multiple Sclerosis. N Eng J Med 2000;343:938-952.

2. Ruggieri M, Iannetti P, Polizzi A, Pavone L, Grimaldi LME: Multiple sclerosis in children under 10 years of age. Neurol Sci 2004;25(Suppl 4):S326-S335.

3. Martinelli V, Rodegher M, Moiola L, Comi G: Late onset multiple sclerosis: clinical characteristics, prognostic factors and differential diagnosis. Neurol Sci 2004;25:S350-S355.

4. Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vécsei L, Milanov I: The epidemiology of multiple sclerosis in Europe. Eur J Neurol 2006;13:700-722.

5. Minderhoud JM, Zwanniken CF: Increasing prevalence and incidence of multiple sclerosis: an epidemiological study in the province of Groningen, the Netherlands. In: Firnhaber W, Lauer K (eds): Multiple sclerosis in Europe: an epidemiological update. Leuchtturm, Darmstadt, 1994.

6. Wraith DC, Goldman M, Lambert PH: Vaccination and autoimmune disease: What is the evidence? Lancet 2003;362:1659-1666.

7. Siegrist C-A: Mechanisms underlying adverse reactions to vaccines. J Comp Path 2007;137:S46-S50.

8. Regner M, Lambert P-H: Autoimmunity through infection or immunization? Nat Immunol 2001;2(3):185-188.

9. Shoenfeld Y, Aron-Maor A: Vaccination and autoimmunity – 'Vaccinosis': a dangerous liaison? J Autoimm 2000;14:1-10.

10. European Medicines Agency: Fith pandemic pharmacovigilance weekly update. EMA weekly Pandemic. 6 January 2010. EMA/4476/2010.

11. Hernán MA, Jick SS, Olek MJ, Jick H: Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurol 2004;63:838-842.

12. Mikaeloff Y, Caridade G, Rossier M, Suissa S, Tardieu M: Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. Arch Pediatr Adolesc Med 2007;161:1176-1182.

13. Zipp F, Weil JG, Einhaupl KM: No increase in demyelinating diseases after hepatitis B vaccination. Nat Med 1999;5:964-965.

14. Ascherio A, Zhang S, Hernán MA, Olek MJ, Coplan PM, Brodovicz K, Walker AM: Hepatitis B vaccination and the risk of multiple sclerosis. N Eng J Med 2001;344:327-332.

15. Touzé E, Fourrier A, Rue-Fenouche C, Rondé-Oustau V, Jeantaud I, Bégaud B, Alpérovitch A: Hepatitis B vaccination and first central nervous system demyelinating event: a case-control study. Neuroepidemiol 2002;21:180-186.

16. DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, Shinefield HR, Mullooly JP, Likosky W, Chen RT; Vaccine Safety Datalink Research Group, National Immunization Program, Centers for Disease Control and Prevention: Vaccinations and risk of central nervous system demyelinating diseases in adults. Arch Neurol 2003;60:504-509.

17. Sturkenboom MCJM, Wolfson C, Roullet E, Heinzlef O, Abenhaim L: Demyelinisation, multiple sclerosis, and hepatitis B vaccination: a population-based study in the UK. Neurol 2000; 54(Suppl 3):A166.

18. Health Council of The Netherlands: General vaccination against hepatitis B revisited. The Hague, Health Council of The Netherlands, 2009; publication no. 2009/03.

19. Health Council of The Netherlands: Vaccination against cervical cancer. The Hague, Health Council of The Netherlands; 2008. Report No.: 2008/08.

20. Lamberts H, Wood M, Hofmans-Okkes IM: International primary care classifications: the effect of fifteen years of evolution. Fam Pract 1992;9:330-339.

21. Van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM, van Bemmel JH: The introduction of computer-based patient records in The Netherlands. Ann Intern Med 1993;119:1036-1041.

22. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH: Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-344.

23. Alonso A, Jick SS, Olek MJ, Hernan MA: Incidence of multiple sclerosis in the United Kingdom: findings from a population-based cohort. J Neurol 2007;254:1736-1741.

24. Fasbender P, Kölmel HW: Incidence of multiple sclerosis in the urban area of Erfurt, Thuringia, Germany. Neuroepidemiol 2008;30:147-151.
25. Grytten N, Glad SB, Aarseth JH, Nyland H, Midgard R, Myhr K-M: A 50-year follow-up of the incidence of multiple sclerosis in Horaland County, Norway. Neurol 2006;66:182-186.
26. Koch-Henriksen N, Bronnum-Hansen H, Hyllested K: Incidence of multiple sclerosis in Denmark 1948-1982: a descriptive nationwide study. Neuroepidemiol 1992;11:1-10.
27. Sundstrom P, Nuystrom L, Forsgren L: Incidence (1988-97) and prevalence (1997) of multiple sclerosis in Vasterbotten County in northern Sweden. J Neurol Neurosurg Psychiatr 2003;74:29-32.
28. Marrie RA: Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol 2004;3(12):709-718.
29. Ebers GC: Environmental factors and multiple sclerosis. Lancet Neurol 2008;7(3):268-277.
30. Debouverie M, Pittion-Vouyovitch S, Louis S, Roederer T, Guillemin F: Increasing incidence of multiple sclerosis among women in Lorraine, Eastern France. Mult Scler 2007;13:962-967.
31. Hirst C, Ingram G, Pickersgill T, Swingler R, Compston DA, Robertson NP: Increasing prevalence and incidence of multiple sclerosis in South East Wales. J Neurol Neurosurg Psychiatry 2009;80(4):386-391.
32. Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, Ebers GC, for the Canadian Collaborative Study Group: Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006;5(11):932-936.
33. Gray OM, McDonnell GV, Hawkins SA: Factors in the rising prevalence of multiple sclerosis in the north-east of Ireland. Mult Scler 2008;14:880-886.
34. Alonso A, Hernán MA: Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurol 2008;71:129-135.
35. Hader WJ, Yee IML: Incidence and prevalence of multiple sclerosis in Saskatoon, Saskatchewan. Neurol 2007;69:1224-1229.
36. Mayr WT, Pittock SJ, McClelland RL, Jorgensen NW, Noseworthy JH, Rodriguez M: Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985-2000. Neurol 2003;61:1373-1377.
37. Waldman A, O'Conner E, Tennekoon G: Childhood multiple sclerosis: a review. Ment Retard Dev Disabil Res Rev 2006;12(2):147-156.
38. Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, Miller E, Andrews N, Stowe J, Salmon D, Vannice K, Izurieta HS, Akhtar A, Gold M, Oselka G, Zuber P, Pfeifer D, Vellozzi C: Importance of background rates of diseases in assessment of vaccine safety during mass immunization with pandemic H1N1 influenza vaccines. Lancet 2009;374(9709):2115-2122.

Chapter 11

Immunity against poliomyelitis in the Netherlands, assessed in 2006 to 2007: the importance of completing a vaccination series

Nicoline A.T. van der Maas
Liesbeth Mollema
Guy A. Berbers
Debbie M. van Rooijen
Harry G. van der Avoort
Marina A. Conyn-van Spaendonck
Hester E. de Melker
Fiona R. van der Klis

Published in:
Eurosurveillance 19(7) 20705 (20/02/2014)
(doi:10.1186/1472-6963-10-237)

Abstract

Europe has been declared polio-free since 2002. Here we describe the seroprotection against poliomyelitis in the Dutch population using banked serum samples. Samples from 1,581 inhabitants of eight municipalities with low vaccination coverage (LVC) and an additional 6,386 samples from a nationwide (NS) group (clinical trial number: ISRCTN20164309; collected in 2006–07) were tested for neutralising antibodies (log^2 reciprocal titres (GMT); non-protection <3) against all three poliomyelitis serotypes. Demographic and epidemiological data were used for statistical regression analysis. Seroprevalence in the NS was 94.6% (type 1), 91.8% (type 2) and 84.0% (type 3). Infants (0–7 months-old) had ≥80% seroprevalence for all serotypes. The highest seroprevalence was found in children, with type 1 and type 2 in five year-olds and type 3 in nine to 10 year-olds. In the LVC group, orthodox protestants, many of whom refuse vaccination, showed seroprevalence rates of 64.9% (type 1), 61.0% (type 2) and 62.1% (type 3). In the NS group, non-Western immigrants and travellers to non-European continents had higher seroprevalences compared to Western immigrants and travellers within Europe, respectively. The Dutch National Immunisation Programme against poliomyelitis has provided good seroprotection, with high and long-lasting GMTs against all serotypes upon completion. The unvaccinated population remains at risk.

Introduction

Poliomyelitis is a severe infectious disease caused by poliovirus, an enterovirus with three serotypes (types 1, 2 and 3). In 90–95% of cases, the infection remains subclinical. In about 1% of the symptomatic cases, poliovirus invades the central nervous system, leading to muscle weakness and acute flaccid paralysis [1]. In 1988, the World Health Organization (WHO) launched a polio eradication initiative [2]. Since then, large vaccination campaigns have decreased the worldwide number of poliomyelitis cases by more than 99%. However, the WHO's goal of worldwide eradication remains unachieved.

Europe has been classified by the WHO as polio-free since 2002, despite the 2010 epidemic that originated in Tajikistan, because its dissemination was interrupted successfully. The Netherlands, where poliomyelitis has been notifiable since 1924 [3], suffered from a large type1 poliomyelitis epidemic in 1956 and three smaller outbreaks in 1971 (type 1), 1978 (type 1) and 1992–93 (type 3) [4-6]. In all of these smaller outbreaks, export of poliovirus to two polio-free countries, the United States (US) and Canada, occurred, but only during the 1971 and 1978 outbreaks symptomatic cases among unvaccinated individuals in US and Canada were reported. The last two outbreaks were restricted to orthodox protestant individuals, most of whom were refusing vaccination because of religious reasons and living in socio-geographically closely clustered communities. Since 1993, no cases of poliomyelitis have been reported in the Netherlands [8-11]. Currently, the risk of reintroduction of poliovirus to the Netherlands is discussed due to silent circulation of wild poliovirus in Israel and cases of poliomyelitis in Syria [12,13].

Vaccination against poliomyelitis, using trivalent inactivated polio vaccine (IPV), was introduced in the Netherlands in 1957 for all individuals born in 1945 and younger. Vaccination is free of charge for all inhabitants of the Netherlands up to the age of 18 years, and participation in the National Immunisation Programme (NIP) is not mandatory. From 1962 onwards, IPV was administered in a combination vaccination strategy, along with the diphtheria, tetanus and whole-cell pertussis vaccine (DTwcP-IPV). Booster vaccinations with DT-IPV at four and nine years of age were added to the NIP in 1965. Initially, infant vaccinations were given at three, four and five months of age, followed by a booster at the age of 11 months, but this schedule was changed to two, three and four months of age in 1999, in response to an upsurge in pertussis [14]. This schedule, i.e. six IPV doses, was in use at the time of this survey (2006–07) and still is. In 2005 the infant doses of whole-cell pertussis vaccine were replaced with the safer acellular pertussis vaccine [15]. Vaccination coverage with the infant vaccinations has been continuously high (>95%) since 1957 [16].

A first nationwide seroprevalence study, performed in 1995–96, aimed to monitor the immunity of the Dutch population against diseases included in the NIP [17]. A second study was performed in 2006–07 [18]. Comparison between these studies enables us to assess the impact of changes in the vaccination schedule and (the absence of) circulation of microorganisms targeted by the NIP. The first survey showed good seroprotection rates against poliomyelitis in the general population [19]. Here we describe and discuss the protection against poliomyelitis in a representative Dutch population sample, including individuals from municipalities with low vaccination coverage (LCV), for whom banked serum samples and corresponding demographic and epidemiologic data, retrieved in the second serosurvey in 2006–07, were available.

Methods

Study population and design

A national NIP sera and data bank was established in 2006–07 to estimate age-specific seroprevalence of antibodies against vaccination-targeted diseases, as described previously [18, 20]. The specimen- and database includes male and female Dutch inhabitants, 0–79 years-old, from 40 municipalities nationwide (nationwide sample (NS); n=6,386), with oversampling of the migrant population. In addition, inhabitants from eight LVC municipalities were included (n=1,518). The demographic and epidemiological data included vaccination and travel history, and other known risk factors.

The study protocol was approved by the Medical Ethics Testing Committee of the Foundation of Therapeutic Evaluation of Medicines (METC-STEG) in Almere, the Netherlands (Clinical Trial Number: ISRCTN 20164309). All participants (or the parent/guardian of minors) provided signed informed consent for blood sampling and data gathering via a questionnaire.

Serology

The serum samples, derived from blood by centrifugation (10 min at 1,000 G), were retrieved from −80 ˚C storage. Poliovirus neutralising antibody titres against serotypes 1, 2, and 3 were determined in a standard neutralisation test (NT) using Sabin vaccine strains as challenge viruses, as recommended by the WHO [21]. Sera were tested in two-fold dilutions series. Quality control samples consisting of virus control and an in-house human serum control were added to each plate. Results were expressed as $\log^2$ reciprocal titres and samples were considered protective if NT titres were ≥8 (i.e. $\log^2$ titre≥3) [22].

Statistical analysis

Seroprevalence and mean $\log^2$ titres, both with 95% confidence intervals (95% CI), were calculated using a sampling weight for each study participant. For the NS group, results were adjusted for age, sex, ethnicity, degree of urbanisation, and a two-stage cluster sampling, taking into account the strata (five regions) and clusters (40 municipalities). For the LVC group, results were adjusted for age and sex; in addition, the LVC population was stratified by vaccination coverage related to religious denomination, as defined by Ruijs et al [23], with orthodox protestants (including Protestant Congregations in the Netherlands, Old Protestant Congregations, Restored Protestant Church and Protestant Congregations) representing low or intermediate vaccination coverage and non-orthodox protestants (including Protestant Bond, Christian Protestant Churches, other Protestant Christians, and other, no or unknown religion) representing moderate to high vaccination coverage.

Linear regression analysis was performed to study the decline of antibodies in individuals who had received the complete NIP vaccination series, consisting of six IPV-containing vaccinations. As such, this analysis was limited to individuals between 10 and 45 years-old, since the sixth IPV-containing vaccination would have been administered at approximately nine years of age and those older than 45 years would have been born before the current NIP strategy.

Logistic regression analysis was performed on the NS group to assess possible risk factors for non-protection (NT<3), using a multivariate model which included all variables with a p-value <0.2 already adjusted for age, sex, degree of urbanisation, and geographic region. To maximise comparability between the three serotypes, the full model was applied without backward selection to each serotype. The results are presented as odds ratios (ORs) with 95% CIs.

All statistical analyses were performed with SAS software (version 9.3) and Microsoft Excel.

Results

Immunity in the nationwide sample

The seroprevalence in the NS sample was 94.6%, 91.8% and 84.0% for poliovirus types 1, 2 and 3, respectively. Mean $\log^2$ titres were 7.39, 6.96 and 6.04 for the three respective types (Table 1).

TABLE 1

Seroprevalence rates and mean log² titres for poliovirus types 1, 2 and 3, the Netherlands, 2006–07 (n=7,967)

Poliovirus serotype	Sample	NT≥3 % (95% CI)	Mean log² titre mean (95% CI)
Type 1	Nationwide sample[a]	94.6 (93.9–95.3)	7.39 (7.32–7.45)
	Dutch citizens and Western immigrants[b]	94.2 (93.4–95.0)	7.30 (7.22–7.37)
	Non-Western immigrants[c]	97.6 (96.7–98.6)	7.83 (7.68–7.98)
	LVC non-orthodox protestants[d]	92.9 (91.7–94.1)	7.33 (7.05–7.60)
	Orthodox protestants[e]	64.9 (57.8–72.1)	5.34 (4.68–6.00)
Type 2	Nationwide sample[a]	91.8 (90.9–92.6)	6.96 (6.89–7.03)
	Dutch citizens and Western immigrants[b]	91.1 (90.3–91.8)	6.84 (6.76–6.92)
	Non-Western immigrants[c]	97.1 (95.8–98.4)	7.57 (7.42–7.72)
	LVC non-orthodox protestants[d]	90.3 (87.8–92.7)	6.66 (6.43–6.88)
	Orthodox protestants[e]	61.0 (50.5–71.4)	4.86 (4.28–5.45)
Type 3	Nationwide sample[a]	84.0 (82.9–85.1)	6.04 (5.96–6.11)
	Dutch citizens and Western immigrants[b]	83.2 (82.2–84.1)	5.91 (5.82–5.99)
	Non-Western immigrants[c]	90.7 (88.9–92.5)	6.68 (6.51–6.86)
	LVC non-orthodox protestants[d]	86.1 (83.6–88.6)	6.21 (5.94–6.48)
	Orthodox protestants[e]	62.1 (54.5–69.7)	4.71 (4.21–5.21)

CI: confidence interval; NT: neutralisation test; LVC: low vaccination coverage.

[a] n=6,386.
[b] n=5,317.
[c] n=1,069.
[d] n=1,038.
[e] n=480.

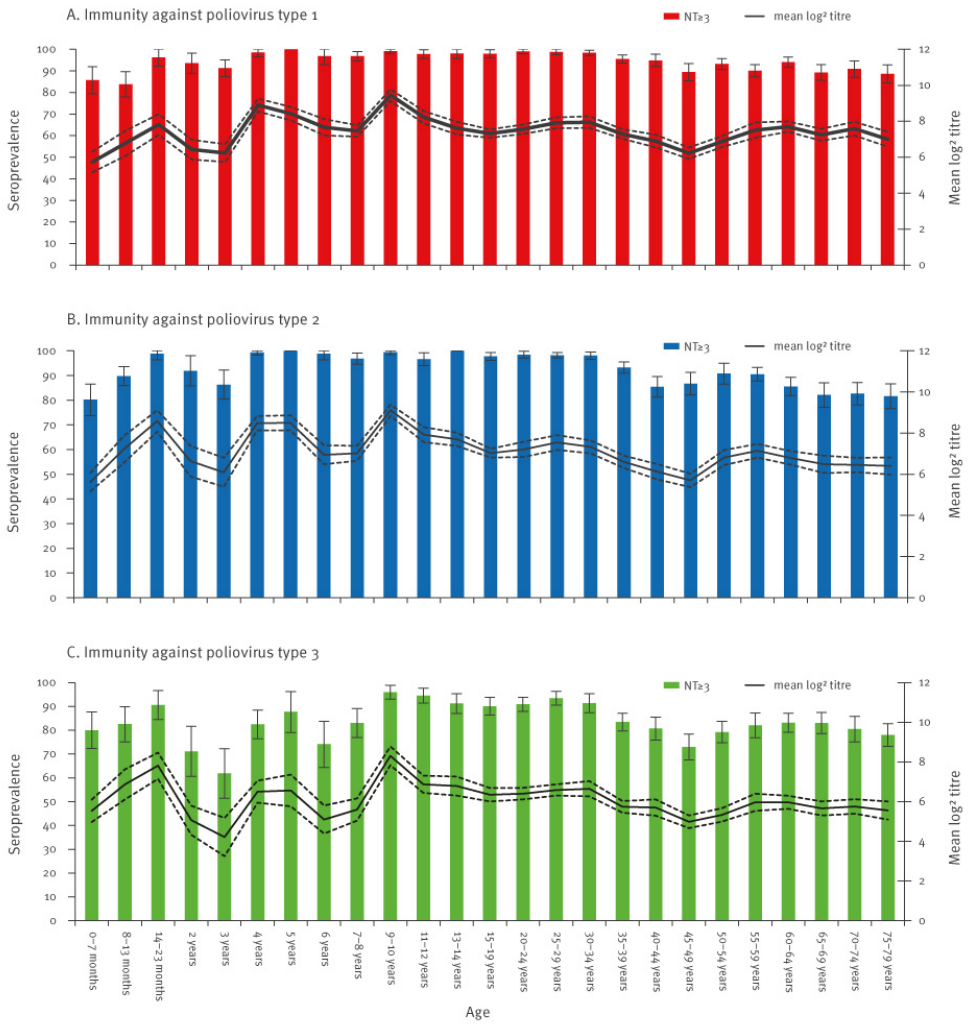
For one month-old infants, who were too young to be vaccinated, the seroprevalence (reflecting maternal antibodies) was 83.0% (type 1), 79.1% (type 2), and 65.9% (type 3). These percentages were higher for the two to four month-old infants, who were eligible for vaccination (maximum of three IPV doses), with seroprevalences of 89.2%, 83.3% and 85.6% for the three serotypes. Owing to waning of antibodies, the seroprevalence percentages decreased thereafter, with the five to 10 month-olds showing 79.7%, 80.8% and 75.0% for the three serotypes, but increased again in the 11 to 13 month-olds, who were eligible for a booster dose, with seroprevalences of 92.1%, 97.4% and 94.7% for the three serotypes. The highest rates of seroprevalence for type 1 and type 2 (both 100%) were found in five year-old children (after the fifth IPV dose at four years of age), and for type 3 (95.9%) in nine to 10 year-olds (after the sixth IPV dose).

Plotting of the mean log² titres of infants and children, stratified by age, indicated the positive effect of booster doses at 11 months and at four and nine years of age (Figure 1). In contrast, plotting of the mean log² titres of adults showed a gradually declining trend up to the age of 45–49 years, followed by an increase in mean log² titre for people born before 1957, who possibly had been in contact with wild-type poliovirus.

The overall seroprevalence and mean log² titres of non-Western immigrants (n=1,069) were higher than those of individuals of Dutch or Western origin (n=5,317).

FIGURE 1

Seroprevalence and mean log² titres for poliovirus types 1, 2 and 3 in the nationwide sample, stratified by age, the Netherlands, 2006–07 (n=6,386)



NT: neutralisation assay.

11

The higher seroprevalence of type 1 and type 2 in the non-Western group was mainly due to higher seroprevalences in children under the age of four years and adults 40 years and older. The increased seroprevalence of type 3 was evenly distributed over the age categories.

Immunity in the low vaccination coverage sample

The seroprevalence in the LVC sample excluding orthodox protestant persons was 92.9%, 90.3% and 86.1% for the three respective serotypes, corresponding to a mean log² titre of 7.33 (type 1), 6.66 (type 2) and 6.21 (type 3) (Table 1).

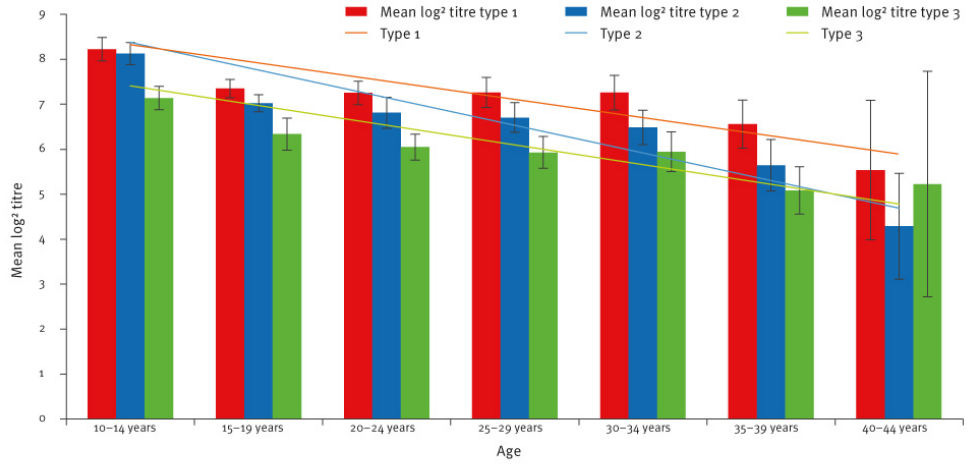
For the orthodox protestant sub-category within the overall LVC sample, both seroprevalence and mean $\log^2$ titres were significantly lower; moreover, analysis of immunity against poliomyelitis in four cohorts in this subcategory, based on date of birth, showed the influence of poliomyelitis outbreaks (Table 2). The results indicated that the youngest cohort, individuals born from 1994 onwards, had not been in contact with wild-type poliovirus, whereas two adult cohorts, i.e. individuals born 1979–93 and 1957–78, had been in contact with type 3 and type 1. This is in agreement with the recorded serotype-specific outbreaks that occurred in 1992–93 and in 1971 and 1978 [6,9]. These outbreaks were controlled with trivalent (1992–93) and monovalent (1971, 1978) live attenuated oral polio vaccine (OPV), which possibly also contributed to the observed seroprevalence rates. The cohort born before 1957 lived in the era before large-scale immunisation and therefore probably encountered wild-type virus regularly, as reflected in the moderate to high seroprevalence rates.

Persistence of antibodies in relation to completion of the poliovirus vaccination strategy in the Dutch National Immunisation Programme

For the NS cohort of 10 to 44 year-olds who had completed the normal immunisation schedule of six IPV-containing vaccinations by the age of nine years, and had not obtained any extra polio antigen-containing vaccinations (n=1,260), the seroprevalence percentages were 98.8% (type 1), 97.5% (type 2) and 90.9% (type 3). Plotting of the mean $\log^2$ titres showed a decreasing trend with age for all serotypes, but the titres remained well above the protection cut-off of 3, indicating that seroprotection had been achieved (Figure 2). Linear regression analysis to assess the relation between mean $\log^2$ titre and age yielded the following slopes: type 1, –0.06 (95% CI: –0.07 to –0.04), type 2, –0.09 (95% CI: –0.10 to –0.08) and type 3, –0.07 (95% CI: –0.09 to –0.05).

FIGURE 2

Poliovirus mean log2 titres in 10 to 44 year-olds in the nationwide sample who completed the NIP vaccination series with no revaccinations, stratified by age, the Netherlands, 2006–07 (n=1,260)



NIP: National Immunisation Programme.

Demographic and vaccination-related risk factors of non-protection

The multivariate logistic regression analysis of risk factors for a non-protective antibody level (NT<3) in the overall NS cohort is presented in Table 3. The lowest seroprevalence for type 1 and type 2 was found in the 0 year-old infants, while the lowest seroprevalence for type 3 was found in the one to four year-olds. Furthermore, non-Western immigrants had higher seroprevalences than Western immigrants or individuals of Dutch origin. Likewise, the cohort who had travelled to Asia, Africa, or South and Central America had higher seroprevalences than the cohort who reported not having travelled to these continents. The cohort that reported practicing a religion that is associated with vaccination refusal had lower seroprevalences than the cohort that did not belong to these religious groups.

Table 2

Seroprevalence rates and mean log^2 titres for poliovirus types 1, 2 and 3 in orthodox protestants, stratified by age, the Netherlands, 2006–07 (n=480)

Poliovirus serotype	Cohort, by birth date	NT≥3 % (95% CI)	Log2 titre mean (95% CI)
Type 1	≥1 Jan 1994[a]	49.7 (37.6–61.8)	4.36 (3.59–5.13)
	≥1 Jan1979 and <1 Jan 1994[b]	52.8 (36.9–68.8)	4.59 (3.50–5.68)
	≥1 Jan 1957 and <1 Jan 1979[c]	72.9 (54.6–91.2)	5.77 (4.41–7.14)
	<1 Jan 1957[d]	80.3 (72.2–88.3)	6.40 (5.56–7.24)
Type 2	≥1 Jan 1994[a]	51.0 (39.5–62.5)	4.33 (3.66–5.00)
	≥1 Jan 1979 and <1 Jan 1994[b]	60.8 (45.2–76.4)	4.83 (3.65–6.01)
	≥1 Jan 1957 and <1 Jan 1979[c]	56.2 (41.4–70.9)	4.61 (3.63–5.60)
	<1 Jan 1957[d]	79.0 (63.0–95.0)	5.83 (4.94–6.72)
Type 3	≥1 Jan 1994[a]	48.2 (36.9–59.5)	3.99 (3.14–4.84)
	≥1 Jan 1979 and <1 Jan 1994[b]	68.7 (51.8–85.6)	5.51 (4.40–6.61)
	≥1 Jan 1957 and <1 Jan 1979[c]	61.7 (45.2–78.3)	4.42 (3.57–5.27)
	<1 Jan 1957[d]	71.1 (63.2–79.0)	5.12 (4.47–5.77)

CI: confidence interval; NT: neutralisation test.

[a] n=190, no wild-type virus circulating.
[b] n=87, type 3 outbreak in 1992–93.
[c] n=100, type 1 outbreaks in 1971 and 1978.
[d] n=103, wild-type virus circulating.

Table 3

Multivariate logistic regression analysis of risk factors for non-protection against poliovirus types 1, 2 and 3 in the nationwide sample, the Netherlands, 2006–07 (n=6,386)

Demographic- or vaccination-related factor	Sub-category	Total n	Poliovirus type 1		Poliovirus type 2		Poliovirus type 3	
			NT<3, %	Adjusted OR (95% CI)	NT<3, %	Adjusted OR (95% CI)	NT<3, %	Adjusted OR (95% CI)
Sex	Male	2,912	6.3	Ref	8.8	Ref	16.7	Ref
	Female	3,474	5.6	0.93 (0.75–1.16)	8.2	0.92 (0.76–1.11)	15.2	0.90 (0.78-–1.04)
Age in years	0	348	19.3	Ref	19.3	Ref	21.8	Ref
	1–4	514	5.3	**0.22 (0.12–0.40)**	6.0	**0.35 (0.19–0.64)**	23.5	**0.69 (0.44–1.08)**
	5–9	620	1.8	**0.09 (0.04–0.20)**	1.3	**0.09 (0.04–0.21)**	12.3	**0.33 (0.20–0.55)**
	10–19	730	1.9	**0.14 (0.06–0.37)**	1.9	**0.11 (0.04–0.26)**	7.8	**0.18 (0.10–0.32)**
	20–29	712	1.1	**0.06 (0.03–0.15)**	1.8	**0.06 (0.02–0.13)**	7.9	**0.12 (0.07–0.22)**
	30–39	715	3.4	**0.07 (0.03–0.16)**	4.8	**0.06 (0.03–0.13)**	13.2	**0.16 (0.09–0.28)**
	40–49	641	7.6	**0.08 (0.04–0.17)**	13.1	**0.12 (0.06–0.24)**	23.1	**0.17 (0.10–0.30)**
	50–59	714	7.8	**0.09 (0.04–0.18)**	8.7	**0.08 (0.04–0.16)**	18.6	**0.14 (0.08–0.25)**
	60–69	799	7.5	**0.09 (0.04–0.18)**	15.0	**0.16 (0.08–0.31)**	16.4	**0.13 (0.07–0.22)**
	70–79	593	10.1	**0.11 (0.05–0.23)**	17.9	**0.18 (0.09–0.35)**	20.4	**0.15 (0.09–0.26)**
Geographic region	North-east	1,505	6.6	Ref	9.1	Ref	16.0	Ref
	Central	1,122	7.1	1.06 (0.69–1.63)	9.9	1.06 (0.72–1.55)	16.3	0.97 (0.72–1.31)
	North-west	1,527	5.1	0.93 (0.67–1.30)	7.0	0.91 (0.68–1.21)	14.7	1.03 (0.83–1.27)
	South-west	1,125	5.0	**0.62 (0.42–0.92)**	8.0	0.82 (0.59–1.15)	15.9	0.93 (0.72–1.19)
	South-east	1,107	5.7	0.83-0.58–1.19)	8.5	0.87 (0.64–1.19)	16.8	1.05 (0.83–1.33)
Degree of urbanisation	Very high	1,399	5.2	Ref	6.5	Ref	14.4	Ref
	High	2,848	6.1	0.86 (0.62–1.19)	8.3	1.06 (0.79–1.41)	15.5	0.92 (0.75–1.13)
	Moderately high	804	6.0	0.74 (0.49–1.13)	10.3	1.20 (0.85–1.70)	18.7	1.04 (0.81–1.35)
	Low	589	7.3	0.79 (0.46–1.36)	10.3	1.07 (0.66–1.74)	16.3	0.87 (0.60–1.27)
	Very low	746	5.4	0.63 (0.40–1.00)	9.1	0.99 (0.66–1.48)	16.5	0.89 (0.66–1.19)
Migrant status	Dutch citizens and Western immigrants	5,317	6.6	Ref	9.5	Ref	17.3	Ref
	Non-Western immigrants	1,069	2.4	**0.42 (0.26–0.67)**	3.0	**0.47 (0.31–0.71)**	8.7	**0.47 (0.35–0.62)**
Educational level[a]	Low	730	4.3	Ref	7.5	Ref	12.3	Ref
	Medium	3,138	6.4	**1.57 (1.03–2.40)**	10.0	**1.48 (1.06–2.08)**	16.0	1.21 (0.93–1.57)
	High	2,403	5.9	**1.70 (1.09–2.67)**	6.8	1.26 (0.87–1.82)	16.8	**1.51 (1.14–2.00)**
	Unknown	115	1.7	0.51 (0.12–2.20)	7.0	1.25 (0.55–2.82)	13.9	1.23 (0.68–2.24)
Extent of vaccination refusal according to religious views	None or minor	6,253	5.7	Ref	8.3	Ref	15.6	Ref
	Moderate to strong	133	15.0	**2.86 (1.66–4.91)**	16.5	**1.97 (1.17–3.31)**	27.1	**1.79 (1.18–2.72)**
Duration in years between last polio-containing vaccination and blood sampling	0	503	10.7	Ref	11.1	Ref	12.9	Ref
	1–3	1,201	3.3	1.46 (0.80–2.69)	3.3	1.16 (0.64–2.10)	13.6	**2.86 (1.84–4.44)**
	4–9	946	1.6	1.60 (0.68–3.77)	1.1	0.80 (0.32–1.99)	8.0	**3.69 (2.17–6.26)**
	10–20	735	0.1	0.19 (0.02–1.54)	1.1	0.96 (0.36–2.57)	7.8	**5.25 (2.93–9.39)**
	21–30	407	3.0	**4.47 (1.70–11.78)**	6.1	**5.97 (2.59–26.58)**	12.0	**7.24 (3.87–13.52)**
	>31	264	11.0	**9.31 (4.13–21.00)**	17.1	**12.54 (5.92–26.58)**	31.8	**18.75 (10.42–33.74)**
	Unknown	103	1.0	0.48 (0.06–3.84)	1.9	0.83 (0.19–3.76)	13.6	4.38 (2.11–9.12)
	Not vaccinated	2,227	10.1	**13.58 (5.09–36.24)**	15.9	**5.28 (2.46–11.31)**	22.7	**21.44 (11.18–41.10)**
Number of polio antigen-containing vaccinations	6 (completed NIP)	1,498	1.3	Ref	2.6	Ref	8.6	Ref
	0–1	2,592	9.0	1.29 (0.47–3.55)	14.5	1.95 (0.99–3.85)	20.3	0.85 (0.49–1.47)
	2–5	1,900	6.3	**2.63 (1.31–5.28)**	6.2	1.04 (0.61–1.80)	17.6	**1.61 (1.15–2.26)**
	6, including single IPV or OPV	68	4.4	1.86 (0.47–7.31)	4.4	0.48 (0.13–1.74)	16.2	1.19 (0.56–2.53)
	≥7	328	0.6	0.61 (0.14–2.75)	1.5	0.67 (0.25–1.81)	4.0	0.59 (0.32–1.10)
Travelling to high-risk regions[b]	No	3,956	7.7	Ref	11.5	Ref	20.0	Ref
	Yes	2,430	2.9	**0.61 (0.46–0.82)**	3.5	**0.44 (0.34–0.58)**	9.1	**0.57 (0.47–0.68)**

CI: confidence interval; IPV: inactivated polio vaccine; NIP: National Immunisation Programme; NT: neutralisation test; OPV: oral polio vaccine; OR: odds ratio.

[a] For children younger than 14 years, the mothers' higher educational level was recorded. Low: no education or only primary school; medium: junior technical school, lower general, or intermediate vocational secondary schooling; high: higher vocational, higher general secondary, pre-university, or university schooling.

[b] Asia, Africa, or South and Middle America.

Statistically significant results are indicated by bold font.

The cohort that had received their last polio antigen-containing vaccination more than 10 years (type 3) or more than 20 years (types 1 and 2) before sampling, or who had never received the vaccination, were at increased risk of having a non-protective antibody level compared to the cohort that had received their last vaccination less than one year before sampling. An increased risk for a non-protective antibody level was also found for individuals with medium-level (types 1 and 2) or high-level (types 1 and 3) education, compared with those with low-level education. Finally, individuals who had started but not completed the NIP vaccination series, i.e. those who had received only two to five polio antigen-containing vaccinations, were found to be at higher risk for non-protective antibody levels than the individuals who had completed the NIP vaccination series, although the difference in risk for serotype 2 did not reach statistical significance.

Discussion

The serosurvey described herein, using samples and data obtained in 2006–07 from across the country, showed that the general population of the Netherlands had an overall high poliovirus vaccination coverage, with protective antibody levels (NT≥3) being at >90% for serotypes 1 and 2 and slightly less (84%) for serotype 3. The seroprotection levels in the youngest population showed a trend of good adherence to the recommended initial vaccination schedule in early life; furthermore, analysis of long-term protection against all three serotypes indicated the benefit of completing the recommended vaccination series, starting in early life and receiving boosters in later childhood. Not surprisingly, the demographic feature of belonging to a religious group that is associated with vaccination refusal was identified as a risk factor for a non-protective antibody level.

These collective results are comparable to those of a previous Dutch seroprevalence study done in 1996-97 [19], as well as several seroprevalence studies from other countries [24-28]. In particular, the previous Dutch study showed similar age-related trends in seroprotection that correspond to the vaccination schedule and natural exposure, although the seroprevalences found in the current study were overall slightly lower. When comparing the current results from the Netherlands with those from other nations, no remarkable differences were observed for the age-specific trends in seroprevalence of type 1 or type 2; however, the seroprevalence trends for type 3 did appear to be lower than those reported in the other studies. Unfortunately, substantial differences in study design precluded direct or systematic comparison of the results, as some of the previous studies used for example age-restricted categories and included individuals with unknown vaccination status. One hypothesis is that the lower seroprevalence of type 3 found in the current study may be related to the whole-cell DTP-IPV-Hib vaccine used in the Netherlands until January 2005, which

may induce lower antibody titres against serotype 3, but this needs further study. A possible future third serosurvey will provide more insight into this.

The low seroprevalence rates of the orthodox protestants in the Netherlands highlight the continued risk of poliomyelitis in this community. This was also reflected in the composition of affected persons in the last three natural outbreaks (type 1 in 1971 and 1978 and type 3 in 1992–93) that occurred in the Netherlands [11]. Compared with the first survey, seroprevalence rates in orthodox protestant individuals were even lower in this second survey [19]. Since 1993, no notifications of poliomyelitis have been reported in the Netherlands. In addition, nationwide laboratory and environmental surveillance yielded no signal of poliovirus circulation, so it can be assumed that no boosting opportunities with wild-type poliovirus have occurred in the Netherlands since 1993 [9,11]. It is well known that vaccine-derived polioviruses originating from OPV vaccines represent a possible route of disease introduction into communities without established seroprotection. This threat is especially applicable to communities with close socio-geographical clustering, such as the Dutch orthodox protestants.

The current study also found that individuals who had received their last IPV-containing vaccination more than 20 years before sampling, were at increased risk of having antibody levels below the protective threshold. However, Abbink et al. previously demonstrated memory immunity against poliomyelitis in their study of 400 elderly people who were ineligible for vaccination but who were likely to have encountered wild-type infection earlier in life [29]. Assuming that vaccination-induced immunity is as effective as natural immunity suggests that adequate vaccination strategies (including initial and booster doses) will produce sufficient and long-term protection.

Another intriguing finding of the current study is that the non-Western immigrant cohort had higher seroprevalence rates and higher mean $\log^2$ titres than the cohort of Dutch citizens and Western immigrants. In contrast, several other studies found no differences [30,31]. It is possible that the differential results reflect differences in study populations, including variations in age, country of birth, national vaccination strategies (i.e. vaccine type and schedule), and previous exposure.

In the current study, individuals travelling to Asia, Africa, or Central and South America also showed higher seroprevalence rates than those who did not travel to these continents. Indeed, the dT-IPV vaccination is strongly recommended by travel medicine physicians [32]. Assuming that many travellers decide to get this vaccination before travelling, it is possible that the number of polio-antigen containing

vaccinations reported in the Dutch NIP registers collected in this study does not accurately reflect the total number of vaccinations an individual has received. In an attempt to address this potential limitation of the current study design, the study participants were requested to provide their personal vaccination booklets that are kept for such travel purposes; however, we cannot exclude that people may have forgotten to bring this certificate.

Finally, the current study found that higher educational level (of the individual or female parent/guardian of a child) was associated with an increased risk for non-protective antibody levels. This finding seems contradictory to the mass of worldwide studies that have shown higher education to be associated with increased healthcare and higher rates of compliance with health-related policies. In particular, a previous analysis of the Dutch NIP questionnaire indicated that lower socio-economic status (which is generally associated with lower education) was associated with lower participation [33]. Two other studies, assessing the uptake of human papilloma virus vaccination and NIP vaccinations in general, reported a similar link between lower socio-economic status and lower vaccination compliance. Thus, the finding from the current study must be investigated in future studies to determine its validity or underlying causes.

The current study design, using data from both a questionnaire and blood sampling of a large random sample of Dutch inhabitants, affords the possibility to extrapolate results to the general population and to assess the potential risk factors of decreased seroprotection. However, any self-reported data (such as vaccination history) carries a risk of being incomplete or incorrect, and may negatively impact study's findings [34]. In addition, the current results may have been impacted by assay-related limitations; for example, the neutralisation test used here and in most seroprevalence studies is recommended by the WHO as the gold standard for detecting viral serotypes, but may yield false positives or negatives and preclude direct comparison between laboratories or between studies [35,36]. However, in the current study, the testing of the nearly 8,000 samples was carried out over a period of one year, which may have helped limit the potential influence of day-by-day variability in the testing method and its results. Moreover, an in-house control serum, calibrated to the WHO standard, was included on each test plate. These technical strategies were carried out to help strengthen the results' representation of the current status of immunity against poliomyelitis in the Netherlands.

In conclusion, age-related variations in seroprevalence rates were found in the NS that were related to the Dutch NIP against poliomyelitis. The lowest rates were found in children younger than 14 months, who would be eligible for a maximum of four IPV

doses, and the highest rates were found in five year-old children, who would have received five polio-antigen containing vaccinations according to the NIP strategy.

Completion of the NIP vaccination series (including all six initial and booster doses) was associated with high and long-lasting seroprotection. In the general population, seroprevalence rates were above the threshold necessary for prevention of poliovirus transmission, estimated at 82–87% given the condition of homogeneous mixing [37], with the exception of one month-old infants and children between five and 10 months of age. Furthermore, the orthodox protestant community remains at high risk due to their refusal of vaccination. Thus, it is important to continue efforts to increase coverage among this population, and improved approaches should be designed with respect to the particular religious arguments that underlie non-compliance with a vaccination programme [38,39]. Finally, conducting updated nationwide serosurveys is important to monitor the effects of the recent extended period (since 1993) without wild-type virus challenges, and to assess the efficacy of changes in the immunisation schedule.

References

1. Huisman J, editor. Immunisatie tegen infectieziekten. [Immunisation against infectious diseases]. Alphen aan de Rijn/Brussel: Stafleu; 1984. Dutch.
2. Forty-first Wolrd Health Assembly. Resolutions and decisions. WHA41.28. Global eradication of poliomyelitis by the year 2000. Geneva: World Health Organization; 1988. Available from: http://www.polioeradication.org/Portals/0/Document/AboutUs/History/WHA.Resolutions.and.Decisions.pdf
3. van Vliet H. Geschiedenis van de meldingsplicht. [History of notification]. Tijdschrift voor infectieziekten. 2009;4(2):51-60. Dutch. Available from: http://www.ariez.nl/DownloadFile.lynkx?guid=b8ffbdc3-fbe0-4d1f-a0ac-90a6b3c73c7d
4. Bijkerk H. Poliomyelitis epidemic in the Netherlands, 1978. Dev Biol Stand. 1979;43:195-206.
5. Bijkerk H, Draaisma FJ, Landheer T, van Os M. [Poliomyelitis epidemic in Staphorst]. Ned Tijdschr Geneeskd. 1972;116(14):549-58. Dutch.
6. Oostvogel PM, van Wijngaarden JK, van der Avoort HG, Mulders MN, Conyn-van Spaendonck MA, Rumke HC, et al. Poliomyelitis outbreak in an unvaccinated community in The Netherlands, 1992-93. Lancet. 1994;344(8923):665-70.
7. Bijkerk H, Draaisma FJ, van der Gugten AC, van Os M. [The poliomyelitis epidemic in 1978]. Ned Tijdschr Geneeskd. 1979;123(39):1700-14. Dutch.
8. Rümke HC, Oostvogel PM, Van Steenis G, Van Loon AM. Poliomyelitis in The Netherlands: a review of population immunity and exposure between the epidemics in 1978 and 1992. Epidemiol Infect. 1995;115(2):289-98.
9. Schaap GJ, Bijkerk H, Coutinho RA, Kapsenberg JG, van Wezel AL. The spread of wild poliovirus in the well-vaccinated Netherlands in connection with the 1978 epidemic. Prog Med Virol. 1984;29:124-40.
10. Centers for Disease Control and Prevention (CDC). Isolation of wild poliovirus type 3 among members of a religious community objecting to vaccination--Alberta, Canada, 1993. MMWR Morb Mortal Wkly Rep. 1993;42(17):337-9.
11. Conyn-van Spaendonck MA, Oostvogel PM, van Loon AM, van Wijngaarden JK, Kromhout D. Circulation of poliovirus during the poliomyelitis outbreak in The Netherlands in 1992-1993. Am J Epidemiol. 1996;143(9):929-35.
12. Anis E, Kopel E, Singer SR, Kaliner E, Moerman L, Moran-Gilad J, et al. Insidious reintroduction of wild poliovirus into Israel, 2013. Euro Surveill. 2013;18(38):pii: 20586
13. World Health Organization (WHO). Polio in the Syrian Arab Republic - update. Geneva: WHO; 2013. Available from: http://www.who.int/csr/don/2013_11_11polio/en/
14. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. Emerg Infect Dis. 2000;6(4):348-57.
15. Gezondheidsraad. Vaccinatie tegen kinkhoest. [Vaccination against pertussis]. Den Haag: Gezondheidsraad; 2004. Dutch. Available from: http://www.gezondheidsraad.nl/sites/default/files/0404nadden.pdf
16. Van Lier A. Vaccinatiegraad Rijksvaccinatieprogramma Nederland; Verslagjaar 2011. [Vaccination coverage National Immunisation Programme of the Netherlands; year of report 2011]. Bilthoven: National Institute for Public

Health and the Environment; 2011. Dutch. Available from: http://www.rivm.nl/dsresource?objectid=rivmp:47976&type=org&disposition=inline&ns_nc=1

17. De Melker HE, Conyn-van Spaendonck MA. Immunosurveillance and the evaluation of national immunization programmes: a population-based approach. Epidemiol Infect. 1998;121(3):637-43.

18. van der Klis FR, Mollema L, Berbers GA, de Melker HE, Coutinho RA. Second national serum bank for population-based seroprevalence studies in the Netherlands. Neth J Med. 2009;67(7):301-8.

19. Conyn-Van Spaendonck MA, de Melker HE, Abbink F, Elzinga-Gholizadea N, Kimman TG, van Loon T. Immunity to poliomyelitis in The Netherlands. Am J Epidemiol. 2001;153(3):207-14.

20. Mollema L, de Melker HE, Hahné SJ, van Weert JW, Berbers G, van der Klis FR. PIENTER 2-project: second research project on the protection against infectious diseases offered by the national immunization programme in the Netherlands. Bilthoven: National Institute for Public Health and the Environment; 2009. Report No.: 230421001. Available from: http://www.rivm.nl/dsresource?objectid=rivmp:11329&type=org&disposition=inline&ns_nc=1

21. World Health Organization (WHO). Guidelines for WHO/EPI collaborative studies on poliomyelitis: standard procedure for determining immunity to poliovirus using the microneutralization test . Geneva: WHO; 1993. Available from: http://apps.who.int/iris/bitstream/10665/70486/1/WHO_EPI_GEN_93.9_eng.pdf?ua=1

22. Robertson SE. The immunological basis for immunisation. Module 6. Poliomyelitis. Geneva: World Health Organization; 1993 WHO/EPI/GEN/9316. Available from: http://www.who.int/ihr/polio1993en.pdf

23. Ruijs WL, Hautvast JL, van Ansem WJ, Akkermans RP, van't Spijker K, Hulscher ME, et al. Measuring vaccination coverage in a hard to reach minority. Eur J Public Health. 2012;22(3):359-64.

24. Diedrich S, Claus H, Schreier E. Immunity status against poliomyelitis in Germany: determination of cut-off values in International Units. BMC Infect Dis. 2002;2:2.

25. Frantzidou F, Diza E, Halkia D, Antoniadis A. A seroprevalence study of poliovirus antibody in the population of northern Greece. Clin Microbiol Infect. 2005;11(1):68-71.

26. Nates SV, Martinez LC, Barril PA, Ferreyra LJ, Giordano MO, Masachessi G, et al. Long-lasting poliovirus-neutralizing antibodies among Argentinean population immunized with four or five oral polio vaccine doses 1 month to 19 years previously. Viral Immunol. 2007;20(1):3-10.

27. Tafuri S, Prato R, Martinelli D, Calvario A, Bozzi A, Labianca M, et al. Serological survey on immunity status against polioviruses in children and adolescents living in a border region, Apulia (Southern Italy). BMC Infect Dis. 2008;8:150.

28. Li XM, Zhang HR, Wang YM. [Analysis of polio antibody levels in healthy population in Beijing in 2007]. Zhongguo Yi Miao He Mian Yi. 2009;15(3):245-8.

29. Abbink F, Buisman AM, Doornbos G, Woldman J, Kimman TG, Conyn-van Spaendonck MA. Poliovirus-specific memory immunity in seronegative elderly people does not protect against virus excretion. J Infect Dis. 2005;191(6):990-9.

30. Diedrich S, Schreier E. [The German Health Interview and Examination Survey for Children and Adolescents (KiGGS): state of immunity against poliomyelitis in German children]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2007;50(5-6):771-4. German..

31. Affanni P, Veronesi L, Rizziero S, Bizzoco S, Bracchi MT, Tanzi ML. Status of immunity against poliomyelitis: a study among European and extra-European young immigrants living in Parma. Acta Biomed. 2005;76(3):157-63.
32. Landelijk Coördinatiecentrum Reizigersadvisering (LCR). Vaccinaties. [Vaccinations]. Amsterdam: LCR. [Accessed Feb 2014]. Dutch. Available from: http://www.lcr.nl/Vaccinaties
33. Mollema L, Wijers N, Hahne SJ, van der Klis FR, Boshuizen HC, de Melker HE. Participation in and attitude towards the national immunization program in the Netherlands: data from population-based questionnaires. BMC Public Health. 2012;12:57.
34. Steens A, Mollema L, Berbers GA, van Gageldonk PG, van der Klis FR, de Melker HE. High tetanus antitoxin antibody concentrations in the Netherlands: a seroepidemiological study. Vaccine. 2010;28(49):7803-9.
35. Wood DJ, Heath AB. Comparability of poliovirus neutralizing antibody tests. Biologicals. 1992;20(4):293-300.
36. Albrecht P, van Steenis G, van Wezel AL, Salk J. Standardization of poliovirus neutralizing antibody tests. Rev Infect Dis. 1984;6 Suppl 2:S540-4.
37. Anderson RM, May RM, editors. Infectious diseases of humans: dynamics and control. New York Oxford University Press; 1991.
38. Ruijs WL, Hautvast JL, van Ijzendoorn G, van Ansem WJ, van der Velden K, Hulscher ME. How orthodox protestant parents decide on the vaccination of their children: a qualitative study. BMC Public Health. 2012;12:408.
39. Ruijs WL, Hautvast JL, van 't Spijker K, van der Velden K, Hulscher ME. Information on vaccination: meeting the needs of unvaccinated youngsters in the Netherlands. Eur J Public Health. 2011;21(3):344-6.

Chapter 12

Performance of a bedside test for tetanus immunity: results of a cross sectional study amongst three emergency departments in the Netherlands in 2012-2013

Nicoline A.T. van der Maas
Robine Donken
Margreet J.M. te Wierik
Corien M. Swaan
Susan J.M. Hahne
Hester E. de Melker

Published in:
Emerg Med J; 2016;0:1–6.
(doi:10.1136/emermed-2015-205412)

Abstract

Introduction

Despite sustained high vaccination coverage and a national guideline by the Health Council (HC-guideline) on tetanus post-exposure prophylaxis (T-PEP), tetanus sporadically occurs in the Netherlands. This study aims to assess the added value of a bedside test for tetanus immunity (Tetanos Quick Stick®; TQS; Ingen BioSciences Group, France), in the context of routine T-PEP in two adult cohorts: those born before introduction of Tetanus Toxoid-vaccination in the National Immunization Programme (NIP) in 1957 (pre-NIP-cohort; n=196) and those born after (NIP-cohort; n=405).

Methods

Adults included at the time of visiting one of three participating emergency departments received T-PEP as per routine recommendations. Subsequently, a nurse performed the TQS and filled in a questionnaire.

We compared the indication for T-PEP based on TQS-results with those based on the HC-guideline and with actually administration of T-PEP, stratified by cohort.

Results

Among the pre-NIP and NIP-cohort, 16% and 9%, respectively, received T-PEP whilst this was not indicated based on the HC-guideline. Furthermore, 8% and 7%, respectively, did not get T-PEP although it was indicated by the guideline.

Comparing the indication derived from the HC-guideline with TQS result found that 22% (pre-NIP-cohort) and 8% (NIP-cohort) were not eligible for T-PEP according to the HC-guideline but had a negative TQS. Conversely, 36% (pre-NIP-cohort) and 73% (NIP-cohort) were eligible for T-PEP according to the HC-guideline but had positive TQS, indicating sufficient tetanus protection.

Conclusion

Use of the TQS would allow better targeting of T-PEP. Furthermore, stricter adherence to the HC-guideline can prevent over-immunization and decrease the risk of tetanus.

Introduction

Tetanus is a serious disease, acquired when spores of the bacterium Clostridium Tetani infect a wound or a new-born's umbilical stump [1 2]. Anaerobic conditions in the wound can lead to the production of the neurotoxin tetanospasmin, which causes muscle contractions and spasms. Tetanus can be lethal without treatment. Because of large-scale vaccination programmes, nowadays the incidence of tetanus is very low in developed countries, including the Netherlands. However, sporadic cases of tetanus still occur in the Netherlands, mainly among adults who receive insufficient tetanus post-exposure prophylaxis (T-PEP) [3].

In the Netherlands, tetanus toxoid (TT) vaccination was included in the National Immunization Programme (NIP) in 1957 for persons born in or after 1951. Since then, vaccination coverage has been continuously high [4], with a coverage of at least 95% for three doses of infant diphtheria-pertussis-tetanus-poliomyelitis (DPT-IPV) vaccine for birth-cohort 1969 onwards. Before start of the NIP, men who attended military service were vaccinated against tetanus. For T-PEP, a national guideline by the Dutch Health Council (HC-guideline) is available (Table 1). Besides this HC-guideline, several other guidelines are used [5].

The current HC-guideline on T-PEP administration is based on age, gender and vaccination history [6]. Previous studies showed that the self-reported history of received vaccinations is an unreliable method to assess the vaccination status of a patient [7 8]. Most patients are unsure on their vaccination status and they do not bring their vaccination booklet when they visit an emergency department (ED) or general practitioner (GP) for an injury [9].
A large population-based serosurvey, performed in 2006-2007 in the Netherlands to assess the immunity against NIP-diseases in the Dutch population, showed that the Dutch population is well protected against tetanus [10 11]. Seroprevalence in persons, eligible for the NIP, amounted to 99% (95%CI 99-100; cut-off≥0.01 IU/ml) with a geometric mean concentration (GMC) of 1.5 IU/ml (95%CI 1.4-1.6). Birth cohorts that were not eligible for NIP-participation, i.e. those born before 1951, had a seroprevalence of 77% (95%CI 75-79) with corresponding GMC of 0.2 IU/ml (95%CI 0.15-0.21). These results may imply that TT and/or anti-tetanus immunoglobulin (TIG) for persons born in these latter cohorts often is given while adequate tetanus immunity exists. Therefore, it might be possible to extend the current period of 10 years between consecutive booster doses as recommended in our country. This was also described by Mallick et al. [2]. On the other hand, the sporadic cases of tetanus that still occur in the Netherlands (0-5 per year for 1997-2014) show that tetanus prophylaxis does not reach all individuals who require this [3].

Table 1.Guideline on tetanus post-exposure prophylaxis after injury stated by the Dutch Health Council (HC-guideline)

Self-reported patient status	Administration of TIG[a]	Booster vaccination with TT[b]
Immuno-compromised	Yes	3 times
Never vaccinated	Yes	3 times
Incompletely vaccinated	Yes	Complete to 3 times
Fully vaccinated[c] without documentation (men born before 1936 and women born before 1950)	Yes	1 time
Fully vaccinated[c] without documentation (men born in/after 1936 and women born in/after 1950)	No	1 time
Fully vaccinated[c] with booster ≥10 years ago.	No	1 time
Fully vaccinated[c] with booster <10 years ago.	No	No

[a]: anti-tetanus immunoglobulin; administered only once
[b]: tetanus toxoid
[c]: a series of 3 TT doses

Since the early years 2000, a bedside test to assess the immunity against tetanus became available. This Tetanos Quick Stick® (TQS; Ingen BioSciences Group, France) was compared to the Enzyme Linked Immunosorbent Assay (ELISA) method, considered as the reference standard to assess tetanus immunity, and was shown to be cost saving in an ED-setting [12-16].
This study aims to assess 1. The adherence to the HC-guideline and 2. The concordance between TQS-result and the eligibility to receive T-PEP based on the HC-guideline. We studied two birth cohorts, i.e. born before and after the introduction of tetanus toxoid vaccination in the Dutch NIP.

METHODS

Setting

This cross-sectional study was conducted in three EDs across the Netherlands between October 8th, 2012 and December 31th, 2013. Patients who visited one of

these EDs with a wound were asked to participate. To be included, participants had to be older than 18 years of age, mentally competent and not in a critical medical situation. This multicentre study adhered to the tenets of the Declaration of Helsinki, was approved by the Medical Ethics Committee, VCMO, situated at Nieuwegein, the Netherlands (NL39940.100.12) and was registered in the Dutch Trial Registry (NTR3530).

Study procedure

Patients eligible for inclusion were invited to participate upon arrival at the ED. They received study information and when agreeing to participate, written consent was obtained. All participants first received T-PEP if indicated, based on the guideline, routinely used in that ED. Afterwards a nurse filled in a questionnaire on year and country of birth, gender, self-reported vaccination status and whether the patient was immunocompromised. Furthermore, the nurse performed the TQS-test and reported the test result in the questionnaire. In case the TQS-test was negative and the participant had not received adequate T-PEP yet, the participant received appropriate T-PEP.

To assess possible differences between study participants and non-participants, age and gender of all adults visiting the EDs and fulfilling the inclusion criteria but not participating in the study were recorded between start of the study and December 31th, 2012.

Birth cohorts

The study population was divided in two cohorts [10]: participants born before 1951 and therefore not eligible for NIP vaccinations (pre-NIP-cohort)and participants born in or after 1951 (NIP-cohort).

Tetanus Quick Stick

The TQS (Tétanos Quick Stick, Gamma SA, Belgium) is a bar shaped device which detects specific anti-tetanus toxoid antibodies in blood (Figure 1). In contrast to an ELISA-assay, the TQS is a bedside test, giving a result within 10 minutes and easy to perform by a nurse in emergency setting. The manufacturer of the used TQS reported a sensitivity and specificity of 96.4% and 100%, respectively, using a cut-off of ≥ 0.1 IU/ml for long term protection. [16] Other studies on the Gamma SA TQS and the TQS of two other manufacturers, all having a cut-off of 0.1 IU/ml, found a sensitivity between 55% and 87.1% and a specificity ranging from 97.5% to 100%[13 16-19].

Blood from a finger prick sample must be placed in a well. Diluent is added to cause migration of the sample through the device. A control line in the result window indicates test-validity. Appearance of a pink line indicates an anti-tetanus antibody

level ≥ 0.1 IU/ml. TQS results of participants, in which no control line appeared or the test result was not filled in were defined as incorrect or unknown.

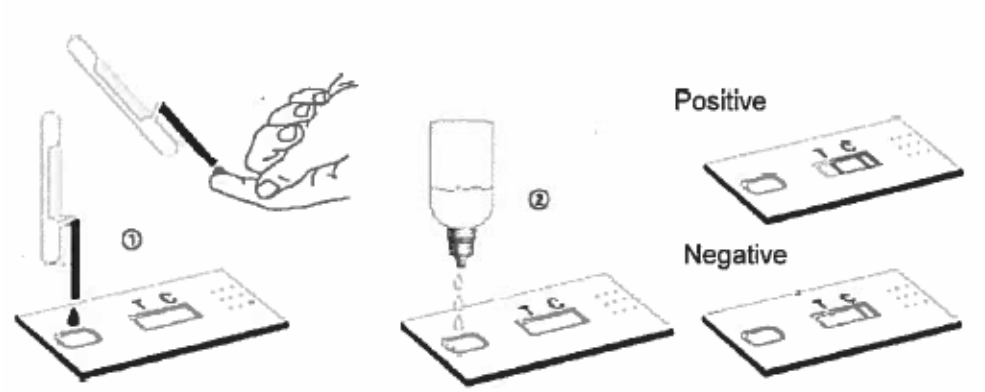


Figure 1.

Statistical analysis

For descriptive characteristics of the participants, means or proportions and 95% confidence intervals (95%CI) were calculated. Differences between the two birth cohorts and between men and women were described using rate differences (RD) and their 95% confidence interval (95%CI) or tested using Pearson's Chi Square or Fisher's exact test (for dichotomous and categorical variables) or student t-test (for continuous variables).

Adherence to the HC-guideline was tested by comparing the administration of T-PEP in the ED with the advice given in the HC-guideline. Next, we compared the recommendation of the the HC-guideline with TQS-results to assess the concordance between these two. In these analysis participants with an unknown or incorrect test result were excluded. In both analyses, percentages of inappropriate T-PEP administration were estimated.

Combining results of the two analyses shows the difference between the current practice and practice exclusively based on TQS-results.

We initially estimated that 379 patients in the pre-NIP-cohort and 371 patients in the NIP-cohort would be sufficient to show a 50% (±10%, 95%CI) discordance between self-reported vaccination status and TQS result (α = 0.05, β=0.20). Interim analysis showed discordance in the pre-NIP-cohort in 20% of the patients, resulting in a required sample size of 244.

Statistical analyses were performed with SAS 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Study population

During the study period, 616 persons agreed to participate. Fifteen persons were excluded due to: absence of informed consent signature (n=8); unknown age (n=4); under 18 years of age (n=3). Therefore, 601 participants could be included in the analyses. Mean age in the two cohorts was 74 and 41 years (median 73y and 43y; Table 2).

Table 2. Demographics of participants, stratified by birth cohort.

	Pre-NIP-cohort[1] (n=196)	NIP-cohort[2] (n=405)	Total (n=601)
Age (years); mean (SD)	74.6 (8.7)	41.6 (12.5)	52.3 (19.2)
Males; n (%)	91 (46.4)[3]	307 (75.8)[4]	398 (66.2)
Immunocompromised; n (%)	8 (4.1%)	6 (1.5)	14 (2.3)

[1]: born < 1-1-1951

[2]: born ≥ 1-1-1951

[3]: 3 participants with unknown gender

[4]: 15 participants with unknown gender

NIP = national immunization programme

In the pre-NIP-cohort, slightly more females were included (p=0.4), whereas there was a statistically significant male predominance in the NIP-cohort (p<0.0001). For 18 participants the gender was unknown.

There were no differences in gender distribution between participants and non-participants, stratified by birth cohort (p=0.4 for both cohorts). Among persons born before 1-1-1951, the mean age did not differ between participants and non-participants (p=0.4). Among persons born from 1951 onwards, non-participants were younger than participants (36 and 41 years, respectively; p<0.0001).

Adherence to the HC- guideline

Administration of T-PEP was consistent with HC-guidelines in 74% and 81% of the pre-NIP-cohort and NIP-cohort, respectively (RD 0.06; 95%CI -0.09 to 0.21; Table 3). In two (pre-NIP-cohort) and 13 (NIP-cohort) participants, the actual administered T-PEP was unknown. Among the pre-NIP and NIP-cohort, 16% and 9% (RD -0.07; 95%CI -0.13 to -0.005), respectively, received T-PEP whilst this was not indicated based on the HC-guideline. Furthermore, 8% and 7% (RD -0.01; 95%CI -0.06 to 0.03), respectively, did not get T-PEP despite an indication based on the guideline.

We found no differences between men and women regarding the concordance between indicated (according to the HC-guideline) and received T-PEP (p=0.26 and p=0.99 for respective cohorts; data not shown).

Table 3. Adherence to the tetanus post-exposure prophylaxis (T-PEP) according to the guideline of the Health Council (HC).

Administered T-PEP→ N (row%)* Eligibility for T-PEP according to HC-guideline↓	Incorrect T-PEP omission N (row%)	Concordance N (row%)	Incorrect surplus T-PEP N (row%)	Un-known N (row%)	Total
Pre-NIP-cohort					
no need for T-PEP [a]	n.a.	22 (59%)	14 (38%)	1 (3%)	37
need for T-PEP [b]	16 (10%)	124 (78%)	18 (11%)	1 (1%)	159
total	16 (8%)	146 (74%)	32 (16%)	2 (1%)	196
NIP-cohort					
no need for T-PEP [a]	n.a.	107 (71%)	33 (22%)	10 (7%)	150
need for T-PEP [b]	27 (11%)	220 (86%)	5 (2%)	3 (1%)	255
total	27 (7%)	327 (81%)	38 (9%)	13 (3%)	405

[a]: Fully vaccinated with booster <10y

[b]: Fully vaccinated with booster ≥10 years ago, fully vaccinated without documentation, incompletely vaccinated, never vaccinated or immune-compromised

*: due to rounding percentages not always sum up to 100%

TQS-test results

Among the total study population (n=601) six (1%) persons had invalid TQS-test-results (control line was not visible). In another five (0.8%) participants, the test result was unknown. Of the remaining participants 402/590 (68%) had a positive and 188/590 (32%) had a negative TQS test result (Table 4).

In the pre-NIP-cohort, 44% were positive compared to 80% in the NIP-cohort. In the pre-NIP-cohort, women less often had a positive test result than men (32%; 32/99 and 56%; 49/88 respectively, RD -0.23; 95%CI -0.43 to -0.04). In the NIP-cohort, no significant differences in the proportion positive were found between the genders (76%; 63/83 and 80%; 243/303 respectively, RD -0.04; 95%CI -0.26 to 0.17).

Twenty two percent of the pre-NIP-cohort was not eligible for T-PEP according to the HC-guideline, but was unprotected based on the TQS result (Table 4). For the NIP-cohort, this percentage was 8% (RD -0.13; 95%CI -0.29 to 0.02).
In contrast, 36% of the pre-NIP-cohort with a positive TQS was eligible for T-PEP according to the HC-guideline. In the NIP-cohort, this percentage was 73%; (RD 0.37; 95%CI 0.23 to 0.51).

In the pre-NIP-cohort, men, who were eligible for T-PEP according to HC-guideline, significantly more often had a positive TQS than women (50%; 33/66 and 24%; 21/86 respectively, RD 0.26; 95%CI 0.06 to 0.46).

Table 3.Eligibility for tetanus post-exposure prophylaxis (T-PEP) according to Health Council (HC)-guideline, related to tetanus quick stick (TQS)-result, stratified by cohort.

TQS-result→ Eligibility for T-PEP↓	Negative N (row%)	Positive N (row%)	total
Pre-NIP-cohort			
no need for T-PEP [a]	8 (22%)	29 (78%)	37
need for T-PEP [b]	98 (64%)	54 (36%)	152
total	106 (56%)	83 (44%)	189
NIP-cohort			
no need for T-PEP [a]	12 (8%)	134 (92%)	146
need for T-PEP [b]	70 (27%)	185 (73%)	255
total	82 (20%)	319 (80%)	401

[a] : Fully vaccinated with booster <10y

[b] : Fully vaccinated with booster ≥10 years ago, fully vaccinated without documentation, incompletely vaccinated, never vaccinated or immune-compromised

Difference between T-PEP administration in daily practice and T-PEP based on TQS-results.

In daily practice, 66 TIG injections were administered to the participants of this study, whilst this would amount to 79 if the HC-guideline was strictly followed and 188 if the TQS-result was decisive (Figure 2).
Furthermore, participants received 437 tetanus toxoid series or doses, while only 407 were needed according to the HC-guideline and 188 if administration was based on the TQS-result.
Relating the administered TT-doses or –series in daily practice to the need for TT based on TQS-result shows 132% over-use (Figure 2). In contrast, we assessed 65% under-administration of TIG.

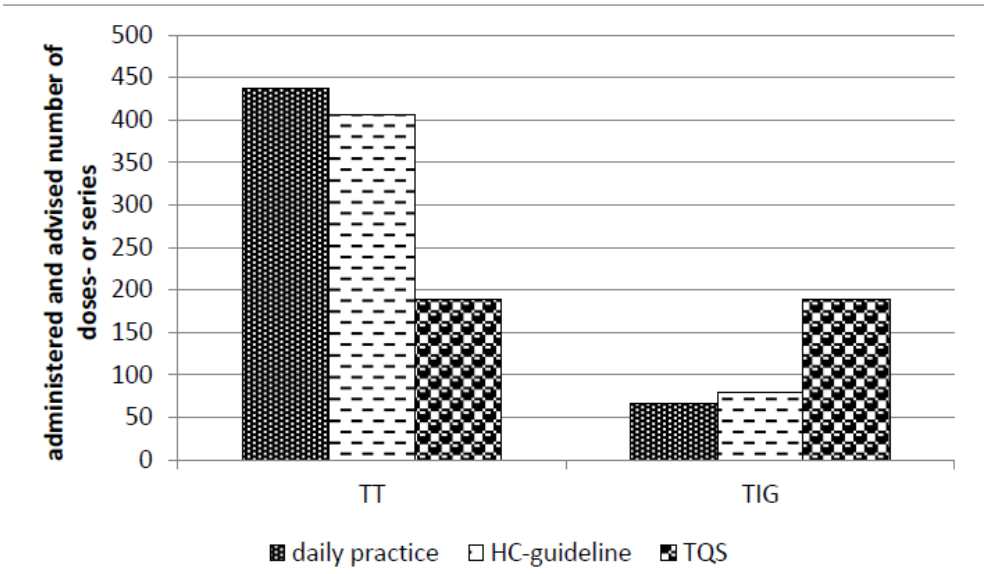


Figure 2.

Discussion

We report the first study on the administration of T-PEP in EDs in the Netherlands. According to the HC-guideline, 19% and 37% of the pre-NIP-cohort and NIP-cohort, respectively, were protected against tetanus and did not need T-PEP. The results of the bedside test for tetanus immunity showed that 44% and 80% of the respective cohorts were protected. Furthermore, we demonstrated that stricter adherence to the HC-guideline and use of the TQS would save TT-doses. Simultaneously, additional TIG-injections should be given, leading to a lower risk of contracting tetanus, especially in elderly.

Non-adherence to current guidelines was also described in other studies [5 20 21]. The resulting overuse of TT and underuse of TIG is in line with a prospective observational study of Talan et al., performed in five EDs across the United States to assess compliance with the tetanus prophylaxis recommendations by the Advisory Committee on Immunization Practices (ACIP) [20]. Te Wierik et al. also addressed that a more systematic administration of TIG probably will help to prevent tetanus [3]. The main limitation in complying fully with the HC-guideline is the fact that the vaccination status is almost entirely self-reported and not verifiable during the ED visit. The ability to check vaccination status online would facilitate compliance with the HC-guideline provided data are available throughout life.

The 68% positive TQS-tests we found is well in line with the proportion assessed in other studies (range 64%-74%), probably because all studies were performed in countries with extensive immunization programmes and included only adults [8 12-14].
T-PEP indication based on TQS results would allow a more complete administration of T-PEP, most pronounced in the pre-NIP-cohort and the female NIP-cohort. At the same time, over-immunization of TT could be prevented, especially in the NIP-cohort. However, repeated TT-immunization is safe [22] and therefore probably no major problem. Nevertheless, NIP policy makers are obliged to arrange vaccinations as efficient as possible.
Using the TQS test, TIG immunizations would likely increase, although the number of truly needed TIG administrations probably will likely be less then we estimated, due to the 0.1 IU/ml cut-off used in this TQS-test. This cut-off is the limit for full long term protection, as stated by World Health Organisation, whereas a value between 0.01 IU/ml and 0.1 IU/ml also implies protection, but probably less durable. These persons probably will not contract tetanus and therefore do not need TIG. TIG should as much as possible only be administered if truly necessary, because of the risks associated with immunization using blood-derived products. Developing a TQS with 0.01 IU/ml would be helpful.
Tetanus toxoid is less expensive than the TQS test, which in turn is less expensive compared with TIG. Therefore, incorporating TQS in all T-PEP decisions will result in an increase of costs for T-PEP. It needs further study to assess whether the use of the TQS in T-PEP indication in the total population or in certain risk groups, e.g. elderly, people with doubtful vaccination history, is cost-effective.
Both the high TQS positivity as well as the high seroprevalence in our country [10] suggest that it is possible to increase the interval between subsequent booster TT-doses in people with a completed infant vaccination series against tetanus. The current HC-guideline advises booster doses every 10 years, irrespective of a completed infant tetanus toxoid vaccination series, (6 doses in the Dutch NIP). In contrast, Public Health England states that a completed vaccination series during childhood (5 doses) offers lifelong protection [23]. A study on tetanus notifications in England from 1984-2000, revealed 175 reports [24]. In 91 cases, the vaccination history could be assessed and all except one had incomplete or absent NIP vaccinations. This is in line with results of Steens et al. who stated that only 0.7% of persons, included in a large seroprevalence study to assess immunity against NIP-diseases in the Netherlands, were not sufficiently protected against tetanus despite a last registered vaccination > 10 years [10]. On the other hand, ACIP advises a booster dose when the last dose is more than 5 years ago [25]. To assess this in more detail, longitudinal seroprevalence data in adults are important.
This study has several strengths. This is the first study in the Netherlands assessing the usefulness of a bedside tetanus immunity test and adherence to the HC-guideline

on T-PEP. Furthermore, routine T-PEP was administered independent of TQS results. The same holds for answering the questionnaires. Therefore, bias related to these aspects will be minimal. Non-participants were slightly younger compared to participants but had a similar sex distribution. Therefore, selection bias will have only a limited effect on our results.

Some limitations must be acknowledged too. In our study, we set TQS as reference standard, but several studies assessed that diagnostic accuracy is not 100% [13 16-19]. While for the test we used in our study the manufacturer reported a sensitivity and specificity of 96.4% and 100%, other studies using the same test found 77% and 97.5%, respectively. For TQS-tests of other manufacturers, lowest estimates were 55% and 97.6%, respectively. Thus some misclassification might have occurred, possibly leading to incorrect conclusions with regard to TQS-over- and under-immunization in some cases. Furthermore, we do not know if the professionals that performed the TQS, executed the test correctly. We instructed them on paper, but did not check correct use and interpretation. This may have led to misclassification also.

Therefore, we recommend assessment of both TQS and ELISA results simultaneously in one set of samples before TQS is recommended for use in daily practice. In particular, those found positive in TQS with a negative vaccination history should be studied in more detail.

Conclusion

Both the use of TQS and a stricter adherence to the HC- guideline on T-PEP can prevent over-administration of tetanus toxoid doses and decrease the risk of contracting tetanus due to more appropriate administration of TIG. The ability to check individual vaccination status online could facilitate a stricter adherence to the HC-guideline, whereas TQS might be of additional value in people with a doubtful or negative vaccination history and in people who were born before 1951 and therefore are not eligible for the NIP but state they are protected. Modelling studies and cost-effectiveness analyses on elongating the interval between subsequent TT-booster doses and the benefit of TQS-use in certain risk groups can inform a revision of the HC-guideline on T-PEP in the Netherlands.

Acknowledgments

We thank all personnel of the emergency departments of the three participating hospitals

1. Meander Medical Centre, Amersfoort
2. Gelderse Vallei, Ede.
3. ZorgSaam Zeeuws-Vlaanderen, location ‘de Honte’, Terneuzen.

References

1. WHO. tetanus; fact sheets. Secondary tetanus; fact sheets 2012. http://www.wpro.who.int/mediacentre/factsheets/fs_20120307_tetanus/en/
2. Mallick IH, Winslet MC. A review of the epidemiology, pathogenesis and management of tetanus. International journal of surgery 2004;**2**(2):109-12.
3. te Wierik MJM, Hahné SJM, van Ooi PC, et al. Tetanus profylaxe na verwonding; check de indicatie voor vaccinatie én immunoglobuline. Ned Tijdschr Geneesk 2013;**157**(A5906).
4. Van Lier A, Oomen PJ, Giesbers H, et al. Immunization coverage National Immunization Programme in the Netherlands. Bilthoven: National Institute for Public Health and the Environment, 2012.
5. Donken R, van der Maas N, Swaan C, et al. The use of tetanus post-exposure prophylaxis guidelines by general practitioners and emergency departments in the Netherlands: a cross-sectional questionnaire study. BMC family practice 2014;**15**(1):112.
6. Gezondheidsraad. Immunisatie tegen tetanus bij verwonding. den Haag, 2003.
7. Gindi M, Oravitz P, Sexton R, et al. Unreliability of reported tetanus vaccination histories. The American journal of emergency medicine 2005;**23**(2):120-2.
8. Stubbe M, Swinnen R, Crusiaux A, et al. Seroprotection against tetanus in patients attending an emergency department in Belgium and evaluation of a bedside immunotest. European journal of emergency medicine : official journal of the European Society for Emergency Medicine 2007;**14**(1):14-24.
9. Alagappan K, Pulido G, Caldwell J, et al. Physician compliance with tetanus guidelines for admitted versus discharged patients. Southern medical journal 2006;**99**(3):234-8.
10. Steens A, Mollema L, Berbers GA, et al. High tetanus antitoxin antibody concentrations in the Netherlands: a seroepidemiological study. Vaccine 2010;**28**(49):7803-9.
11. van der Klis FR, Mollema L, Berbers GA, et al. Second national serum bank for population-based seroprevalence studies in the Netherlands. Neth J Med 2009;**67**(7):301-8.
12. Stubbe M, Mortelmans LJ, Desruelles D, et al. Improving tetanus prophylaxis in the emergency department: a prospective, double-blind cost-effectiveness study. Emergency medicine journal : EMJ 2007;**24**(9):648-53.
13. Hatamabadi HR, Abdalvand A, Safari S, et al. Tetanus Quick Stick as an applicable and cost-effective test in assessment of immunity status. The American journal of emergency medicine 2011;**29**(7):717-20.
14. McVicar J. Should we test for tetanus immunity in all emergency department patients with wounds? Emergency medicine journal : EMJ 2013;**30**(3):177-9.
15. Elkharrat D, Espinoza P, De la Coussaye J, et al. [Inclusion of a rapid test in the current Health Ministry Guidelines with the purpose of improving anti-tetanus prophylaxis prescribed to wounded patients presenting at French Emergency Departments]. Medecine et maladies infectieuses 2005;**35**(6):323-8.
16. Elkharrat D, Sanson-Le-Pors MJ, Arrouy L, et al. Evaluation of a bedside immunotest to predict individual anti-tetanus seroprotection: a prospective concordance study of 1018 adults in an emergency department. Emergency medicine journal : EMJ 2010;**27**(1):36-42.
17. Colombet I, Saguez C, Sanson-Le Pors MJ, et al. Diagnosis of tetanus immunization status: multicenter assessment of a rapid biological test. Clin Diagn Lab Immunol 2005;**12**(9):1057-62.
18. Paulke-Korinek M, Rendi-Wagner P, Kundi M, et al. Pretravel consultation: rapid dipstick test as a decision guidance for the application of tetanus booster vaccinations. Journal of travel medicine 2008;**15**(6):437-41.
19. Ardelean-Jaby D, Kaddari-Himeur F, Nkana-Tameze K, et al. Evaluation of blood test TQS (Tetanos Quick Stick) used in emergency units. Immuno-analyse and Biologie specialisee 2002;**17**:330-35.
20. Talan DA, Abrahamian FM, Moran GJ, et al. Tetanus immunity and physician compliance with tetanus prophylaxis practices among emergency department patients presenting with wounds. Annals of emergency medicine 2004;**43**(3):305-14.

21. Savage EJ, Nash S, McGuinness A, et al. Audit of tetanus prevention knowledge and practices in accident and emergency departments in England. Emergency medicine journal : EMJ 2007;**24**(6):417-21.
22. Halperin SA, Sweet L, Baxendale D, et al. How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? Pediatr Infect Dis J 2006;**25**(3):195-200.
23. HPA. Tetanus. Secondary Tetanus 2013. http://www.nhs.uk/conditions/Tetanus/Pages/Introduction.aspx.
24. Rushdy AA, White JM, Ramsay ME, et al. Tetanus in England and Wales, 1984-2000. Epidemiol Infect 2003;**130**(1):71-7.
25. CDC. updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine in adults aged 65 years and older - Advisory Committe on Immunization Practices (ACIP), 2012. Secondary updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine in adults aged 65 years and older - Advisory Committe on Immunization Practices (ACIP), 2012 2012. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6125a4.htm.

Chapter 13

General discussion

Discussion

Surveillance enables countries to monitor and assess the impact of vaccination strategies and activities for reducing the morbidity and mortality of vaccine-preventable diseases (VPDs) (1). Collection, analysis, and interpretation of surveillance data is vital in guiding vaccination policies and programmes to ensure that immunisation targets are reached. For each vaccine-preventable disease, this requires continual assessment of vaccination coverage, incidence, safety, and circulating pathogen, and immune-surveillance of the target population and the population as a whole (2). This way, trends are monitored and potential problems are detected. More in-depth research can be required to obtain additional data, e.g. to verify signals and answer questions arising through surveillance (3). In this thesis, we focussed on disease-, safety- and immune surveillance (**chapters 2, 3 and 11**) and epidemiological studies (**chapters 4-10 and 12**) of VPDs in the Netherlands. We aimed also to illustrate the strong and weak points of the present surveillance systems, the data sources used in the epidemiological studies, and the necessary logistics.

This discussion will address the strengths and limitations shown in the studies included in this thesis and follow with in-depth scrutiny of the strengths and weaknesses of the overall VPD surveillance system in the Netherlands. For the future, we provide recommendations for improvement to ensure timely and high-quality surveillance for current and new vaccine-preventable diseases. This improvement will contribute to reducing health problems related to infectious diseases through effective prevention.

Main study findings and strengths and limitations regarding the surveillance systems now in use

In **chapter 2** we used nationwide collected data on pertussis disease (mandatory notifications and data on hospital discharge diagnoses) to calculate age-specific incidence rates and to retrospectively assess trends in pertussis disease in relation to changes in the pertussis vaccination schedule. We showed that the three changes in the pertussis vaccination schedule in the period 1999 – 2005, advised by the Health Council, decreased incidence rates of pertussis notifications and hospitalizations among the age groups eligible for the (additional) pertussis vaccination. At the time of the respective advisories, these notification and hospitalization data were also used by the Health Council, showing the relevance of this kind of continual disease surveillance. However, data also showed that overall pertussis incidence rates increased over time and that young, not yet (fully) vaccinated infants did not profit from the measures taken. These findings were exemplified by the continually high incidence rates in infants in the first months of life and the considerable peak in pertussis disease during the 2012 outbreak in this most vulnerable group. Based on these data, the Health Council recently advised that maternal pertussis vaccination be offered to all women in their third trimester of pregnancy in the Netherlands (4).

This use of data to drive vaccine policy underlines the importance of VPD disease surveillance. Likewise, data on the course and severity of disease are important in deciding whether a new vaccine should be introduced. Availability of these data, through mandatory notifications or by use of various registries, is a key factor in VPD surveillance. Also relevant is identification of risk groups, e.g. premature infants, but at the moment these types of data are not available in the datasets applied to Dutch surveillance. They are nevertheless crucial for advice on, for example, maternal (pertussis) vaccination or rotavirus immunisation. Increasing the detail of existing registries or linkage to other registries that contain this type of information may overcome this problem. Furthermore, data derived from the hospitalisation discharge diagnoses registry and death statistics are required but nowadays become available only after a delay of at least one calendar year, making them less useful in case timely evaluation is warranted, e.g. during an outbreak. Data on hospitalisation and death included within the mandatory notifications would enable a more real-time

evaluation. We studied whether the current mandatory data give a reliable estimate of pertussis hospitalisations and deaths by means of a capture-recapture analysis in **chapter 3**.

In **chapter 3**, we assessed the completeness of reporting of hospitalisations (within the mandatory notifications and within the national hospital discharge diagnoses registry) and deaths (in the mandatory notifications and the death registry of Statistics Netherland). Results showed a substantial underreporting of both hospitalisations as well as deaths in all registries and all age groups. This underreporting is important to take into account, as it influences, for instance, cost-effectiveness estimates used by the Health Council. Having multiple data sources makes it possible to assess the underreporting that is inherent to passive surveillance systems (5, 6). Repeating such assessment on a regular basis can show possible changes in the ranges of underreporting. The availability of a third data source, to take into account in capture-recapture analysis, could also favor more reliable estimates. Trying to decrease underreporting, e.g. by facilitating mandatory reporting, may be required to improve surveillance.

In the above study, we looked for identical cases in both registries by using identifying data and disease data. For instance, with respect to hospitalisations in children under two years of age, we used month and year of birth, four digits of the postal code, sex, and onset date of disease. However, these data do not enable very accurate matching. They allowed only rough estimates of the completeness of disease reporting, with substantial inaccuracies in the estimated number of yearly hospitalisations of 25 (<2 years of age) and 38 (≥ 2 years of age). Such uncertainties affect cost-effectiveness analyses or vaccine-effectiveness estimates. Therefore, the use of more specific linking variables, e.g. a unique identifier, is warranted for obtaining reliable data. Potential privacy issues are discussed later in this chapter.

Newborns in the first months of life and in particular prematurely born children are the most vulnerable groups for severe infections like pertussis and at highest need for improved protection by vaccination (7-9). In view of the introduction of maternal pertussis immunisation to protect the newborns alongside mothers themselves, we performed a retrospective medical record study of 0-2- year-old children hospitalised for pertussis. These records were selected from the nationwide hospitalisation discharge registry, also used in the studies from chapters 2 and 3. We assessed the

clinical course and treatment of pertussis in relation to gestational age and vaccination status (**chapter 4**). We were able to obtain data on 57% of eligible pertussis hospitalisations together with linked data from the vaccination registry. This way, we found that vaccine effectiveness of the first pertussis vaccination was lower in preterm than in term infants. Furthermore, preterm infants were overrepresented within the hospitalised cohort and showed a slightly higher risk of complications and increased duration of intensive care stay. Data from the hospital discharge diagnoses were required for this study. However, the need for informed consent from the hospital board/treating physician, the privacy issues, and inaccurate data for linkage as well as the missing data resulted in a significant loss, i.e. from 676 to 379, of medical records that contained the desired information for analyses. Likewise, the logistics of informed consent of the hospitals and the custodian of the hospital discharge registry, plus privacy and linking issues, proved costly and highly time-consuming, leading to substantial delay of study results. As this type of study contributes to the policy on maternal vaccination and shows the need for more insight into advantages of second-versus third-trimester maternal vaccination, a more timely availability of these data is relevant to the international discussion on maternal vaccination. Although the limitations described above are inherent to epidemiological studies, we think substantial improvement is required, e.g. authorisation to perform certain VPD surveillance without informed consent from patients, treating physicians, or database custodians; accurate variables for reliable linkage, and automated extraction of medical record data. Improvement would facilitate adequate, high-quality, and timely monitoring of the risks and benefits of mass vaccination programmes that in turn would improve vaccination strategies and thereby public health.

As is well known, the Netherlands is inhabited by a group of Orthodox Protestants who refuse vaccination based on religious grounds and live in socio-geographically clustered communities in the 'Bible Belt'. In this group, a measles outbreak occurred in 2013-2014 (10). In **chapters 5 and 6**, we evaluated vaccine effectiveness and tolerability of an early MMR vaccination, offered to 6-to-14- month-old children during this outbreak. Early MMR vaccination was offered because infants of this age group are at increased risk for more severe measles. Moreover, as measles is no longer endemic, newborns are less well protected by maternal antibodies, which have

decreased since measles vaccination was introduced (11, 12). Data on effectiveness and tolerability of this early MMR are scarce and mainly derived from studies in low-income countries, which urged the need to collect such data during this outbreak in the Netherlands. We contacted parents of eligible infants, using data of the vaccination registry within Praeventis. Using questionnaire data filled in by parents of participating children, together with laboratory confirmation of a possible measles infection, we found a crude and adjusted early MMR vaccine effectiveness of 94% (95%CI 79%-98%) and 71% (-72% - +95%), respectively. Furthermore, this early MMR vaccination was well tolerated, with the lowest frequencies of adverse events found in infants aged 6-8 months. These results will inform the Outbreak Management Team in case of a future measles outbreak. Such an outbreak will not only spread in the Bible Belt, if the number of susceptibles is again sufficient, but might also occur in the general population if vaccination coverage drops further (13). During recent years, coverage of all NIP vaccinations during childhood is slowly decreasing. From birth cohort 2013 onwards, coverage of MMR1 is below 95% and dropping, which threatens the goal of measles and rubella elimination (14). These findings are also of value for policy-making in other European countries, as measles outbreaks occur regularly within Europe nowadays (15, 16). Likewise, they contribute to the discussion on timing of the first MMR dose within the Dutch NIP schedule.

The possibility of using data from the centralised vaccination registry to invite people to participate in a study was an efficient way to contact parents. After their permission, we were able to validate the vaccination status of participating infants in the vaccination registry. However, a low participation rate hampered the assessment of robust estimates. It may have been higher if we had been allowed to send the invitation to participate in the study simultaneously with the invitation for the early MMR vaccination, instead of four weeks later as we were requested to do. This interval intended to give parents time to decide on early MMR vaccination unhampered by knowledge of the study. This experience shows that we need to involve people more in the monitoring of mass vaccination programmes and to convince them of the need for close monitoring. Increased involvement may help to increase participation.

In 2009 an influenza A(H1N1) pandemic spread across the world (17). The first case in the Netherlands was reported on April 30. This pandemic required the set-up of a

mass vaccination programme, which started by the end of October 2009. In **chapters 7 and 8,** two epidemiological studies on the safety of this pandemic influenza vaccination are described. A paper-based questionnaire survey (**chapter 7**) among more than 3000 people vaccinated by their general practitioner (GP) showed that local and systemic adverse events were reported less frequently after the first and second pandemic vaccination as compared to seasonal vaccination, indicating that adjuvanted influenza vaccinations are well tolerated and there is no negative impact on the safety of three subsequent influenza doses. This is valuable information in case of a next influenza pandemic. To perform the study, we invited people when they visited their GP practice for seasonal and pandemic influenza vaccinations (i.e. 3 vaccination moments), which was very labor-intensive. We needed to rely on self-reported vaccination data, as we were not allowed to verify vaccination status in the GP medical records. This stricture hampered causality assessment of the solicited adverse events. Finally, data on the number of invited people in each practice as a denominator were not available either, which may have led to biased frequencies. Set-up of a centralised influenza vaccination registry could overcome these problems.

During the pandemic, all pregnant women were advised to be vaccinated for protection of both mother and child. In the study on adverse pregnancy outcomes after pandemic influenza vaccination during pregnancy (**chapter 8**), we invited pregnant women by using routine prenatal screening data on infectious diseases. These data are stored in Praeventis, similar to the NIP vaccination registry. Participants filled in a questionnaire which, upon permission, we linked to data of the Netherlands Perinatal Registry. We also retrieved infant data from the child health care and the general practitioner. We found no increased risk of adverse pregnancy outcomes in vaccinated women. Likewise, infants of mothers vaccinated during pregnancy did not differ from infants of unvaccinated women with respect to weight-for-age, length-for-age, head-circumference-for-age, developmental scores, and infection-related GP -contacts in their first year of life. Therefore, our data confirm the conclusion that adjuvanted influenza vaccination during pregnancy is safe (18). These data contribute to the general knowledge on maternal immunisation against influenza, which is an attractive and effective way to protect both mothers during pregnancy and newborns in their first months of life.

Inviting pregnant women based on data from the routine prenatal screening data on infectious diseases stored in Praeventis was an efficient way of obtaining data. Afterwards, however, there was a stern debate as to whether we were allowed to use these data. Though prenatal screening data on infectious diseases is stored in Praeventis, these data are not part of the vaccination registry and might be considered not for our use. Also, we could use only self-reported vaccination status, possibly leading to inadvertently misclassifying pregnant women as vaccinated or unvaccinated. Finally, we encountered problems in linking questionnaire data with data of the Netherlands Perinatal Registry due to inaccurate data for linkage. These problems illustrate that we need to reconsider what is required for optimal (safety) surveillance of vaccine-preventable diseases and mass campaign policies. As with studies on the tolerability of pandemic influenza vaccinations (**chapter 7**), a centralised influenza vaccination registry and authorisation to use it for influenza surveillance is desirable. Likewise, accurate variables for linkage would have increased data quality, efficiency, and timeliness of these studies. Permission to use data stored in other registries for VPD surveillance (e.g. to select pregnant women) would be helpful.

Alongside the 2009 influenza pandemic vaccination campaign, a catch-up campaign to vaccinate 13- to-16-year-old girls against human papilloma virus (HPV) infection was organised in 2009 (19). For both mass vaccination campaigns, background rates of several adverse events following immunisaton (AEFI) were assessed. **Chapters 9 and 10** deal with background rates of Guillain-Barré syndrome (GBS, **chapter 9**) and Multiple Sclerosis (MS, **chapter 10**), assessed in view of preparedness for pandemic influenza vaccination and HPV vaccination, respectively. Such background rates enable researchers, regulators, and policy-makers to put AEFI reports into perspective, as AEFI can occur in temporal association with the vaccination without being caused by it. We assessed those background rates in a large general practitioners (GP) database (Integrated Primary Care Information, or IPCI) containing anonymised information (codes and narratives) on demographics, signs, symptoms, diagnosis, clinical findings, specialist referrals, laboratory results, hospitalisations, and drug prescriptions (20). With respect to GBS in chapter 9, we found no increasing incidence rate (IR) over time. However, IRs did increase with age. Furthermore, we put effort into case validation using a short questionnaire to the GP. This revealed a

positive predictive value of 49%, i.e. in more than half of the cases, GBS diagnosis was not confirmed by the GP.

We did find an increase over time in MS diagnoses (chapter 10), coinciding with a decrease in the lag-time between symptoms and diagnosis, which was significant for women. This suggests that the found increase is likely due to improved diagnostics and not a real increase, which is important to take into account in vaccinovigilance.

Inclusion of more than 2.3 million person years in these studies and good representation of the Dutch population was advantageous, leading to more reliable estimates. Likewise, the ability to use free text along with codes on disease increases data validity (21). On the other hand, selection of cases by means of free text is also labor intensive and thus costly. Furthermore, case validation using a short questionnaire to the GP showed rather low positive predictive values and underlines the importance of cross validation through specialist letters or chart review to prevent overestimation (22, 23). Unfortunately, there was a suboptimal participation rate among GPs with respect to this validation step, perhaps due to extra workload and low priority. Rates of more rare diseases or disorders (e.g. background rates < 1 per 500,000) may not be reliable due to low numbers; collaboration between databases and pooling of data might be a solution to this problem. To increase usefulness for VPD surveillance, more automated case selection and validation, e.g. using machine-learning techniques, is helpful. Furthermore, permission to link GP data to vaccination data without informed consent of the GP and the patient would enable to use these databases also to study more efficiently the associations between vaccinations and adverse events, like HPV vaccination in relation to migraine (24) and chronic fatigue syndrome. Currently, the latter is allowed only after permission, leading to high risk of bias, low participation rates, and untimely results. A trusted third party can perform the linkage to ensure privacy. Accurate variables for linkage, e.g. a unique identifier, are a prerequisite.

Immune responses after natural infection or vaccination are the topic of **chapters 11 and 12**. Nationwide immunosurveys are performed about every 10 years (Peiling Immunisatie Effect Nederland Ter Evaluatie van het Rijksvaccinatieprogramma, or PIENTER). They started in 1995/1996, with a second survey in 2006/2007 and data collection for a third survey in 2016/2017 (25-27). For these cross sectional PIENTER studies, individuals aged 0 to 80 years are invited to provide a blood sample and

questionnaire data to assess their immune status. These surveys are a structural part of current NIP surveillance and result in detailed knowledge on immunological correlates of protection against vaccine-preventable and other infectious diseases in the Netherlands.

In **chapter 11** we studied antibody presence against poliomyelitis. We found that over 84% of individuals in the general Dutch population have protective antibody levels against poliomyelitis. This indicates that following a completed national vaccinaton programme, protection against poliomyelitis is high and long-lasting. In contrast, seroprevalence among the Orthodox Protestants ranged between 61% and 65%, and age-specific rates clearly showed the impact of previous outbreaks. These estimates are an important part of poliomyelitis surveillance in view of the polio eradication. Because of the Bible Belt, the Netherlands still has a susceptible population. However, because of the robustness of surveillance, we can preserve its status as a 'low-risk country' (28, 29). PIENTER data are also of use in case of a potential poliomyelitis outbreak, for example during the sudden increase of Syrian refugees arriving at a time of poliomyelitis outbreaks in Syria (November 2013) or following the industrial spill of wild poliovirus type 2 in a Dutch plant that produces inactivated polio vaccine (IPV), as happened in April 2017. The first two PIENTER surveys, from 1995/96 and 2006/2007, yielded a mine of information used to guide VPD policy. However, these surveys are costly and labor-intensive, and their participation rates are declining. It is important to explore ways to improve participation rates, e.g. self-sampling, expanding PIENTER office hours, and digitalisation. Increased engagement of the general public in the monitoring of infectious diseases will increase participation. Naturally, the cross-sectional nature of these surveys hampers insight into individual changes in immune protection over time. To overcome this problem, the third survey in 2016-2017 included the possibility for a longitudinal component for a subset of participants.

Due to continually high vaccination coverage, tetanus is a rare disease in the Netherlands (27). Besides tetanus vaccination within the NIP, tetanus vaccination may be advised after wounding, as described in a Health Council guideline on tetanus post-exposure prophylaxis (T-PEP) (30). The epidemiological study to assess the added value of a 20-minute bedside test for tetanus immunity (TQS test) in **chapter 12** showed that adherence to the Health Council guideline on T-PEP can be improved.

Furthermore, in a substantial number of cases the result of the TQS test was not in agreement with the advice laid down in the Health Council guideline. Up to one fifth of the participants were not eligible for T-PEP according to the guideline, but had a negative test result with antibody levels below 0.1 IU/ml, indicating non-protection. Conversely, up to 73% was eligible for T-PEP but had a positive test result, i.e. ≥0.1 IU/ml, indicating long-term protection. Overall, we found over-immunisation with tetanus toxoid and under-immunisation with tetanus immuno-globulins. The possibility to verify a person's tetanus vaccination status would have benefitted this study, as vaccination status is crucial in the T-PEP guideline. Verifiable vaccination status would also be a great advantage for T-PEP in general.

Written evidence of tetanus vaccination is requested in the T-PEP guideline algorithm, and since most people cannot hand this over when they visit the emergency department (ED), many EDs follow the adage 'better safe than sorry'. The same holds for other vaccinations administered in individual health care settings. Therefore, a centralised registry including all administered vaccinations (i.e. individual and via mass vaccination programmes) that allows online consultation by the public and professionals, is advantageous for medical care.

Surveillance and epidemiological studies covered in this thesis proved valuable for the monitoring of mass vaccination programmes in the Netherlands. However, several limitations and challenges have been identified. It is important to discuss how to improve surveillance systems and how to retrieve more detailed data without high additional costs. Improved surveillance systems should result in more timely and in-depth results of benefits and risks of vaccine-preventable diseases and limit the need for more costly and time-consuming additional epidemiological studies. Regarding the surveillance systems used in our studies, several ways for improvement can be identified. The first recommendation would be the use of centralised and validated vaccination records, followed by the ability to accurately link data of different registries. Related privacy issues and the need for informed consent from patients, physicians, and database custodians must be weighed against the impact for public health and the need to have knowledge on benefit/risk profiles of mass vaccination programmes. Furthermore, the advantage of using routinely collected medical record

data for surveillance will greatly improve insight into current data on disease course and risk groups, and allow more personalised medicine. As these improvements cannot be implemented without engagement of health care professionals, the general public, and other stakeholders, it is necessary to discuss them with all parties involved and to increase their engagement in the surveillance of vaccine-preventable diseases. These recommendations will be discussed in more detail in the following sections.

Improvement of current VPD surveillance system:

- Use of centralised and validated vaccination records
- Accurate linking of different registries by means of a unique identifier or other very specific variables
- Permission to use routinely collected medical record data for VPD surveillance
- No need for informed consent from patients, physicians, and database custodians
- Ensuring privacy by means of a Trusted Third Party

Engagement of all stakeholders is a prerequisite for all above recommendations.

Registration of vaccination status

From way back, registration of vaccinations of the two mass vaccination programmes in the Netherlands has been organised differently, and this influences the possibilities for surveillance. While the National Immunisation Programme has a centralised vaccination registry, stored within Praeventis, vaccinations within the seasonal influenza vaccination programme are registered in the medical records of general practitioners. A centralised vaccination registry has great advantages for surveillance, as demonstrated in the studies described in **chapters 4-6, 8 and 11**.

Such a centralised registry can be linked to the population registry and therefore always contains accurate and reliable information on name, home address, and date of birth. This information can be used to invite people for studies, as occurred in the studies included in **chapters 5, 6 and 8**. This targeted invitation is efficient and enables researchers to select a specific group of possible study participants.

Furthermore, a centralised registry contains vaccination records at an individual level, enabling researchers to use validated data (**chapters 4-6 and 11**) instead of self-reported vaccination status (**chapters 7, 8 and 12**), as self-reported vaccination status is found to be unreliable (31-33). Also, a registry can give detailed insight into vaccination coverage, which can be stratified by sex, age, and/or by region, municipality, or even postal code if needed (34). Such insights can identify risk groups, which is important during infectious disease outbreaks. The register can be used to send personalised invitations for vaccinations, not only for routine immunisation programmes, but also for mass vaccination campaigns during an outbreak, e.g. the early MMR vaccination during the last measles outbreak in 2013-2014 or the influenza A(H1N1) pandemic in 2009 (10, 17, 34). If the registry is accessible online, the public and health care personnel could check a vaccination status and update if necessary.

In Denmark since 2012-2014, a nationwide vaccination registry is in place, an upgrade of their long-standing NIP registry that includes all administered vaccinations, i.e. immunisations within and outside national programmes (35). Reporting of all administered vaccinations is mandatory for health care personnel, but also citizens can register the immunisations they receive. Doctors can validate and, if necessary, correct those vaccinations (36). Citizens and health care personnel have online access to their own vaccination data and to the vaccination status of their patients, respectively. Norway has a comparable system (37).

In the Netherlands, a nationwide centralised influenza registry was discussed during the 2009 influenza pandemic (38), in case it would be necessary to offer vaccination to the entire population. However, during the course of the pandemic the Centre for Infectious Disease Control, the Health Council, and the Ministry of Health, Welfare and Sports decided to offer targeted vaccination while using existing ways to register vaccinations. A dedicated vaccination registry was set up only for the pandemic vaccinations offered to children aged 6 months to 5 years and household members of infants < 6 months of age. Studies clearly showed that local storage of vaccination status hampered validation of patient vaccination status (33) and led to suboptimal estimates of vaccine effectiveness (39). Locally stored data also led to inaccuracies of vaccination coverage estimates during outbreaks due to the lack of precise denominators, even though this information is crucial for outbreak management (40).

Similar disadvantages were also encountered in Sweden in relation to safety surveillance. The Swedish medical products agency performed in-depth studies on the association between narcolepsy and Pandemrix®, one of the pandemic vaccines (41). They concluded that data collection was very time-consuming and offered inaccurate data on vaccination status. Therefore they urged installation of a centralised influenza vaccination registry.

These findings underline the value of a centralised influenza vaccination register, and as these issues are not limited to a pandemic situation but also apply to seasonal influenza (e.g. in case influenza vaccination of pregnant women is implemented), such a registry is recommended.

Beside NIP and influenza vaccinations, a central registry including individual vaccinations that are not part of a mass vaccination programme is advisable. The Health Council has stated that use of licensed vaccinations, not included in a mass vaccination programme, needs to be promoted (42). The Health Council also has urged that adequate monitoring of the risks and benefits of these vaccinations be put in place. However, given the current surveillance systems, monitoring of VPDs outside mass immunisation programmes is very complicated. For example, the Health Council recently advised introduction of universal mass rotavirus vaccination (43). However, when the cost appears infeasible, the Health Council advised that a targeted risk-group approach would be more cost-effective. In case of targeted risk-group vaccination, vaccination status needs to be included in the individual medical record, but denominators of eligible infants are unknown, hampering good surveillance. As validated vaccination records are the cornerstone of good coverage estimates and of disease- and safety -surveillance, a centralised vaccination registry also including these immunisations is an important facet of adequate VPD surveillance (44).

Instead of three separate registries, i.e. for NIP, influenza, and vaccinations outside mass immunisation programmes, we recommend upgrading the logistics of the current NIP vaccination registry. From only including vaccinations as part of the NIP and up till 19 years of age, it could expand to include all people living in the Netherlands and their entire spectrum of vaccinations (44). It is of great importance that this registry is available online for each individual to register immunisations and check their vaccination status. Similar rights should be granted to treating physicians or other dedicated medical personnel. Likewise, the organisation designated for VPD

surveillance by the government, i.e. the Centre for Infectious Disease Control, should be authorised to use those data for VPD surveillance.

If such a vaccination registry is in place, registration and validation of administered vaccinations need to be promoted. It is important to have a user-friendly system and to avoid double entry through integration of the register into existing electronic patient-record systems at GPs, hospitals, and travel clinics.

In addition to positive effects for surveillance, such a vaccination registry will also benefit clinical practice, e.g. the tetanus vaccination status can be checked when a wounded person visits the emergency department, thereby avoiding unnecessary tetanus toxoid vaccinations (45). Clinicians can check and if necessary update a patient's vaccination status in preparation for travel or before starting immunosuppressive medication. The latter becomes more and more important as the Dutch population gets older and the number of people using immune-modulating drugs is increasing (46).

Making vaccination data accessible online for individuals may improve self-management, public engagement, and overall vaccination coverage. As people become more involved and responsible for their health, they will probably become more aware of vaccinations and their usefulness throughout life (47-50). The use of vaccination applications for mobile devices and text messaging to remind someone of an appointment for vaccination can further improve public engagement.

Recommendation:

1. Instalment of a centralised vaccination registry including all people living in the Netherlands and covering the entire spectrum of vaccinations, i.e. current infant NIP, seasonal influenza vaccinations, travel-related vaccinations and other individual vaccinations such as post-exposure prophylaxis
2. Authorisation of the organisation that is designated for VPD surveillance by the government to use these vaccination data for surveillance in view of improved and timelier benefit/risk balances of vaccine-preventable diseases and optimisation of public health

Benefits for VPD surveillance:

Detailed and accurate information on vaccination coverage

Accurate vaccine effectiveness estimates

Improved causality assessment as part of improved safety surveillance

Access to validated vaccination records in surveillance and epidemiological studies

Possibility to invite specific groups for specific studies

Other benefits:

Improved clinical practice

Increased involvement of health care personnel in prevention through vaccination

Increased public involvement by self-management

Challenges:

Protection of privacy

Compliance of treating physicians

Completeness of vaccination records

Avoidance of double entry

Costs and sustainability

Linking mother and child records in the light of maternal vaccination

Linking to other registries for disease- safety, pathogen- and immuno-surveillance

Data linkage, privacy, and informed consent in relation to VPD surveillance

All data and registries used in the studies of this thesis contain personal and medical data. For mandatory notifications, permission to use those data for public health on a local level is described in the Public Health Act (51) but in general, identifying personal and medical data may only be used after permission from the patient, which is regulated by law (52-54). To protect privacy of patients, professionals, and organisations, registry data are intentionally anonymised or pseudonymised before they are made available to analysts at the national level, e.g. by degrading a date of birth to only year of birth or including only digits of the postal code instead of a full zip code. These procedures limit the possibility of accurate linking, which is

disadvantageous for accurate VPD surveillance that aims to gain insight into benefit/risk balances of vaccinations and improve public health. This disadvantage was clearly shown in **chapters 3, 4 and 8** of this thesis, in which we used identifying variables to link different registries.

According to current law, informed consent of patients to use their medical data is not needed if 1. seeking permission is impossible or requires a too great an effort **and** if 2. the study serves public interest **and** 3. the study cannot be performed without requested data **and** 4. the patient did not oppose usage of data for statistics.

Although jurisprudence and the Dutch Data Protection Authority (autoriteit persoonsgegevens) further define 'great effort' and 'public interest', professionals are unsure about their exact meaning. Some stay on the safe side and do not share medical record data without permission of the patient despite the public interest of a study. These differences in opinion played a role in the medical record study in **chapter 4** and resulted in long study duration and suboptimal participation.

On 25 May 2018, the General Data Protection Regulation (GDPR or AVG: Algemene Verordening Gegevensbescherming) will become effective (55). This law further strengthens and extends privacy legislation, which will also become similar in all European countries. In line with the current situation, this new GDPR demands informed consent of all persons before their medical data are stored in a database. Its exceptions regarding collection without informed consent are identical to current legislation. However, organisations are allowed to collect medical data without informed consent based on those grounds, only if this is explicitly regulated by law. At this moment, the government has no intention to formalise by law such a special position of the Centre for Infectious Disease Control, although the Ministry of Health, Welfare and Sports assigned it with the monitoring of the NIP and influenza vaccinations. Furthermore, the new GDPR defines even pseudonymised data as identifying data, and therefore pseudonymised data must be treated in the same way as identifying data. This new legislation can hamper use of and linkage with e.g. vaccination registry data. Likewise, it will be become more difficult to perform medical record studies, as described in **chapter 4**.

Alongside the transition of the responsibility for the NIP to municipalities, which is anchored in the newly amended Public Health Act (51), explicit parental consent for the central registration of NIP vaccinations will be implemented in near future. If this

procedure leads to a substantial percentage of parents refusing storage of infants' vaccination data and an outbreak of e.g. poliomyelitis is emerging, it is unknown whether these infants are vaccinated or not. On an individual level, parents may not know if their infant is at risk but if they have a vaccination booklet, seeking advice from medical doctors with expertise on vaccinations can solve this problem. However, on a population level, this situation may result in insufficient insight into the risks and threats of an outbreak, which hampers the instalment of adequate outbreak control measures.

Furthermore, to use registration data of vaccinations that are not included in this National Immunisation Programme for VPD surveillance, separate informed consent is needed. For example, if rotavirus vaccination for risk groups instead of universal rotavirus vaccination is implemented in the near future, vaccination status will be entered into the medical record. Organisations assigned by the government to survey VPDs can use those data for rotavirus surveillance only if it is explicitly asked by the pediatrician during the informed consent process. This procedure must be coordinated with the pediatricians of all children involved, which is time-consuming and (in my personal opinion) also confusing for parents.

Therefore, it is advisable to clearly regulate by law that VPD surveillance is a dedicated task of the Centre for Infectious Disease Control, serves public interest and can be performed without informed consent, as is the case already in several other European countries. To this end, data that are crucial for surveillance, e.g. vaccination data, need to be collected and stored in the interest of public health and made available to authorised parties without need for informed consent. Likewise, adequate identifying information, e.g. a unique identifier, would allow reliable linkage of registries as part of VPD surveillance, again without permission. A trusted third party , as used in the medical record study in **chapter 4**, might be called in to ensure optimal privacy during linkage (56).

Statistics Netherlands have a unique position, regulated in the Statistics Netherlands Act, that is similar to what we recommend for the Centre for Infectious Disease Control. They are allowed to use identifying variables, e.g. the social security number, to link different registries for research (57).

In the Nordic countries, comparable legislation for public health institutes is in place, despite GDPR being operative in those countries. All inhabitants have a unique

identifying number, and public health institutes are allowed to use that number for linkage of several nationwide registries (35, 58). Together with a nationwide vaccination register, this linkage enhances the possibilities for VPD surveillance. For example, Denmark produced nationwide estimates of adverse pregnancy outcomes after the influenza A (H1N1) vaccination (59, 60), and several Scandinavian countries assessed the risk of autoimmune, neurological, and venous thromboembolic AEFI following HPV vaccination (61). Norwegian researchers need permission from an Ethics Committee for linking data from different registries (58, 62). Researchers in Denmark are allowed to use and link data without informed consent when data are used for 'statistical and scientific purposes of significance to society' (63). This variable operation of GDPR is an example for policy development with respect to privacy and public health in the Netherlands. Organisations with a dedicated task in infectious disease control will benefit from a unique position with less strict privacy legislation, thereby contributing to reduced health problems related to infectious diseases.

Recommendations:

1. Central storage of data essential for VPD surveillance, accessible without informed consent
2. Legal authorisation of organisations assigned by the government to survey VPDs to do this without the need for informed consent
3. Permission to these organisations to use identifying data for linkage of different registries and databases

Benefits for VPD surveillance:

Precise knowledge of vaccination status

More reliable information during outbreaks

More accurate, complete, and detailed results

More real-time results

Timely detection of changes in the vaccine's benefit/risk balance

Other benefits:

Less administration for treating physicians

More timely information for clinicians during outbreaks

More reliable information for individuals in relation to VPDs

Challenges:

Political engagement and change of law

Definition of data that are essential for VPD surveillance

Commitment from professionals, public, and other stakeholders

Protection of privacy as much as possible, e.g. through use of trusted third parties

Transparency of procedures used for VPD surveillance

Use of routinely collected medical record data

We used routinely collected medical record data in the studies from **chapters 4, 9 and 10** in which we collected in-depth information on pertussis hospitalisations and background rates of Guillain-Barré syndrome and Multiple Sclerosis, respectively. Nowadays, personal health records are digitalised, stored in large databases, and available with only a short delay of time. VPD surveillance must use these data more frequently and intensely, as they contain a wealth of information. Some of these registries contain only codes, some both code and free text. The latter can give more specific information on the disease. It can also lead to inclusion of more possible cases, i.e. when a disorder is described only in free text, and not coded. On the other hand, searching this free text is labor-intensive and therefore costly. In general, information is entered by medical doctors or other trained personnel; it can be used without extra workload for the medical doctors and is available near real-time. These electronic health care records can be harnessed to advance public health goals in general and VPD surveillance in specific (64). Use of these medical record data can lead to increased insight into more severe courses of VPDs (**chapter 4**, medical record study on pertussis hospitalisations) or Adverse Events Following Immunisation (**chapters 9 and 10**, background rates of Guillain-Barré syndrome and Multiple Sclerosis), especially if accurate vaccination data are available within the electronic health records or linkage with a centralised vaccination registry is possible. However, before

electronic health record-derived data can be used for VPD surveillance, some challenges must be overcome (64). First, underrepresented subgroups, e.g. healthy adults, can lead to incompleteness of sampling, which may also be an issue in the currently used surveillance systems. In general, selection bias must be taken into account; comparisons with e.g. immune surveillance data can help to quantify this bias. Secondly, the registries need to contain large numbers of patient records with sufficient follow-up time to also enable surveillance of more rare disorders. As manual data extraction and validation is very labor intensive, automation of processes needs to be promoted. Furthermore, systems of electronic health records must be interoperable, and metrics supporting assessment of population health and VPDs and their risk factors need to be integrated into the systems. Training in coding systematics and structured filling in of medical records should be integrated into the bachelor and master of medical science. Last but not least, privacy must be ensured.

The above cannot be achieved without the engagement of and collaboration with treating physicians. Therefore, it is important that both medical personnel and surveillance experts acknowledge that they need each other. Surveillance can use data reported and collected by medical professionals and the other way around: medical doctors can improve their clinical care by using evidence from surveillance and epidemiological studies. Likewise, usefulness for surveillance and epidemiological studies should be taken into account when the infrastructure of health care data is adapted. Finally, patients should be involved in these discussions, as they are the owners of their medical data. Of course, spin-off of this collaboration and increased use of medical record data goes beyond VPD surveillance.

In our three studies that used routinely collected data, data extraction was performed manually, a labor-intensive process. More automated data extraction would result in more timely data and also provide the opportunity to repeat studies on a regular basis. Therefore it is recommended to increase the use of routinely collected medical record data and organise data extraction in an automated way.

Several studies on the feasibility of using those medical record data are ongoing in the Netherlands. For instance, the Integrated Primary Care Database, through which the background rates of Guillain-Barré syndrome and Multiple Sclerosis were assessed, was used to look for associations between HPV vaccination and respectively migraine (24) and chronic fatigue syndrome. Likewise, data from the NIVEL Primary Care

Database gain insight into respiratory infections (65) and the Integrated Alert and Response System (ICARES) aims to detect clusters of infectious diseases, using CPRD-, DBC- and DOT-codes (66). Currently, this ICARES system is being used to study severe acute respiratory infections (SARI) as part of the surveillance of respiratory infections (67).

In the USA, comparable automated near real-time passive monitoring systems using medical care data are in place. For example, safety surveillance was improved by the development of the Vaccine Safety Datalink system (68). Electronic health care data, including vaccination records, are used to monitor Adverse Events Following Immunization (AEFI) in near real-time using rapid-cycle analysis (69). In the long term, if a widespread network of medical record data in primary and secondary care is in place and VPD surveillance through this network is successful, there will be no need any more for specific registries like mandatory notifications (64). After all, medical doctors ask for laboratory confirmation when they suspect a patient of an infectious disease, and the request is recorded in the medical file. Likewise, the test result should be recorded. All this information can be extracted directly from the medical record without transfer to a disease notification registry.

Recommendation:
Increasing the use of routinely collected medical record data in an automated way

Benefits for VPD surveillance:
Increased, more in-depth and more timely insight into severe courses of VPDs
Ability to continually monitor AEFI

Other benefits:
Infrastructure useful for surveillance of other public health issues

Challenges:
Creation of a research mindset in medical doctors that leads to more structured medical records
Interoperability of electronic health records
Inclusion of metrics for population health, VPDs, and their risk factors
Commitment from medical doctors
Costs and sustainability
Guaranteed privacy

Collaboration between public health, clinical care, and general public

The recommendations discussed above will not be effective without the engagement and collaboration of health care personnel, patients, the general public, and other stakeholders.

In general, medical doctors are reluctant to disclose patient information due to concerns about the extent to which public health agencies are dependable to protect health information ('trusting beliefs') and the possibility of loss due to disclosing health information ('risk beliefs') (70). This general reluctance is in contrast with the openness to share and disseminate data in most of the Nordic countries (63). More insight into attitudes and beliefs underlying these differences in openness could help to increase the willingness for collaboration between public health and clinical care in the Netherlands.

In addition, public health professionals should nurture a relationship of respect and trust with patients and the public, not just during an outbreak but before times of urgent need (71). They need to collaborate with and make use of clinicians, because surveys show that their opinions and advice have a large impact on people's attitude towards e.g. vaccinations (72, 73). Communication with general public should be transparent and address both benefits and risks of vaccine-preventable diseases, vaccinations, and surveillance, as many people believe public health institutes communicate only the benefits and not the risks (74). Such mistrust must be taken seriously and dealt with, e.g. by discussing the recommendations with a public panel, the Dutch Patient Federation, a forum of groups that are eligible for vaccinations, or their representatives.

Conclusion

VPD surveillance in the Netherlands has a long track record and has always been of high quality. However, both the NIP and the influenza surveillance system have changed little over the years, while health care and the world are changing fast.

Due to rapid digitalisation and automation plus the need for more detailed and timely results and increased emphasis on privacy and informed consent, VPD surveillance risks falling short of expectations in the foreseeable future. Financial constraints play

a role together with an increasing workload in public health and clinical care. Therefore, increased efforts to renew the surveillance systems, making use of modern technologies as much as possible, are very important.

Consultation of and collaboration among surveillance experts, public health experts, clinicians, the public, and other stakeholders can overcome possible hurdles, increase trust, and pave the way towards a modernised VPD surveillance system that can inform professionals, policy-makers, and public with timely and accurate estimates on coverage, disease burden, and safety as well as in-depth insights into immunogenicity and pathogen changes.

Recommendations

As accurate and accessible vaccination data are the cornerstone of VPD surveillance, implementation of a centralised national vaccination register, containing data on all inhabitants in the Netherlands on all vaccinations and accessible to public and professionals, would be a major improvement for VPD surveillance.

To avoid untimely results or insignificant data due to low numbers, all professionals and relevant stakeholders need to agree that VPD surveillance is an essential part of public health that should be allowed the use of data without informed consent of patient or third parties. Furthermore, this authorisation needs to be regulated by law.

As linking or automated exchange among registries and medical information systems is beneficial for VPD surveillance, its strong promotion is warranted. Sufficient identifying variables or a unique identifier are crucial for accurate linkage and exchange. Logistics must be organised to guarantee privacy as much as possible. As another precautionary measure, trusted third parties can be used.

Timeliness of data, especially on more severe disease stages, can be achieved if data from medical records or other databases are available on a regular basis, e.g. monthly or weekly, automated exchange or linking is performed as soon as those data are available, and data in medical records can be attuned to the needs of VPD surveillance.

Public health, medical doctors, the general public, and other stakeholders of infectious disease control need to collaborate more closely and communicate more intensely.

References

1. Organization WH. Immunization surveillance, assessment and monitoring [Available from: http://www.who.int/immunization/monitoring_surveillance/en/.
2. Begg N, Miller E. Role of epidemiology in vaccine policy. Vaccine. 1990;8(3):180-9.
3. Chen RT, Orenstein WA. Epidemiologic methods in immunization programs. Epidemiol Rev. 1996;18(2):99-117.
4. Gezondheidsraad. Vaccinatie tegen kinkhoest: doel en strategie. Den Haag: Gezondheidsraad; 2015.
5. Gibbons CL, Mangen MJ, Plass D, Havelaar AH, Brooke RJ, Kramarz P, et al. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. BMC Public Health. 2014;14:147.
6. Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. Am J Public Health. 1995;85(12):1706-9.
7. Bonhoeffer J, Siegrist CA, Heath PT. Immunisation of premature infants. Arch Dis Child. 2006;91(11):929-35.
8. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. Arch Dis Child. 2017.
9. Riise OR, Laake I, Vestrheim D, Flem E, Moster D, Riise Bergsaker MA, et al. Risk of Pertussis in Relation to Degree of Prematurity in Children Less Than 2 Years of Age. Pediatr Infect Dis J. 2017;36(5):e151-e6.
10. Knol M, Urbanus A, Swart E, Mollema L, Ruijs W, van Binnendijk R, et al. Large ongoing measles outbreak in a religious community in the Netherlands since May 2013. Euro Surveill. 2013;18(36):pii=20580.
11. Mollema L, Smits GP, Berbers GA, Van Der Klis FR, Van Binnendijk RS, De Melker HE, et al. High risk of a large measles outbreak despite 30 years of measles vaccination in The Netherlands. Epidemiol Infect. 2014;142(5):1100-8.
12. Waaijenborg S, Hahne SJ, Mollema L, Smits GP, Berbers GA, van der Klis FR, et al. Waning of Maternal Antibodies Against Measles, Mumps, Rubella, and Varicella in Communities With Contrasting Vaccination Coverage. J Infect Dis. 2013.
13. Van Lier A, Geraedts JLE, Oomen P, Giesbers H, Van Vliet H, Drijfhout I, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2016. Bilthoven: National Institute for Public Health and the Environment; 2017. Report No.: 2017-0010.
14. World Health Organization rOfE. Eliminating measles and rubella and preventing congenital rubella infection; WHO European Region strategic plan 2005-2010. Copenhagen; 2005.
15. Datta SS, O'Connor PM, Jankovic D, Muscat M, Ben Mamou MC, Singh S, et al. Progress and challenges in measles and rubella elimination in the WHO European Region. Vaccine. 2017.
16. O'Connor P, Jankovic D, Muscat M, Ben-Mamou M, Reef S, Papania M, et al. Measles and rubella elimination in the WHO Region for Europe: progress and challenges. Clin Microbiol Infect. 2017;23(8):504-10.
17. Stein ML, Van Vliet H, Timen A. Chronological overview of the 2009 H1N1 pandemic and the response of the Centre for Infectious Disease Control (Cib) of the National Institute for Public Health and the Environment (RIVM). Bilthoven: National Institute for Public Health and the Environment; 2010. Report No.: 2151320001/2010.
18. Keller-Stanislawski B, Englund JA, Kang G, Mangtani P, Neuzil K, Nohynek H, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. Vaccine. 2014;32(52):7057-64.
19. de Melker HE, Conyn-van Spaendonck MA, Boot HJ, Coutinho RA. [Introduction to vaccination against cervical cancer]. Ned Tijdschr Geneeskd. 2009;153(14):658-61.
20. Lamberts H, Wood M, Hofmans-Okkes IM. International primary care classifications: the effect of fifteen years of evolution. Fam Pract. 1992;9(3):330-9.
21. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med. 1999;38(4-5):339-44.
22. Bogliun G, Beghi E. Validity of hospital discharge diagnoses for public health surveillance of the Guillain-Barre syndrome. Neurol Sci. 2002;23(3):113-7.
23. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barre syndrome worldwide. A systematic literature review. Neuroepidemiology. 2009;32(2):150-63.
24. Schurink-Van't Klooster TM, de Ridder MA, Kemmeren JM, van der Lei J, Dekker F, Sturkenboom M, et al. Examining a possible association between human papilloma virus (HPV) vaccination and migraine: results of a cohort study in the Netherlands. Eur J Pediatr. 2015;174(5):641-9.
25. De Melker HE, Conyn-van Spaendonck MA. Immunosurveillance and the evaluation of national immunization programmes: a population-based approach. Epidemiol Infect. 1998;121(3):637-43.
26. van der Klis FR, Mollema L, Berbers GA, de Melker HE, Coutinho RA. Second national serum bank for population-based seroprevalence studies in the Netherlands. Neth J Med. 2009;67(7):301-8.

27. Schurink-van 't Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands; surveillance and developments in 2016-2017. Bilthoven: National Institute for Public Health and the Environment; 2017. Report No.: 2017-0143.
28. World Health Organization rOfE. 30th Meeting of the European Regional Certification Commission for Poliomyelitis Eradication. Copenhagen: WHO; 2016.
29. Benschop KSM, van der Avoort HG, Jusic E, Vennema H, van Binnendijk R, Duizer E. Polio and measles down the drain: Environmental Enterovirus Surveillance in the Netherlands, 2005-2015. Appl Environ Microbiol. 2017.
30. Gezondheidsraad. Immunisatie tegen tetanus bij verwonding. den Haag; 2003. Report No.: 2003/11.
31. Gindi M, Oravitz P, Sexton R, Shpak M, Eisenhart A. Unreliability of reported tetanus vaccination histories. The American journal of emergency medicine. 2005;23(2):120-2.
32. Stubbe M, Swinnen R, Crusiaux A, Mascart F, Lheureux PE. Seroprotection against tetanus in patients attending an emergency department in Belgium and evaluation of a bedside immunotest. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2007;14(1):14-24.
33. Steens A, Wijnans EG, Dieleman JP, Sturkenboom MC, van der Sande MA, van der Hoek W. Effectiveness of a MF-59-adjuvanted pandemic influenza vaccine to prevent 2009 A/H1N1 influenza-related hospitalisation; a matched case-control study. BMC Infect Dis. 2011;11:196.
34. van Lier A, Oomen P, de Hoogh P, Drijfhout I, Elsinghorst B, Kemmeren J, et al. Praeventis, the immunisation register of the Netherlands: a tool to evaluate the National Immunisation Programme. Euro Surveill. 2012;17(17).
35. Grove Krause T, Jakobsen S, Haarh M, Molbak K. The Danish vaccination register. Euro Surveill. 2012;17(17).
36. Krause TG. The Danish vaccination register; a never ending story Copenhagen: Statens Serum Institute; 2014 [Available from: https://www.fhi.no/globalassets/dokumenterfiler/moba/pdf/the-danish-vaccination-register--a-never-ending-story.pdf.
37. Pebody R. Vaccine registers--experiences from Europe and elsewhere. Euro Surveill. 2012;17(17).
38. VWS P. Landelijk Draaiboek vaccinatie Nieuwe Influenza A(H1N1). Den Haag: VWS; 2009.
39. Wijnans EG. The Benefits and Risks of Pandemic Influenza Vaccines: Erasmus Universiteit Rotterdam; 2015.
40. van Lier A, Steens A, Ferreira JA, van der Maas NA, de Melker HE. Acceptance of vaccination during pregnancy: Experience with 2009 influenza A (H1N1) in the Netherlands. Vaccine. 2012;30(18):2892-9.
41. Läkemedelsverket. Studie av tidsförhållanden mellan Pandemrix-vaccination och narkolepsi. Uppsala: Läkemedelsverket; 2016. Report No.: 1.1.1-2016-050830.
42. Gezondheidsraad. Het individuele, collectieve en publieke belang van vaccinatie. Den Haag: Gezondheidsraad; 2013. Report No.: 2013/21; ISBN 978-90-5549-973-1.
43. Gezondheidsraad. Vaccinatie tegen rotavirus. Den Haag: Gezondheidsraad; 2017. Report No.: 2017/16.
44. Crowcroft NS, Levy-Bruhl D. Registries: An essential tool for maximising the health benefits of immunisation in the 21st century. Euro Surveill. 2017;22(17).
45. van der Maas NA, Donken R, Te Wierik MJ, Swaan CM, Hahne SJ, de Melker HE. Performance of a bedside test for tetanus immunity: results of a cross-sectional study among three EDs in the Netherlands in 2012-2013. Emergency medicine journal : EMJ. 2016.
46. Hoefnagel J, Sonder GJ, visser L. Afweeronderdrukker beperkt vaccinatieopties. Medisch Contact. 2016;25(23 juni 2016):28-30.
47. Hofstetter AM, DuRivage N, Vargas CY, Camargo S, Vawdrey DK, Fisher A, et al. Text message reminders for timely routine MMR vaccination: A randomized controlled trial. Vaccine. 2015;33(43):5741-6.
48. Hofstetter AM, Vargas CY, Camargo S, Holleran S, Vawdrey DK, Kharbanda EO, et al. Impacting delayed pediatric influenza vaccination: a randomized controlled trial of text message reminders. Am J Prev Med. 2015;48(4):392-401.
49. Stockwell MS, Catallozzi M, Camargo S, Ramakrishnan R, Holleran S, Findley SE, et al. Registry-linked electronic influenza vaccine provider reminders: a cluster-crossover trial. Pediatrics. 2015;135(1):e75-82.
50. Stockwell MS, Hofstetter AM, DuRivage N, Barrett A, Fernandez N, Vargas CY, et al. Text message reminders for second dose of influenza vaccine: a randomized controlled trial. Pediatrics. 2015;135(1):e83-91.
51. Wet publieke gezondheid den Haag: ministerie van Binnenlandse Zaken en Koninkrijkrelaties; [Available from: http://wetten.overheid.nl/BWBR0024705/2016-08-01.
52. Wet bescherming persoonsgegevens den Haag: ministerie van Binnenlandse Zaken en Koninkrijkrelaties; [Available from: http://wetten.overheid.nl/BWBR0011468/2017-03-10.
53. Gebruik van medische gegevens den Haag: Authoriteit Persoonsgegevens; [Available from: https://autoriteitpersoonsgegevens.nl/nl/onderwerpen/gezondheid/gebruik-van-medische-gegevens.

54. Wet op de beroepen in de individuele gezondheidszorg den Haag: ministerie van Binnenlandse Zaken en Koninkrijkrelaties; [Available from: http://wetten.overheid.nl/BWBR0006251/2016-08-01.
55. Veiligheid MvJe. Wetsvoorstel Uitvoeringswet Algemene verordening gegevensbescherming Den Haag [Available from: https://www.rijksoverheid.nl/documenten/kamerstukken/2017/12/13/wetsvoorstel-uitvoeringswet-algemene-verordening-gegevensbescherming.
56. Vetrouwde derde partij: wikipedia; [Available from: https://nl.wikipedia.org/wiki/Vertrouwde_derde_partij.
57. zaken mvE. wet op Centraal Bureau voor Statistiek Den Haag2003 [Available from: http://wetten.overheid.nl/BWBR0015926/2017-01-01.
58. Trogstad L, Ung G, Hagerup-Jenssen M, Cappelen I, Haugen IL, Feiring B. The Norwegian immunisation register--SYSVAK. Euro Surveill. 2012;17(16).
59. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ. 2012;344:e2794.
60. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. JAMA. 2012;308(2):165-74.
61. 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.
62. Hagerup-Jenssen M, Kongsrud S, Riise OR. Suboptimal MMR2 vaccine coverage in six counties in Norway detected through the national immunisation registry, April 2014 to April 2017. Euro Surveill. 2017;22(17).
63. Mitchel Z. the Epidemiologist's dream: Denmark 2016 [Available from: https://www.slideshare.net/RespiratoryEffectivenessGroup/the-epidemiologists-dream-denmark.
64. Paul MM, Greene CM, Newton-Dame R, Thorpe LE, Perlman SE, McVeigh KH, et al. The state of population health surveillance using electronic health records: a narrative review. Popul Health Manag. 2015;18(3):209-16.
65. Teirlinck AC, Van Asten L, Brandsema P, Dijkstra F, Donker G, Van Gageldonk-Lafeber AB, et al. Surveillance of influenza and other respiratory infections in the Netherlands: winter 2016/2017. bilthoven: National Institute for Public Health and the Environment; 2017. Report No.: 2017-0096.
66. Groeneveld GH, Dalhuijsen A, Kara-Zaitri C, Hamilton B, de Waal MW, van Dissel JT, et al. ICARES: a real-time automated detection tool for clusters of infectious diseases in the Netherlands. BMC Infect Dis. 2017;17(1):201.
67. RIVM. SARI surveillance Bilthoven: RIVM; 2016 [Available from: http://www.rivm.nl/Onderwerpen/L/Luchtweginfecties/SARI.
68. Prevention CfDCa. Vaccine Safety Datalink (VSD) Atlanta: CDC; [Available from: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html.
69. McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine. 2014;32(42):5390-8.
70. El Emam K, Mercer J, Moreau K, Grava-Gubins I, Buckeridge D, Jonker E. Physician privacy concerns when disclosing patient data for public health purposes during a pandemic influenza outbreak. BMC Public Health. 2011;11:454.
71. Mackay IM, Arden K. Public Health and Emerging Disease Outbreaks: Why Talking to the Community is a Good Idea: InfectionControl.tips; 2015 [Available from: https://infectioncontrol.tips/2015/11/14/public-health-and-emerging-disease-outbreaks-why-talking-to-the-community-is-a-good-idea/.
72. Giambi C, Fabiani M, D'Ancona F, Ferrara L, Fiacchini D, Gallo T, et al. Parental vaccine hesitancy in Italy - Results from a national survey. Vaccine. 2018.
73. Harmsen IA, Doorman GG, Mollema L, Ruiter RA, Kok G, de Melker HE. Parental information-seeking behaviour in childhood vaccinations. BMC Public Health. 2013;13:1219.
74. Paulussen TG, Hoekstra F, Lanting CI, Buijs GB, Hirasing RA. Determinants of Dutch parents' decisions to vaccinate their child. Vaccine. 2006;24(5):644-51.

Appendix

Nederlandse samenvatting

In Nederland worden twee landelijke vaccinatieprogramma's uitgevoerd. Het Rijksvaccinatie programma (RVP) is gericht op baby's en kinderen tot 18 jaar en startte in 1957. Het Nationaal Programma Griepppreventie (NPG) is gestart in 1997 en is bedoeld voor alle volwassenen van 60 jaar en ouder en voor kinderen vanaf 6 maanden en volwassenen die een groter risico lopen op ernstige ziekte.
Het Centrum Infectieziektebestrijding (CIb) voert surveillance van beide vaccinatieprogramma's uit, samen met andere partijen. Surveillance is het continu verzamelen van gegevens, die gebruikt kunnen worden om effecten van de vaccinatieprogramma's te meten en deze programma's indien nodig te verbeteren. De surveillance bestaat uit vijf pijlers, namelijk het bepalen van de vaccinatiegraad en de veiligheid van de vaccinaties, ziekte- en ziektekiem-surveillance en de bewaking van de immuniteit, ook wel immuno-surveillance. Met behulp van een goedlopend surveillance programma van hoge kwaliteit kan een vaccinatieprogramma aangepast en verbeterd worden. Goede surveillance draagt bij aan vertrouwen in en acceptatie van het vaccinatieprogramma door de bevolking en de betrokken professionals.
Met de studies in dit proefschrift laten we de goede kanten en de beperkingen van drie pijlers van het huidige surveillance systeem zien. Hierbij richten we ons op ziektesurveillance, veiligheid van vaccinatie en immuno-surveillance. Verder doen we aanbevelingen om deze pijlers te optimaliseren.

Bij de ziektesurveillance hebben we ons vooral gericht op kinkhoest. In **hoofdstuk 2** hebben we laten zien dat veranderingen in het vaccinatieschema tegen kinkhoest die zijn door gevoerd in 1999, 2001 en 2005, elk hebben geleid tot een lager aantal (incidentie) kinkhoestmeldingen en kinkhoestopnames bij kinderen tussen 6 maanden en ongeveer 8-9 jaar. Ondanks deze aanpassingen is echter de incidentie van kinkhoest bij jonge en nog niet (volledig) gevaccineerde baby's niet afgenomen. Ook is het aantal meldingen van kinkhoest bij adolescenten en volwassenen toegenomen over de jaren. De surveillance systemen die we gebruikten waren geschikt om retrospectief de impact van aanpassingen in het vaccinatieprogramma te onderzoeken.
Het is bekend dat er bij de meeste surveillance systemen een onderrapportage is. Gegevens over opnames in het ziekenhuis vanwege kinkhoest en overlijden ten gevolge van kinkhoest worden ieder in twee systemen geregistreerd. In **hoofdstuk 3** hebben we de onderrapportage van opnames en sterfte door kinkhoest in elk van de twee bronnen berekend. Deze bleek aanzienlijk in beide rapportagesystemen en was aanwezig voor alle leeftijdsgroepen. Het koppelen van gevallen van kinkhoest tussen de verschillende bronnen werd bemoeilijkt door het ontbreken van nauwkeurige koppel-variabelen. Vervolgens hebben we gekeken of kinkhoest vaker voorkwam en ernstiger verliep bij te vroeg geboren zuigelingen (**hoofdstuk 4**). Bij een statusonderzoek onder kinderen, die vanwege kinkhoest waren opgenomen in het ziekenhuis tussen 2005 en 2014, waren te vroeg geboren kinderen over

vertegenwoordigd. Bij deze te vroeg geboren kinderen bleek het ziektebeloop ernstiger dan bij op tijd geboren kinderen. Ook was de effectiviteit van de eerste kinkhoestvaccinatie minder goed dan bij op tijd geboren kinderen. Bij dit onderzoek werden we beperkt door de noodzaak om toestemming te vragen aan alle ziekenhuizen vanwege aan privacy gerelateerde zaken. Daarnaast ontbraken goede data om de medische gegevens nauwkeurig te kunnen koppelen aan het vaccinatieregister. Tenslotte ontbrak in een deel van de dossiers informatie over de zwangerschapsduur, die we ook niet mochten opvragen tegelijk met de koppeling aan het vaccinatieregister. Dit leidde ertoe dat slechts 56% van de cases compleet was qua gegevens. Tevens hebben deze zaken er voor gezorgd dat de studie veel langer heeft geduurd dan gepland. Om de privacy van ziekenhuizen te beschermen, hebben we gebruik gemaakt van een derde partij, die de koppeling heeft uitgevoerd, een zogenaamde 'Trusted Third Party'.

In 2013-2014 speelde een mazelen epidemie in de bible belt. Dit is een gebied binnen Nederland, waar veel mensen wonen, die zich uit geloofsovertuiging niet laten vaccineren. In dit gebied is er meer kans op verspreiding van mazelen, waartegen de algemene Nederlandse bevolking beschermd is door een hoge vaccinatiegraad. Vanwege deze toegenomen kans op verspreiding en omdat mazelen op deze leeftijd ernstig kan verlopen, kregen kinderen tussen de 6 en 14 maanden een vervroegde vaccinatie tegen mazelen aangeboden (de bof-mazelen-rodehond vaccinatie; BMR). Ouders van kinderen die in aanmerking kwamen voor deze vervroegde BMR werden benaderd op basis van gegevens uit het centrale vaccinatieregister. De vaccinatiestatus van de kinderen in het onderzoek werd ook gecontroleerd in dit register. In **hoofdstuk 5** hebben we berekend hoe effectief deze vervroegde vaccinatie tussen de 6 en 14 maanden was in bescherming tegen mazelen. Op basis van de data vonden we dat de effectiviteit van de vaccinatie tegen mazelen, bof en rodehond rond de 70% was. Ook bleek de vervroegde BMR vaccinatie veilig te zijn: lokale en algemene bijwerkingen werden het minst gemeld bij de jongste kinderen (**hoofdstuk 6**).

Ook voor de vaccinatiecampagne in 2009 tegen de Mexicaanse griep (influenza A(H1N1), was monitoring van de veiligheid een belangrijk onderdeel. In **hoofdstuk 7** beschrijven we dat mensen na twee inentingen met het pandemische griepvaccin niet meer bijwerkingen rapporteerden dan na de eerder toegediende vaccinatie tegen de seizoensgriep. Om aan deze gegevens te komen, is aan iedereen toestemming gevraagd tijdens de massa vaccinaties tegen de seizoens- en de pandemische griep die de huisartsen in de herfst van 2009 organiseerden. Deze manier van werven was erg arbeidsintensief. Het onderzoek vond plaats op basis van de gegevens die de deelnemers zelf rapporteerden. Helaas konden we deze informatie niet controleren in het medisch dossier van de huisarts. Daardoor was het bij voorbeeld niet mogelijk om

goed in kaart te brengen of de bijwerkingen echt veroorzaakt werden door de vaccinatie, waardoor ook de frequentie van mogelijke bijwerkingen vertekend kunnen zijn. Voor een betere surveillance is betere toegang tot het medisch dossier nodig. Ook een centraal register voor griepvaccinaties kan zorgen voor betere surveillance.
Deze pandemische vaccinatie werd ook aangeboden aan vrouwen in het tweede of derde trimester van hun zwangerschap. Om de veiligheid van de vaccinatie bij deze zwangere vrouwen te onderzoeken, werden ze uitgenodigd met behulp van gegevens van het screeningsprogramma van infecties tijdens de zwangerschap, het zogenoemde PSIE programma. Bij gevaccineerde vrouwen bleek geen verhoogd risico op negatieve zwangerschapsuitkomsten, zoals vroeggeboorte, kinderen die klein zijn voor hun zwangerschapsduur of andere uitkomsten als overlijden van het kindje of opname op de neonatale intensive care, voor te komen. In hun eerste levensjaar waren kinderen van gevaccineerde moeders vergelijkbaar met kinderen van niet gevaccineerde moeders wat betreft groei en ontwikkeling. Bovendien hadden ze evenveel contacten met de huisarts voor infecties (**hoofdstuk 8**). Ook hier was de beperking van het onderzoek dat we moesten werken met de zelf gerapporteerde vaccinatiestatus zonder controle in het medisch dossier. Mogelijk zijn hierdoor vrouwen ten onrechte als 'gevaccineerd' of 'ongevaccineerd' geclassificeerd. Ook was koppeling met andere dataverzamelingen lastig, ondanks toestemming van de deelnemende vrouwen.

Als nieuwe leeftijdsgroepen in aanmerking komen voor vaccinatie kan dit leiden tot melding van nieuwe mogelijke bijwerkingen. Deze mogelijke bijwerkingen, bij voorbeeld suikerziekte of migraine, komen bij mannen en vrouwen van alle leeftijden met een bepaalde frequentie voor. Dit noemen we ook wel achtergrond-incidenties. Bij zo'n nieuwe vaccinatie kan er echter een oorzakelijk verband tussen de mogelijke bijwerking en de vaccinatie worden gelegd, terwijl dit er eigenlijk niet is, omdat de vaccinatie en de mogelijke bijwerking bij toeval vlak na elkaar optreden. Gebruikmakend van een grote database met coderingen en vrije tekst in medische dossiers van huisartsen, is de incidentie van het Guillain-Barré syndroom (GBS) als voorbereiding op de pandemische griepvaccinatie bepaald (**hoofdstuk 9**). Daarnaast hebben we ook de incidentie van Multiple Sclerosis (MS) bepaald als voorbereiding op de invoering van vaccinatie tegen humaan papilloma virus in 2009 (**hoofdstuk 10**). Incidenties van GBS bleven gedurende 1996-2008 gelijk. Maar op basis van een korte vragenlijst voor de huisartsen berekenden we dat in meer dan de helft van de gevallen de GBS diagnose, gevonden in de database, niet bevestigd werd door de huisarts. Tussen 1996 en 2008 zagen we wel een toename in de incidentie van MS. Deze toename viel samen met een verkorting van de tijd tussen de eerste verschijnselen en het stellen van de diagnose. Onze bevindingen suggereren dat de toename in incidentie waarschijnlijk veroorzaakt is door verbeterde diagnostiek en dus geen daadwerkelijke toename was. De mogelijkheid om vrije tekst van het medische dossier te gebruiken verhoogt de data validiteit, maar is tegelijkertijd ook

arbeidsintensief. Koppeling van deze database aan het vaccinatieregister kan onderzoek naar mogelijke bijwerkingen verbeteren. Als dit alleen maar mag na toestemming van de huisarts en de cliënt, is er een groot risico op vertekening van de resultaten.

Vanaf 1995 wordt er elke 10 jaar een groot onderzoek onder een groep 0-80 jarige inwoners van Nederland uitgevoerd om te onderzoeken hoe goed Nederlandse inwoners beschermd zijn tegen infectieziekten (PIENTER-onderzoek, immuno-surveillance). Deze PIENTER studies hebben gezorgd voor een schat aan informatie over infectieziekten en de effecten van vaccinaties. Wel moet gezegd worden dat deze onderzoeken erg kostbaar zijn en dat de bereidheid om deel te nemen minder wordt. In **hoofdstuk 11** hebben we de gegevens van de eerste en de tweede studie gebruikt om de bescherming tegen de drie typen van poliomyelitis te bepalen. Gegevens lieten zien dat 94,6%, 91,8% en 84,0% van de algemene bevolking in Nederland beschermd is tegen respectievelijk poliomyelitis type 1, type 2 en type 3. Daarentegen zijn Orthodox Protestanten beschermd in 64,9% (type 1), 61,0% (type 2) en 62,1% (type 3). Een afgerond RVP zorgt dus voor goede bescherming met langdurig hoge antistof concentraties tegen alle drie de poliomyelitis serotypen.

In Nederland krijgen kinderen tot hun 9de jaar in totaal 6 vaccinaties tegen tetanus. De tetanus bacterie zit o.a. in straatvuil. Je bent alleen beschermd als je hoge antistofconcentraties tegen tetanus in je bloed hebt. Daarom krijgen mensen, die een wond hebben, soms een extra vaccinatie tegen tetanus of zelfs kant-en-klare antistoffen (tetanus post-expositie profylaxe; T-PEP). Dit staat beschreven in een richtlijn van de Gezondheidsraad. In het onderzoek van **hoofdstuk 12** hebben we de toegevoegde waarde van een sneltest voor de tetanus post-expositie profylaxe bepaald. Resultaten lieten zien dat de T-PEP richtlijn niet altijd wordt gevolgd. Ongeveer 20% van de deelnemers kwam volgens de richtlijn niet in aanmerking voor T-PEP, maar was volgens de sneltest toch niet beschermd tegen tetanus. Daarentegen had meer dan 70% van de deelnemers een positieve sneltest, maar kwam volgens de richtlijn ook in aanmerking voor T-PEP. De resultaten van de studie waren meer betrouwbaar geweest als we de vaccinatie status van de deelnemers hadden kunnen controleren in een vaccinatie register. Zo'n register zou ook de T-PEP beslissingen en medische zorg in z'n algemeenheid ten goede komen.

De studies in dit proefschrift waren enerzijds belangrijk voor de surveillance van grootschalige vaccinatie programma's, maar resultaten werden anderzijds ook beïnvloed door beperkingen en ontbrekende gegevens. Om de surveillance van vaccinaties te verbeteren doen we de volgende aanbevelingen:

1. Het uitbreiden van het huidige RVP vaccinatieregister tot een centraal vaccinatieregister, waarin alle vaccinaties van alle inwoners van Nederland worden geregistreerd. Dit zal leiden tot een verbetering van de surveillance van vaccinaties omdat nauwkeurige en gemakkelijk verkrijgbare vaccinatie gegevens de hoeksteen van surveillance van vaccinaties vormen. Dit register moet dan toegankelijk zijn voor de burgers zelf en voor professionals.
2. Alle betrokken partijen moeten het erover eens zijn dat surveillance van vaccinaties een essentieel onderdeel is van de publieke gezondheidszorg, dat uitgevoerd mag worden zonder specifieke toestemming vooraf van de patiënt of andere partijen. Deze toestemming moet in wetgeving worden vast gelegd. Dit zorgt voor het tijdig beschikbaar zijn van resultaten en leidt tot minder verlies van gegevens.
3. Nauwkeurige koppeling van of automatische uitwisseling tussen verschillende registers voor de surveillance van vaccinaties. Om dit mogelijk te maken moeten de registers nauwkeurige koppelvariabelen of een uniek persoonlijk nummer bevatten. Om de privacy zoveel mogelijk te waarborgen, kan de koppeling worden uitgevoerd door een 'Trusted Third Party'.
4. Medische data, die routinematig in de zorg worden verzameld, bijvoorbeeld gegevens uit huisarts- of ziekenhuisdossiers, moeten met zo min mogelijk vertraging beschikbaar komen voor de surveillance van vaccinaties. Deze dossiers moeten dan worden aangevuld met gegevens, die voor de publieke gezondheid van belang zijn.

Samenwerking met en betrokkenheid van alle partijen die een rol hebben bij vaccinaties (artsen, gevaccineerden, ouders van gevaccineerde kinderen, algemene bevolking, overheid, beheerders van databases) is een belangrijke voorwaarde voor het succes van bovenstaande aanbevelingen.

Appendix

Dankwoord

Ik vond het schrijven van de introductie en discussie van dit proefschrift moeilijker dan gedacht, maar het schrijven van dit dankwoord is een zeker ook een grote uitdaging! Niet te langdradig, maar ook niemand vergeten. Niet te saai, want het is één van de weinige onderdelen van een proefschrift, die bijna iedereen leest.

Allereerst wil ik jou, Lieke, bedanken voor alle hulp, suggesties en steun, die je hebt gegeven. Toen ik je in februari 2016 vroeg of je mijn promotor wilde zijn, vertelde je dat je vereerd was. Die uitspraak vond ik te veel eer voor mij, want ik heb vooral heel veel geleerd van jouw visie op en ideeën over dit gezamenlijke project.

Daarnaast ben jij, Hester, als co-promotor en direct leidinggevende, ook een onmisbare en belangrijke schakel geweest in mijn promotie traject. Dank je wel dat je me in 2010 hebt binnen gehaald in de RVP surveillance groep, ondanks het feit er wat twijfels waren of ik wel een goede epidemioloog zou zijn. Dank ook dat je me hebt geholpen om verder te groeien, mijn epidemiologische expertise uit te bouwen en mijn plannen om te promoveren ook te concreet te maken.

Als influenza expert ben jij, Wim, een ideale co-promotor, omdat je een echte vraagbaak bent, bij wie ik alle feiten rondom influenza en influenza surveillance kon checken. Dank ook voor al je input en hulp bij de introductie en discussie van dit proefschrift. Die input beperkte zich zeker niet alleen tot influenza; ik heb veel van je geleerd.

Geachte leden van de beoordelingscommissie, Prof. dr. Coutinho, Prof. dr. Bont, Prof. dr. Wulffraat, Prof. dr. Hoebe en dr. Bruijning-Verhagen, hartelijk dank voor het lezen en goedkeuren van mijn proefschrift en alle tijd, die jullie hieraan hebben besteed.

Dank aan de oud collega's van de RVP-veiligheidsbewaking. We hebben samen veel mee gemaakt, stormen doorstaan maar ook veel plezier gehad. Patricia, jij hebt mij kennis laten maken met epidemiologie. Dank daarvoor. Ik mocht de cursus "Epidemiologisch onderzoek: opzet en interpretatie" in het prachtige "Rolduc" seminarie volgen. Het werk binnen de RVP-veiligheidsbewaking heeft mede mijn kijk op surveillance gevormd. Dat veiligheid van vaccinaties nog steeds een speciaal plek in mijn hart heeft, laat dit proefschrift ook wel zien.
Irmgard, jij was ook onderdeel van deze groep. Maar voordat ik daar kwam werken, waren wij al BFFs. Het was even wennen om ook zakelijk met elkaar om te gaan, maar we hebben hier een mooie draai aan gegeven. Ik heb weleens gekscherend gezegd: "jij mag mijn paranimf zijn als ik achter een rollator m'n proefschrift ga verdedigen." Het is toch nog iets sneller gelukt! Dank voor je onvoorwaardelijke vriendschap. Daar ben ik echt heel blij mee.

Dank ook alle collega's van de EPI-RVP-groep. Door samen te werken aan de surveillance van het RVP en alle gesprekken hierover, is mijn kennis over surveillance verder verbreed en verdiept en heb ik uiteindelijk besloten om dit om te zetten in een proefschrift. Ik voel me thuis en welkom in 'onze' RVP-groep, en dat heeft alles te maken met jullie! Alies, jij had in 'Word' al een mooie basis gemaakt voor de editing van elk hoofdstuk. Heel fijn dat ik dat mocht gebruiken. Zelfs voor de 'afloop' had je weer snel een oplossing. Super! Jeanet, fijn dat je mijn paranimf wilde zijn. Jij bent binnen de RVP-groep de epidemioloog met veiligheid als aandachtgebied, ook een beetje mijn favoriete onderwerp. Heel fijn dat ik soms mee mag denken met wat jij doet op dit boeiende onderwerp. Dank ook voor al je wijze lessen in de epidemiologie, je opbeurende woorden als ik t soms moeilijk had. Daarnaast kunnen we gelukkig ook lekker kletsen over allerlei zaken, die niets met vaccinaties en bijwerkingen te maken hebben. Laten we daar vooral mee doorgaan!

Ik wil ook de rest van de EPI-collega's, collega's van andere CIb centra en mensen van buiten het RIVM, waar ik mee samen werk, hartelijk bedanken voor de belangstelling, de verbaasde uitroepen ("ik dacht dat jij al lang gepromoveerd was") en de motiverende gesprekken over promoveren, infectiezieke en de bestrijding hiervan, vaccinaties, surveillance en allerlei andere boeiende onderwerpen.
Marianne, als voormalig centrumhoofd van EPI ben jij mijn praktijkopleider geweest voor de opleiding tot arts M&G. We hebben samen veel interessante gesprekken gevoerd rondom opleiding en promotie en ik heb veel van je geleerd. Veel dank hiervoor. Ik heb regelmatig gedacht aan je nuancerende opmerking dat zo'n boekje toch ook maar een momentopname is en meestal op een plank of stapel terecht komt, als ik weer zat te zwoegen op een zin, die niet wilde lopen.

Dit proefschrift had ik niet kunnen vullen zonder de medewerking van alle co-auteurs. Dank voor al jullie input op de verschillende versies van alle artikelen. Als ik de eerste versie naast de definitieve versie leg, hebben jullie een wereld van verschil gemaakt!

Lieve familie en vrienden, ook jullie dank voor jullie belangstelling, meelevende appjes, e-mailtjes, telefoontjes en persoonlijke gesprekken. Hopelijk krijg ik nu weer meer tijd om samen met jullie leuke dingen te doen.

Dorien, dank voor je hulp bij het zoeken van een toepasselijke kaft voor dit proefschrift. Door jou heb ik Pinterest ontdekt! Uiteindelijk is het iets heel anders geworden, dan wij gepland hadden, maar jouw tip om de foto voor zich zelf te laten spreken heb ik gelukkig opgevolgd.

Jordy, jij hebt weinig mee gekregen van mijn ‘promotie stress’, omdat je al heerlijk op jezelf woont. Toch was je altijd belangstellend en vroeg naar de laatste stand van zaken. Heel lief.

Eric, je hebt me soms geplaagd met m’n boekje maar me vooral geduldig voorzien van koffie, thee, kerstkransjes, paaseitjes en ander lekkers als ik thuis weer achter m’n laptop zat. Lief dat je me zo een beetje hebt verzorgd.

En tenslotte Willem. Jij bent mijn liefste en mijn maatje, al heel lang. We hebben het goed samen. Dank voor je steun, je geduld en alles wat jij nu doet omdat ik er geen tijd voor heb. Ruim 2 jaar geleden zonk onze zeilboot en besloten we om hem te verkopen nadat hij op kosten van de verzekering helemaal gerenoveerd was. Terugkijkend op ons leven zonder boot, vraag ik me af hoe we ooit weekenden vrij konden maken om lekker te gaan varen. Ik beloof dat ik meer vrije tijd ga creëren en wie weet, is er dan ook weer tijd voor een boot(je).

Appendix

About the author

Nicoline van der Maas was Born in 's-Hertogenbosch, the Netherlands, on April 19, 1963. At nine years of age she moved with her parents to Utrecht. There she attended the 'Christelijk Gymnasium' and completed her exam in 1981. She studied Medicines at the Utrecht University and finished her medical degree in 1988.

Thereafter she became a teacher in study courses related to medicines for senior vocational students.

In 2003 she started to work at the National Institute for Public Health and the Environment (RIVM). As a researcher she was part of the team that was responsible for the passive safety surveillance system of the National Immunisation Programme. One year later she became head of this unit. In 2009 she finished a master in Epidemiology at the 'EMGO Institute for Health and Care' (VU). In 2010 she switched jobs within RIVM and started to work as an epidemiologist within the unit 'epidemiology and surveillance of the National Immunisation Programme'.

During her work at RIVM she participated/participates in several European projects on vaccinovigilance, e.g. VAESCO (vaccine adverse events monitoring and communication), Advance (accelerated development of vaccine benefit-risk collaboration in Europe) and EUpert LabNet (European pertussis laboratory network).

In January 2016 she started with the course of Public Health specialist (arts Maatschappij & Gezondheid) at NSPOH (Netherland School of Public & Occupational Health). At the same time, she decided to concretize her plan for a PhD. She defends her thesis on June 12, 2018 and the course of Public Health specialist will end on July 6, 2018.

Nicoline is married with Willem and has two adult sons, Jordy and Eric.

Appendix

List of publications

This thesis.

1. **van der Maas NAT**, Mooi FR, de Greeff SC, Berbers GAM, Conyn-Spaendonck MAE, de Melker HE. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? Vaccine. 2013;31(41):4541-7.
2. **van der Maas NAT**, Hoes J, Sanders EAM, de Melker HE. Severe underestimation of pertussis related hospitalizations and deaths in the Netherlands: A capture-recapture analysis. Vaccine. 2017;24(35):4162-6.
3. Woudenberg T, **van der Maas NA**, Knol MJ, de Melker H, van Binnendijk RS, Hahne SJ. Effectiveness of Early Measles, Mumps, and Rubella Vaccination Among 6-14-Month-Old Infants During an Epidemic in the Netherlands: An Observational Cohort Study. J Infect Dis. 2017.
4. **van der Maas NA**, Woudenberg T, Hahne S, de Melker HE. Tolerability of early measles-mumps-rubella vaccination in infants aged 6-14 months during a measles outbreak in the Netherlands in 2013-2014. J Infect Dis. 2015.
5. **van der Maas NA**, Godefrooij S, Bondt PE, de Melker HE, Kemmeren J. Tolerability of 2 doses of pandemic influenza vaccine (Focetria(R)) and of a prior dose of seasonal 2009-2010 influenza vaccination in the Netherlands. Hum Vaccin Immunother. 2016:1-6.
6. **van der Maas N**, Dijs-Elsinga J, Kemmeren J, van Lier A, Knol M, de Melker H. Safety of vaccination against influenza A (H1N1) during pregnancy in the Netherlands: results on pregnancy outcomes and infant's health: cross-sectional linkage study. BJOG. 2015.
7. **van der Maas NA**, Kramer MA, Jacobs BC, van Soest EM, Dieleman JP, Kemmeren JM, et al. Guillain-Barre syndrome: background incidence rates in The Netherlands. J Peripher Nerv Syst. 2011;16(3):243-9.
8. Kramer MA, **van der Maas NA**, van Soest EM, Kemmeren JM, de Melker HE, Sturkenboom MC. Incidence of Multiple Sclerosis in the General Population in the Netherlands, 1996-2008. Neuroepidemiology. 2012;39(2):96-102.
9. **van der Maas N**, Mollema L, Berbers G, van Rooijen D, van der Avoort H, Conyn-Van Spaendonck M, et al. Immunity against poliomyelitis in the Netherlands, assessed in 2006 to 2007: the importance of completing a vaccination series. Euro Surveill. 2014;19(7).
10. **van der Maas NA**, Donken R, Te Wierik MJ, Swaan CM, Hahne SJ, de Melker HE. Performance of a bedside test for tetanus immunity: results of a cross-sectional study among three EDs in the Netherlands in 2012-2013. Emergency medicine journal : EMJ. 2016

Other publications

1. van der Lee S, Stoof SP, van Ravenhorst MB, van Gageldonk PGM, **van der Maas NAT**, Sanders EAM, et al. Enhanced Bordetella pertussis acquisition rate in adolescents during the 2012 epidemic in the Netherlands and evidence for prolonged antibody persistence after infection. Euro Surveill. 2017;22(47).
2. van der Lee S, Kemmeren JM, de Rond LGH, Ozturk K, Westerhof A, de Melker HE, et al. Elevated Immune Response Among Children 4 Years Of Age With Pronounced Local Adverse Events After The Fifth Dtap Vaccination. Pediatr Infect Dis J. 2017.
3. Scheepers ED, van Lier A, Drijfhout IH, Berbers G, **van der Maas NAT**, de Melker HE, et al. Dutch national immunization schedule: compliance and associated characteristics for the primary series. Eur J Pediatr. 2017.

4. Kemmeren JM, **van der Maas NA**, de Melker HE. Comparison of the tolerability of newly introduced childhood vaccines in the Netherlands. Eur J Pediatr. 2017.
5. van Twillert I, Bonacic Marinovic AA, van Gaans-van den Brink JA, Kuipers B, Berbers GA, **van der Maas NA**, et al. The Use of Innovative Two-Component Cluster Analysis and Serodiagnostic Cut-Off Methods to Estimate Prevalence of Pertussis Reinfections. PLoS One. 2016;11(2):e0148507.
6. **van der Maas NA**, van Aerde K, Bont LJ, Bekker MN, Rots N, de Melker HE. [Infection prevention in newborns through maternal vaccination: current insights and developments]. Ned Tijdschr Geneeskd. 2016;160:D411.
7. Kristensen M, van Lier A, Eilers R, McDonald SA, Opstelten W, **van der Maas N**, et al. Burden of four vaccine preventable diseases in older adults. Vaccine. 2016;34(7):942-9.
8. Kemmeren J, Honsbeek M, Dijkstra F, de Lange M, **van der Maas N**, Smallenburg R, et al. Comparison of different collection methods for reported adverse events following pandemic and seasonal influenza vaccination. Vaccine. 2016;34(34):3961-6.
9. Kamp L, Lehmann B, **van der Maas NAT**. Maternale kinkhoestvaccinatie. Bijblijven. 2016.
10. Verbeek NE, **van der Maas NA**, Sonsma AC, Ippel E, Vermeer-de Bondt PE, Hagebeuk E, et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. Neurology. 2015;85(7):596-603.
11. McDonald SA, Teunis P, **van der Maas N**, de Greeff S, de Melker H, Kretzschmar ME. An evidence synthesis approach to estimating the incidence of symptomatic pertussis infection in the Netherlands, 2005-2011. BMC Infect Dis. 2015;15(1):588.
12. Woestenberg PJ, van Lier A, **van der Maas NA**, Drijfhout IH, Oomen PJ, de Melker HE. Delayed start of diphtheria, tetanus, acellular pertussis and inactivated polio vaccination in preterm and low birth weight infants in the Netherlands. Pediatr Infect Dis J. 2014;33(2):190-8.
13. Verbeek NE, Jansen FE, Vermeer-de Bondt PE, de Kovel CG, van Kempen MJ, Lindhout D, et al. Etiologies for seizures around the time of vaccination. Pediatrics. 2014;134(4):658-66.
14. van Lier A, van Erp J, Donker GA, **van der Maas NA**, Sturkenboom MC, de Melker HE. Low varicella-related consultation rate in the Netherlands in primary care data. Vaccine. 2014;32(28):3517-24.
15. Te Beest DE, Henderson D, **van der Maas NA**, de Greeff SC, Wallinga J, Mooi FR, et al. Estimation of the serial interval of pertussis in Dutch households. Epidemics. 2014;7C:1-6.
16. Romio S, Weibel D, Dieleman JP, Olberg HK, de Vries CS, Sammon C, et al. 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.
17. Mooi FR, **Van Der Maas NA**, De Melker HE. Pertussis resurgence: waning immunity and pathogen adaptation - two sides of the same coin. Epidemiol Infect. 2014;142(4):685-94.
18. Donken R, **van der Maas N**, Swaan C, Wiersma T, Te Wierik M, Hahne S, et al. The use of tetanus post-exposure prophylaxis guidelines by general practitioners and emergency departments in the Netherlands: a cross-sectional questionnaire study. BMC family practice. 2014;15(1):112.
19. 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(8):1246-54.
20. Verbeek NE, **van der Maas N**A, Jansen FE, van Kempen MJ, Lindhout D, Brilstra EH. Prevalence of SCN1A-Related Dravet Syndrome among Children Reported with Seizures

following Vaccination: A Population-Based Ten-Year Cohort Study. PLoS One. 2013;8(6):e65758.
21. Lugner AK, **van der Maas N**, van Boven M, Mooi FR, de Melker HE. Cost-effectiveness of targeted vaccination to protect new-borns against pertussis: Comparing neonatal, maternal, and cocooning vaccination strategies. Vaccine. 2013.
22. Dodd CN, Romio SA, Black S, Vellozzi C, Andrews N, Sturkenboom M, et al. International collaboration to assess the risk of Guillain Barre Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. Vaccine. 2013;31(40):4448-58.
23. van Lier A, Steens A, Ferreira JA, **van der Maas NA**, de Melker HE. Acceptance of vaccination during pregnancy: Experience with 2009 influenza A (H1N1) in the Netherlands. Vaccine. 2012;30(18):2892-9.
24. Lammers AJ, **van der Maas N**, Peters EJ, Meerveld-Eggink A, Sanders EA, Kroon FP. [Prevention of severe infections in patients with hyposplenism or asplenia]. Ned Tijdschr Geneeskd. 2012;156(44):A4857.
25. van't Klooster TM, Kemmeren JM, de Melker HE, Vermeer-de Bondt PE, **van der Maas NA**. Two doses of pandemic influenza A(H1N1) vaccine: tolerability in healthy young children in the Netherlands. Hum Vaccin. 2011;7(10):1048-54.
26. van 't Klooster TM, Kemmeren JM, **van der Maas NA**, de Melker HE. Reported adverse events in girls aged 13-16 years after vaccination with the human papillomavirus (HPV)-16/18 vaccine in the Netherlands. Vaccine. 2011;29(28):4601-7.
27. van Lier A, **van der Maas NA**, Rodenburg GD, Sanders EA, de Melker HE. Hospitalization due to varicella in the Netherlands. BMC Infect Dis. 2011;11:85.
28. Kemmeren JM, **van der Maas NA**, de Melker HE. Parental reports of adverse events following simultaneously given dT-IPV and MMR vaccines in healthy 9-year-old children. Eur J Pediatr. 2011;170(3):339-45.
29. Kemmeren JM, Timmer SS, **van der Maas NA**, de Melker HE. Comparison of the tolerability of an acellular pertussis-containing vaccine given as the fifth booster dose in differently primed children. Vaccine. 2011;29(26):4373-7.
30. Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ. 2011;343:d3908.
31. de Greeff SC, van Buul LW, Westerhof A, Wijga AH, van de Kassteele J, Oostvogels B, et al. Pertussis in infancy and the association with respiratory and cognitive disorders at toddler age. Vaccine. 2011;29(46):8275-8.
32. David S, Vermeer-de Bondt P, **van der Maas N**. [Increase in localised symptoms in 4-year-olds following revaccination with DaPT-IPV]. Ned Tijdschr Geneeskd. 2010;154:A980.
33. **van der Maas NA**, Kemmeren JM, de Melker HE. [Safety of the bivalent human papillomavirus vaccine--results following administration of more than 192,000 doses]. Ned Tijdschr Geneeskd. 2009;153:A964.
34. **van der Maas NA**, Bondt PE, de Melker H, Kemmeren JM. Acute cerebellar ataxia in the Netherlands: a study on the association with vaccinations and varicella zoster infection. Vaccine. 2009;27(13):1970-3.
35. Kemmeren JM, Vermeer-de Bondt PE, **van der Maas NA**. Discolored leg syndrome after vaccination--descriptive epidemiology. Eur J Pediatr. 2009;168(1):43-50.
36. Jacobs BC, Wijnans L, Sturkenboom M, **van der Maas NAT**. Guillain-Barré syndrome and the new Influenza A(H1N1) virus. Ned Tijdschr Geneesk. 2009;153(A1490).

37. Zomer TP, van Duynhoven YT, Mangen MJ, **van der Maas NA**, Vennema H, Boot H, et al. Assessing the introduction of universal rotavirus vaccination in the Netherlands. Vaccine. 2008;26(29-30):3757-64.
38. Vermeer-de Bondt PE, **van der Maas NA**. The effect of age and dose number on the risk of collapse (hypotonic-hyporesponsive episode) after pertussis vaccination. Pediatr Infect Dis J. 2008;27(4):355-7.
39. David S, Vermeer-de Bondt PE, **van der Maas NA**. Reactogenicity of infant whole cell pertussis combination vaccine compared with acellular pertussis vaccines with or without simultaneous pneumococcal vaccine in the Netherlands. Vaccine. 2008;26(46):5883-7.
40. **van der Maas NA**, David S, Kemmeren JM, Vermeer-de Bondt PE. [Safety surveillance in the National Vaccination Programme; fewer adverse events with the DTP-IPV-Hib vaccine after the transition to an acellular pertussis component in 2005]. Ned Tijdschr Geneeskd. 2007;151(49):2732-7.
41. Bults M, Kemmeren JM, **van der Maas NA**. Adverse events following booster doses of diphtheria-tetanus-inactivated poliovirus and acellular pertussis vaccines for 4-year-old children in The Netherlands. Vaccine. 2007;25(29):5272-7.
42. Boot HJ, Wallenburg I, de Melker HE, Mangen MJ, Gerritsen AA, **van der Maas NA**, et al. Assessing the introduction of universal human papillomavirus vaccination for preadolescent girls in The Netherlands. Vaccine. 2007;25(33):6245-56.
43. Vermeer-de Bondt PE, Dzaferagic A, David S, **van der Maas NA**. Performance of the Brighton collaboration case definition for hypotonic-hyporesponsive episode (HHE) on reported collapse reactions following infant vaccinations in the Netherlands. Vaccine. 2006;24(49-50):7066-70.