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ADVANCE system testing: Benefit-risk analysis of a marketed vaccine using multi-criteria decision analysis and individual-level state transition modelling

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ABSTRACT

Background: The Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE) is a public-private collaboration aiming to develop and test a system for rapid benefit-risk (B/R) monitoring of vaccines using electronic health record (eHR) databases in Europe. Proof-of-concept studies were designed to assess the proposed processes and system for generating the required evidence to perform B/R assessment and near-real time monitoring of vaccines. We aimed to test B/R methodologies for vaccines, using the comparison of the B/R profiles of whole-cell (wP) and acellular pertussis (aP) vaccine formulations in children as an example.

Methods: We used multi-criteria decision analysis (MCDA) to structure the B/R assessment combined with individual-level state transition modelling to build the B/R effects table. In the state transition model, we simulated the number of events in two hypothetical cohorts of 1 million children followed from first pertussis dose till pre-school-entry booster (or six years of age, whichever occurred first), with one cohort receiving wP, and the other aP. The benefits were reductions in pertussis incidence and complications. The risks were increased incidences of febrile convulsions, fever, hypotonic-hyporesponsive episodes, injection-site reactions and persistent crying. Most model parameters were informed by estimates (coverage, background incidences, relative risks) from eHR databases from Denmark (SSI), Spain (BIFAP and SIDIAP), Italy (Pedianet) and the UK (RCGP-RSC and THIN). Preferences were elicited from clinical and epidemiological experts.

Results: Using state transition modelling to build the B/R effects table facilitated the comparison of different vaccine effects (e.g. immediate vaccine risks vs long-term vaccine benefits). Estimates from eHR databases could be used to inform the simulation model. The model results could be easily combined with preference weights to obtain B/R scores.

Conclusion: Existing B/R methodology, modelling and estimates from eHR databases can be successfully used for B/R assessment of vaccines.

Abbreviations: ADVANCE, Accelerated Development of VAccine beNefit-risk Collaboration in Europe; aP, acellular pertussis; B/R, benefit-risk; eHR, electronic health record; HHE, hypotonic-hyporesponsive episode; ISR, injection-site reaction; MCDA, multi-criteria decision analysis; PROTECT, Pharmacoepidemiological Research on Outcome and Therapeutics; POC, proof-of-concept; RR, relative risk; VE, vaccine effectiveness; wP, whole-cell pertussis.

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1. Introduction

The Accelerated Development of VAccine beNefit-risk Collaboration in Europe project (ADVANCE), launched in 2013 and funded by the Innovative Medicines Initiative (IMI), is a public-private partnership aiming to develop and test a system for rapid benefit-risk (B/R) assessment and near-real time monitoring of vaccines in the post-marketing setting [1] (see Appendix for list of consortium members). A series of proof-of-concept (POC) studies were designed to assess the proposed processes and system. The present study aimed to test a methodology for the B/R assessment of vaccines and assess the use of European electronic health record (eHR) databases for informing the B/R assessment.

There are several methodologies for B/R assessments that can support medical decision-making [2]. In particular, the B/R 'effects table' is widely used following its introduction in European Public Assessment Reports. However, other tools exist, including frameworks, metrics, estimation and modelling techniques, as well as preference elicitation techniques [2,3]. The 'Pharmacoepidemiological Research on Outcome and Therapeutics' (PROTECT) consortium completed pioneering work in identifying, organising and appraising B/R assessment tools [4]. Based on their experience drawn from eight case studies, they recommended a systematic approach containing five generic steps; (1) planning, (2) evidence gathering, (3) analysis, (4) exploration and (5) communication, rather than a one-size-fits-all approach [5]. However, up to now, most B/R methodologies have been developed for medicinal products while the B/R assessment of vaccines may require different methods [5].

When conducting a B/R assessment in a post-marketing setting, different information sources can be used, including clinical trials, observational studies and systematic literature reviews. Currently, there is a growing interest in using large eHR databases to study vaccine outcomes (e.g. Vaccine Safety Datalink [6], the Post-Licensure Rapid Immunization Safety Monitoring programme [7] and ADVANCE [1]) since these potentially enable real-world vaccine effects to be studied on a large scale in geographical diverse settings.

To explore B/R assessment methodology for vaccines and the use of large eHR databases for informing the B/R model, we compared the B/R profiles of whole-cell (wP) and acellular pertussis (aP) vaccine formulations in children prior to their pre-school-entry booster as a test case. This test case was selected to mimic the introduction of a new vaccine, where systematic monitoring of changes in B/R profile over time would be needed. This POC study was undertaken for system testing and not to inform clinical, regulatory or public health decisions on pertussis vaccination.

2. Methods

2.1. Benefit-risk analysis

We used multi-criteria decision analysis (MCDA) to structure the B/R assessment following the PROTECT recommendations and ISPOR guidelines [5,8,9]. MCDA provides a structured, stepwise approach for the assessment and comparison of different treatment alternatives for benefit and risk outcomes [10]. However, the measures for the vaccine benefits (i.e., vaccine effectiveness or impact) and vaccine risks (i.e. risk ratios or rate ratios) are different, with typically the vaccine benefits being long-term and the vaccine risks being immediate and short-term. To facilitate their comparison, we used individual-based state transition modelling with parameters informed by multi-country eHR database studies on pertussis vaccination coverage, benefits and risks [11–13]. The results of the state transition model were then combined with preference weights solicited from clinical and epidemiological experts to obtain overall B/R scores.

2.2. Multi-criteria decision analysis

Details on the different MCDA steps and their application are given below.

Step 1: Establishment of the decision context

The test case was the comparison of the B/R profiles of wP and aP vaccine formulations in children prior to their pre-school-entry booster (or six years of age, whichever occurred first) in Europe. Vaccines containing wP have been available since the 1940s whereas aP containing vaccines were developed and used from the mid-1990s. Most European countries replaced wP with aP, and Poland is the only country in Europe where a wP vaccine formulation is still included in the childhood vaccination programme [11].

Step 2: Identification of key benefit and risk criteria (value tree)

The initial value tree was discussed and agreed by clinical and epidemiological experts from public health, vaccine manufacturers and academia (Fig. 1). In the final tree, indirect effects were omitted for simplicity, limb swelling was combined with other injection-site reactions to avoid double-counting; and convulsions were defined as febrile convulsions. The final value tree contained reductions in pertussis and its complications (convulsions, pneumonia and death) as benefit outcomes and febrile convulsions, fever, hypotonic-hyporesponsive episodes (HHE), injection-site reactions (ISR) and persistent crying as risk outcomes.

Step 3: Identification of data sources

The parameters of the B/R model were based on results for vaccination coverage, benefits and risks from the ADVANCE multi-country eHR database studies where possible [11–13]. The following databases were included in this study: SSI (Denmark), BIFAP and SIDIAP (Spain) and RCGP RSC and THIN (UK), PEDIANET (Italy). Detailed information on the databases can be found in [11–14].

Step 4: Construction of the benefit-risk effects table

We used an individual-based state transition simulation model to build the B/R effects table. For the participating countries (i.e., Denmark, Italy, Spain and the UK), we built two hypothetical cohorts of 1,000,000 children followed from their first pertussis dose until their pre-school booster (or six years of age). One cohort was vaccinated with wP, the other with aP. Unvaccinated children were not included as the B/R assessment focused on direct effects only (Fig. 1). To avoid the impact of time-varying confounding or changes in the background incidence rates on the wP-aP comparison, the two hypothetical cohorts were identical with respect to the age-specific background incidence rates, vaccination coverage and age at vaccination. Only the vaccine type-specific parameters (i.e., VE and RR) were varied between the aP and wP hypothetical cohorts.

The parameters for the simulation model were informed by the results from the ADVANCE multi-country eHR database studies on pertussis vaccination coverage, benefits and risks with the exception of pertussis vaccine effectiveness and pertussis complication incidence rates, which were not available when this B/R analysis was undertaken [11–13,15–18]. Since the vaccination schedules are different across countries, the dose-specific vaccination coverage and age at vaccination were kept country-specific whereas the

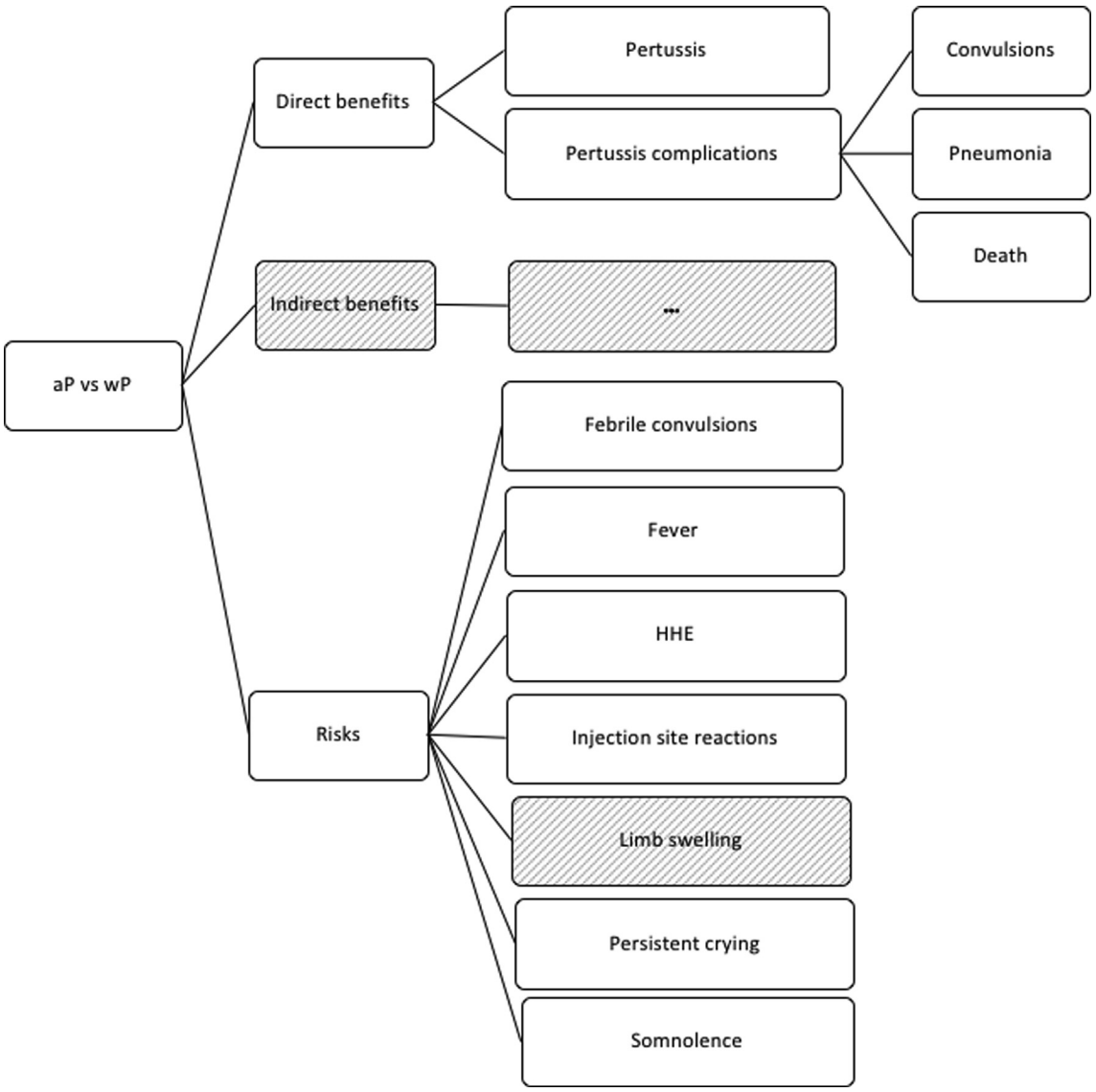

Fig. 1. Initial and final pertussis vaccination outcome trees. The outcomes that were not retained for the final outcome tree are shaded in grey. (aP: acellular pertussis vaccines; wP: whole-cell pertussis vaccines; HHE: hypotonic-hyporesponsive episodes).

background incidence rates and vaccine-type-specific RRs were pooled across countries to increase precision. To take into consideration age-related dependencies, a finely disaggregated age-structure (monthly from first dose to age two and 3-monthly afterwards) was used. Within each cohort, the expected number of events for each outcome was estimated through Monte Carlo simulation based on 1000 simulation draws. Median and 95% uncertainty intervals were obtained to account for uncertainty in model parameters. The simulation models were developed using R version 3.4.0 [19]. The model input parameters are summarised in Table 1.

Step 4.1: model input parameters: coverage

To reflect recent practice, most recent coverage estimates with at least two years of follow up were obtained from the ADVANCE coverage POC study (e.g. Denmark, Spain and UK: birth cohort 2010; Italy: birth cohort 2007) [11]. The 2- and 3-dose country-specific coverage rates at 24 months old and the age at vaccination were estimated for children who had received at least 1 dose (Fig. 2).

Step 4.2: model input parameters: benefits

The incidence of pertussis in unvaccinated children was derived from the incidence for those who had received only one dose (since unvaccinated children were excluded from the database study) and an estimate of the 1-dose vaccine effectiveness obtained from the literature [12,16]. To reflect recent epidemiology, data from 2005 onwards were used to estimate age-specific pertussis incidences, which were then pooled across databases using random effects *meta*-analyses (Fig. 3) [20].

Step 4.3: model input parameters: risks

Baseline incidences (2005 onwards) were used from primary care databases (BIFAP, RCGP RSC, THIN and PEDIANET) for fever, ISR, persistent crying and somnolence (since these mild outcomes are more likely to be reported in primary care); from the hospital discharge database (SSI) for febrile convulsions (since this is a severe outcome likely to require hospitalisation); and from all databases (primary care and hospital-based) for HHE (since this can be a mild to severe outcome and therefore could be captured in

Table 1
Cohort simulation: overview of model parameters.

Parameter	Mean [95% CI]		Distribution	Source(s)
	aP	wP		
Coverage				
Coverage at 24 months	Fig. 2		Binomial distribution on number of vaccinated children. Probability of being vaccinated is the coverage at 24 mos.	[11]
Age at vaccination (in months)	Fig. 2		Empirical distribution	[11]
Benefits*				
Pertussis				
Age-specific incidence among unvaccinated subjects (/100.000 py) (<6 years)	Fig. 3		Empirical: incidences in children with 1 dose only divided by $(1 - VE_{d1})$, VE_{d1} = 74%	[12,16]
Vaccine effectiveness – dose 1	0.66 [0.56; 0.71]	0.7 [0.62; 0.72]	Log-normal on Rate ratio (RR = 1 – VE). Meta-analysed 3-dose VE estimate multiplied with VE ratio = 74.1%	[17,16]
Vaccine effectiveness – dose 2	0.83 [0.71; 0.89]	0.88 [0.84; 0.94]	Log-normal on Rate ratio (RR = 1 – VE). Meta-analysed 3-dose VE estimate multiplied with VE ratio = 93.6%	[17,16]
Vaccine effectiveness – dose 3	0.89 [0.76; 0.95]	0.94 [0.89; 0.97]	Log-normal on Rate ratio (RR = 1 – VE). Meta-analysed estimate	[17]
Pertussis-related pneumonia (age-specific % of cases with complications)	<6 months: 11.8%; 6–11 months: 8.6%; 1–4 years: 5.4%		Binomial distribution on number of cases with complications. Probability of developing complication is age-specific	[18]
Pertussis-related febrile seizures (age-specific % of cases with complications)	<6 months: 1.4%; 6–11 months: 0.7%; 1–4 years: 1.2%		Binomial distribution on number of cases with complications. Probability of developing complication is age-specific	[18]
Pertussis-related deaths (age-specific % of cases with complications)	<6 months: 0.8%; 6–11 months: 0.1%; 1–4 years: <0.1%		Binomial distribution on number of cases with complications. Probability of developing complication is age-specific	[18]
Risks**				
Febrile convulsions				
Age-specific baseline incidence (/1000 py)	Fig. 4		Empirical	[13]
Rate ratio (0-3d) – dose 1	0.89 [0.51; 1.57]	1.15 [0.63; 2.11]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-3d) – dose 2	0.94 [0.79; 1.11]	1.51 [0.71; 3.19]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-3d) – dose 3	2.19 [1.69; 2.83]	1.89 [1.55; 2.31]	Log-normal on Rate ratio Meta-analysed estimate.	[13]
Fever				
Age-specific baseline incidence (/1000 py)	Fig. 4			[13]
Rate ratio (0-3d) – dose 1	1.18 [1.08; 1.29]	1.92 [1.84; 2.00]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-3d) – dose 2	0.89 [0.81; 0.99]	1.47 [1.42; 1.54]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-3d) – dose 3	1.17 [0.98; 1.39]	1.85 [1.78; 1.92]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Hypotonic-hyporesponsive episodes				
Age-specific baseline incidence (/1000 py)	Fig. 4			[13]
Rate ratio (0-2d) – dose 1	2.72 [1.49; 4.96]	1.70 [1.30; 2.24]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-2d) – dose 2	1.42 [0.73; 2.79]	0.71 [0.36; 1.42]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-2d) – dose 3	1.65 [0.81; 3.39]	1.34 [1.01; 1.78]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Injection site reactions				
Age-specific baseline incidence (/1000 py)	Fig. 4			[13]
Rate ratio (0-2d) – dose 1	1.38 [1.15; 1.65]	2.12 [1.89; 2.38]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-2d) – dose 2	1.78 [1.09; 2.91]	2.42 [2.13; 2.74]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-2d) – dose 3	1.65 [0.81; 3.39]	2.19 [1.95; 2.45]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]

Table 1 (*continued*)

Parameter	Mean [95% CI]		Distribution	Source(s)
	aP	wP		
Persistent crying				
Age-specific baseline incidence (/1000 py)	Fig. 4			[13]
Rate ratio (0-1d) – dose 1	1.56 [0.97; 2.50]	4.60 [3.89; 5.45]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-1d) – dose 2	1.28 [0.92; 1.76]	2.76 [1.90; 4.01]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-1d) – dose 3	1.05 [0.57; 1.92]	2.13 [1.82; 2.47]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Somnolence				
Age-specific baseline incidence (/1000 py)	Fig. 4			[13]
Rate ratio (0-3d) – dose 1	3.01 [1.30; 7.00]	4.47 [1.74; 11.5]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-3d) – dose 2	2.16 [1.60; 2.90]	1.10 [0.70; 1.71]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]
Rate ratio (0-3d) – dose 3	1.29 [0.78; 2.14]	1.94 [1.28; 2.94]	Log-normal on Rate ratio. Meta-analysed estimate.	[13]

Abbreviations: aP = acellular pertussis vaccine, CI = confidence interval, d = days, mos = months, py = person-year, RR = Rate ratio, VE = vaccine effectiveness.
*Pertussis: Probability of developing pertussis is derived from the age-specific incidence in unvaccinated subjects multiplied with (1-VE), where VE is dose-dependent. Probability of developing pertussis complications is age-specific, with the age-specific probabilities being derived from the literature **Risk events: probability of a risk event outside the risk window is derived from the age-specific incidence. Probability of an event during the risk windows is derived from the age-specific incidence multiplied with the corresponding RR.

any database). The age-specific number of events and person time were combined across databases to obtain pooled incidences, which were subsequently smoothed using LOWESS (Fig. 4) [21]. The database-specific rate ratios of adverse events during the exposure risk windows (by vaccine type and dose) were obtained using a self-controlled case series method, which were subsequently pooled using random-effects *meta*-analyses (estimates in Table 1) [13].

Steps 5–6: Definition of value functions and preference weights

Four clinical and epidemiological experts and three observers attended a preference elicitation workshop. The experts were volunteers from the ADVANCE consortium and the workshop was organised in compliance with ISPOR guidelines. After a face-to-face training session on preference elicitation and practicing MCDA swing-weighting using D-Sight software (www.d-sight.com) it was agreed to simplify the preference elicitation as the participants found the swing-weighting difficult to understand, especially when non-linear value functions were selected. It was therefore decided to restrict to linear value functions and express, for each outcome, the number of events that would be equivalent to one pertussis event (with pertussis being considered as the most severe outcome). For each outcome, the lower limit of the linear value function was defined as the minimum lower limit of the 95% uncertainty intervals of the number of events in both the hypothetical wP and aP cohort whereas the upper limit of the linear value function was defined as the maximum upper limit of the 95% uncertainty intervals.

Step 7: Calculation of the benefit-risk scores

The overall B/R scores for the wP and aP formulations (BR_j) were calculated as follows:

$$BR_j = \sum_{i}^{I} w_i \left(1 - \frac{N_{ij}^{*} - minN_i}{maxN_i - minN_i}\right) \times 100$$

This represents a linear value function, with $N_{ij}^{*} = max\left(minN_i, \min(N_{ij}, maxN_i)\right)$, where N_{ij} N_{ij} is the median number of events in the hypothetical cohort j for event type i, where $minN_i$ $minN_i$ and $maxN_i$ $maxN_i$ are the lower and upper limit of the linear value function and where w_i $w_i$is the preference weight. The preference weights were standardized so their sum was equal to one. This implies that the 'perfect' vaccine (with the number of events N_{ij} equal to its minimum $minN_i$ for each outcome) would have a B/R score of 100. To have a robust central tendency measure N_{ij} not affected by outliers the median number of events was chosen.

Step 8: Performing sensitivity analyses

The impact of data uncertainty (as reflected by the 95% uncertainty intervals of the number of events within the hypothetical populations) was assessed through Monte Carlo simulation with 1000 simulation runs, assuming normal distributions for the number of events for each outcome. The impact of preference weights was assessed by halving and doubling a single non-standardised preference weight, while keeping the others constant, and then standardising again.

3. Results

3.1. Model input parameters: coverage, benefits and risks

Almost all children in each of the four countries, who received the first dose, completed the schedule, with the 3-dose coverage

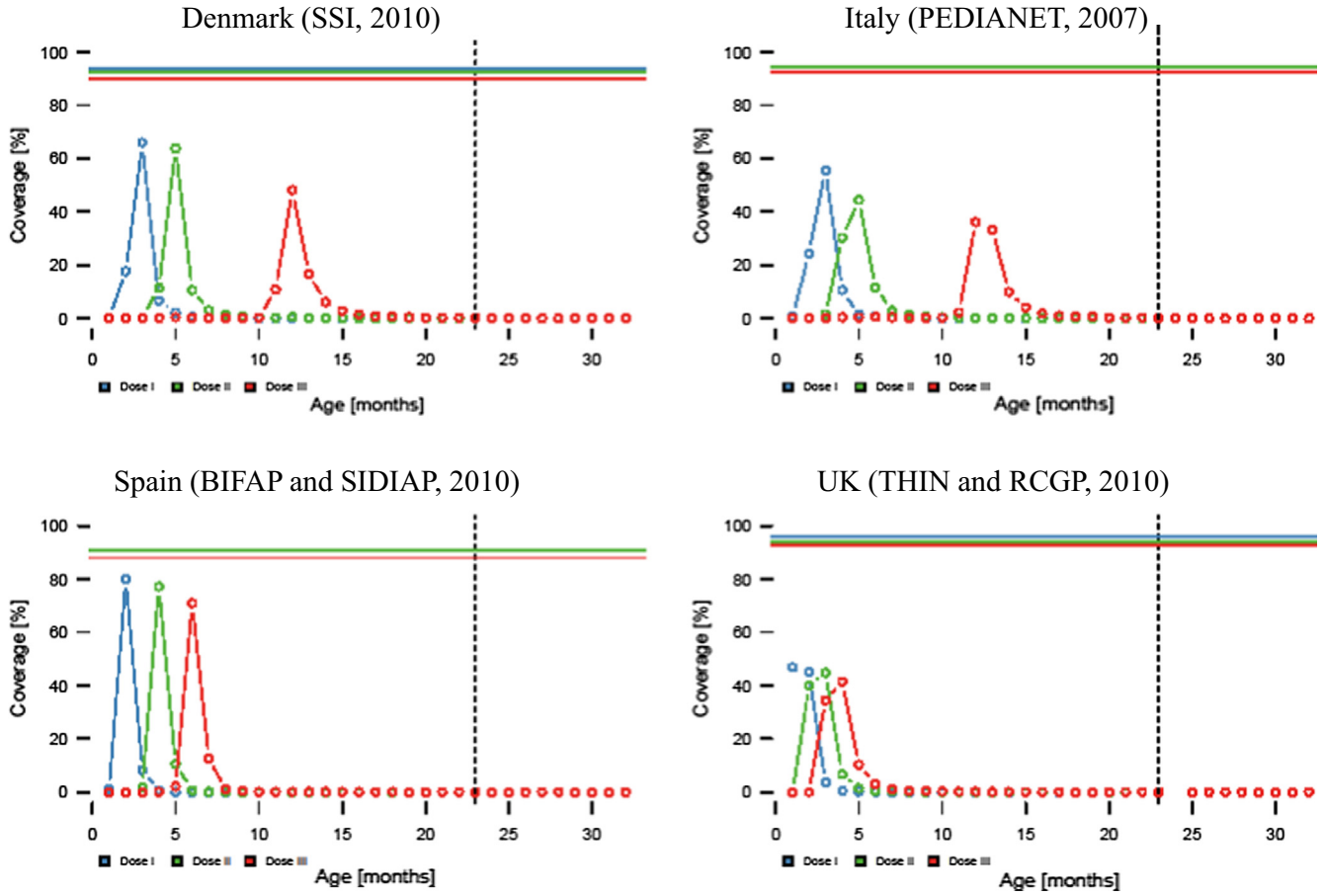

Fig. 2. Age-specific vaccination coverage rates (%) for children who received at least one dose, by dose and country (Denmark, Spain and UK: birth cohort 2010; Italy: birth cohort 2007). The horizontal lines at the top indicate coverage for children aged 24 months for each dose. Data from [11].

rate ranging from 95.7% to 97.9% (Fig. 2). The age at vaccination differed across countries in line with the national recommendations. In Spain and the UK, all three doses were administered within the first 10 months of life whereas in Italy and Denmark, the 3rd dose was administered between 10 and 15 months of age. Pertussis incidence after first dose (birth cohorts 2005 onwards) was highest in children aged 2–3 months in all databases, although substantial database heterogeneity existed, particularly for the two youngest age groups (as indicated by the I^2 statistic >75%) (Fig. 3). The smoothed baseline risks are given in Fig. 4, clearly showing age trends for all event types. The rate ratios of adverse events during the exposure risk windows are given in Table 1.

3.2. Model results: benefit/risk effects table

The total expected number of events for vaccine-related plus - unrelated outcomes, for both the wP and aP cohorts, are summarised in Table 2. These estimates reflect the impact of vaccination on the total disease burden in the population assuming the UK 2-dose and 3-dose vaccination coverage rates and age at vaccination. Similar results were obtained assuming the vaccination coverage rates and age at vaccination in Denmark, Italy and Spain (Supplementary tables S1, S2 and S3).

3.3. Preference weights

Good consensus was reached among the participants for all outcomes during the preference elicitation workshop (Fig. 5a). The experts attributed higher preference weights to the benefit of preventing pertussis than to the risks of vaccination, with an averaged standardised preference weight of 92.8% for prevented pertussis (Table 2, Fig. 5a).

3.4. Calculation of the benefit-risk scores

Prevented pertussis was shown to make the largest contribution to the overall B/R scores and was the most strongly discriminating factor between aP and wP (Fig. 5b).

3.5. Impact of data uncertainty

The Monte Carlo distributions of the overall B/R scores by vaccine type showed higher scores for wP than for aP, although there was substantial overlap (Fig. 5c). Changes in the preference weights for pertussis and febrile convulsions had the largest impact on the overall B/R score for wP whereas changes in the preference weight for fever had the largest impact on the overall B/R score for aP (Fig. 5d).

4. Discussion

These results demonstrated how existing B/R methodology can be used for post-marketing B/R assessment of vaccines using evidence on vaccination coverage, benefits, and risks that was obtained through dedicated studies in eHR databases. We adopted a structured approach for the B/R assessment as recommended by the PROTECT project. To this end, we used MCDA and combined MCDA with modelling to build the B/R effects table. Although

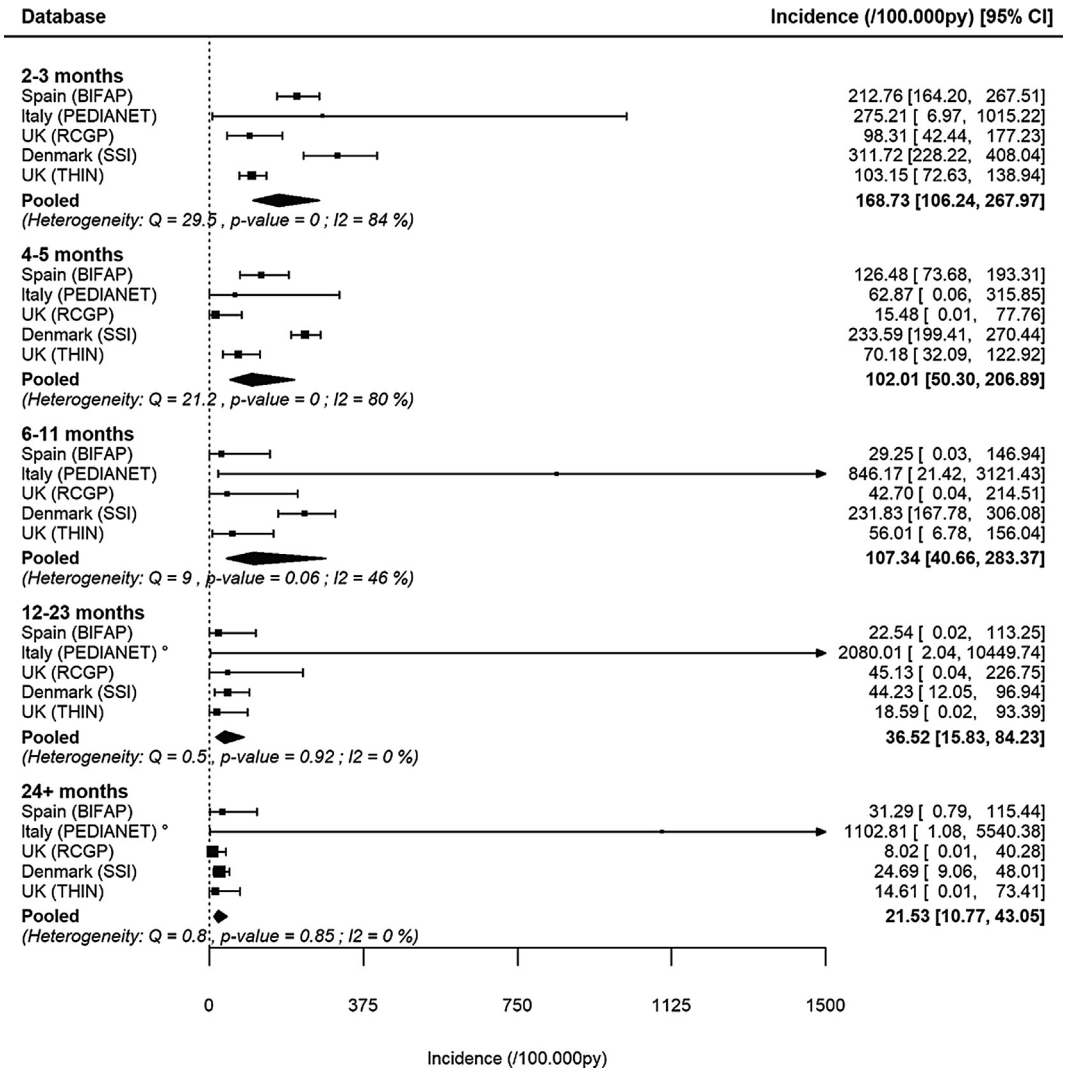

Fig. 3. Database-specific and meta-analysed pertussis incidence (/100.000 person-years (py)) among children who received one dose, by age group, 2005 onwards [12]. Estimates that were considered to be outliers, i.e. absolute value of the studentised residual was >2.5 (indicated by *) were excluded from the meta-analysis. Study heterogeneity was investigated by the chi-squared test for heterogeneity, (p-values <0.05 indicate a significant amount of heterogeneity), and quantified using the I^2 statistic with low, moderate and high levels of heterogeneity corresponding to I^2 values of 25%, 50% and 75%, respectively.

MCDA has been used for vaccines before, to our knowledge, this is the first time it has been combined with simulation modelling techniques to build a B/R effects table [22].

More specifically, we used an individual-based state transition simulation model to build the B/R effects table, expressed as the total number of simulated events for the different benefit and risk outcomes within the aP and wP hypothetical cohorts. Both cohorts were identical with respect to the age-specific background incidence rates and vaccination coverages. Only the vaccine type-specific parameters (i.e., vaccine benefits and risks) were varied between the two cohorts. This approach avoids the wP-aP comparison being biased by time-varying confounding or changes in the background incidence rates over time. Such bias would have affected a simple comparison of event rates between populations using aP and wP vaccines as the two vaccine types were used in very distinct time periods. In addition, the simulation approach facilitated the comparison of different vaccine effects, while accounting for differences in age at vaccination, number of doses given, age-specific baseline risks and differences in outcome-specific risk windows. We simulated the total number of events (i.e. vaccine-related and -unrelated) to assess the impact of vaccination on the total disease burden. We also complemented MCDA with additional Monte Carlo simulations assessing the impact of data uncertainty on the overall B/R scores, which broadened the use of MCDA to decision-making under uncertainty. Additional sensitivity analyses in which the preference weights were varied enabled to assess the robustness of the B/R scores to changes in preference weights. We used an individual-level state transition simulation model to build the B/R effects table since we considered only direct effects, however, dynamic transmission models could have been used if indirect effects were to be considered as well.

Evidence that can be used to inform the post-marketing B/R assessment models comes from diverse sources, potentially covering different geographical areas and populations, and is of variable quality; here we assessed how evidence generated from eHR databases could be used [23]. Compared with using available published evidence, the approach we used has the advantage that different model parameters can be consistently estimated with high levels of granularity, within the same study population.

We have shown how preference weights can be easily combined with the results from simulation models to obtain overall B/R scores. We obtained preference weights from clinical and

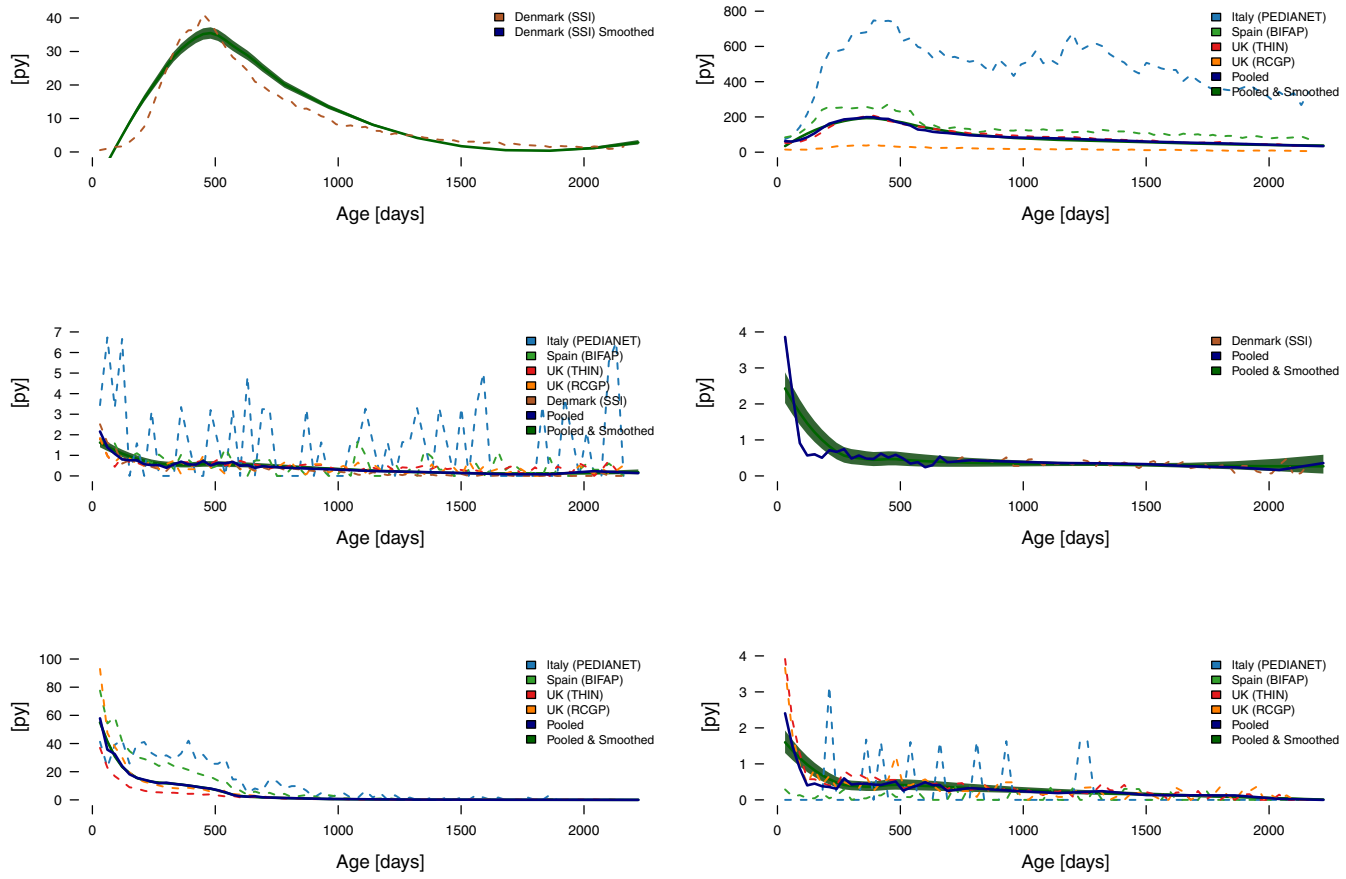

Fig. 4. Database-specific, pooled and LOWESS smoothed pooled estimates (with 95% CI) for age-specific baseline incidences (/1000 persons-years (py)) by risk outcome, 2005 onwards [13,21].

Table 2
Benefit/risk effects table, lower and upper limit of linear value functions and standardized averaged preference weights for the outcomes of interest.

	Benefit/risk effects table Number of events* Median [95% uncertainty intervals]		Linear value function		Preference weights (%)
Event	aP	wP	Lower limit	Upper limit	Averaged
Benefits (favourable effects)					
Pertussis	1292 [686; 2467]	698 [440; 1186]	420	2500	92.8
Pertussis complications					
Convulsions	15 [5; 30]	8 [2; 16]	n.a.	n.a.	n.a.
Death	3 [0; 8]	2 [0; 5]	n.a.	n.a.	n.a.
Pneumonia	101 [51; 188]	56 [34; 93]	n.a.	n.a.	n.a.
Risks (unfavourable effects)					
Febrile convulsions	69,702 [68,899; 70,564]	69,377 [68,730; 70,054]	68,000	71,000	3.8
Fever	539,768 [538,798; 540,702]	541,063 [540,102; 542,017]	540,000	541,500	2.4
Hypotonic-hyporesponsive episodes	2283 [2187; 2382]	2262 [2167; 2355]	2100	2400	0.9
Injection site reactions	2819 [2709; 2930]	2896 [2782; 3003]	2700	3000	0.1
Persistent crying	25,477 [25,135; 25,859]	26,690 [26,268; 27,139]	25,000	27,500	<0.01
Somnolence	1783 [1689; 1877]	1799 [1704; 1917]	1600	2000	<0.01

* Cohort simulation model; number of events in a hypothetical cohort of 1 million children followed from first dose till pre-school booster; one cohort received aP, the other wP. The vaccination coverage and age at vaccination are reflective of the UK. n.a. = data was not available at the time of the preference elicitation and these outcomes were excluded from the overall B/R score.

epidemiological experts as we believed they would have a good understanding of both the benefits and risks of vaccination. We solicited preferences using MCDA swing-weighting, which is one of the most efficient methods of obtaining preference weights as preferences can be solicited during a one-day workshop. However, it requires training and a thorough understanding of the preference elicitation methodology by the participants. In our experience, the participants found the use of strongly non-linear value functions in the swing-weighting process difficult. Therefore, we simplified the preference elicitation by asking the participants to express the severity of each event by giving the number of outcome events that would be equivalent to one pertussis event.

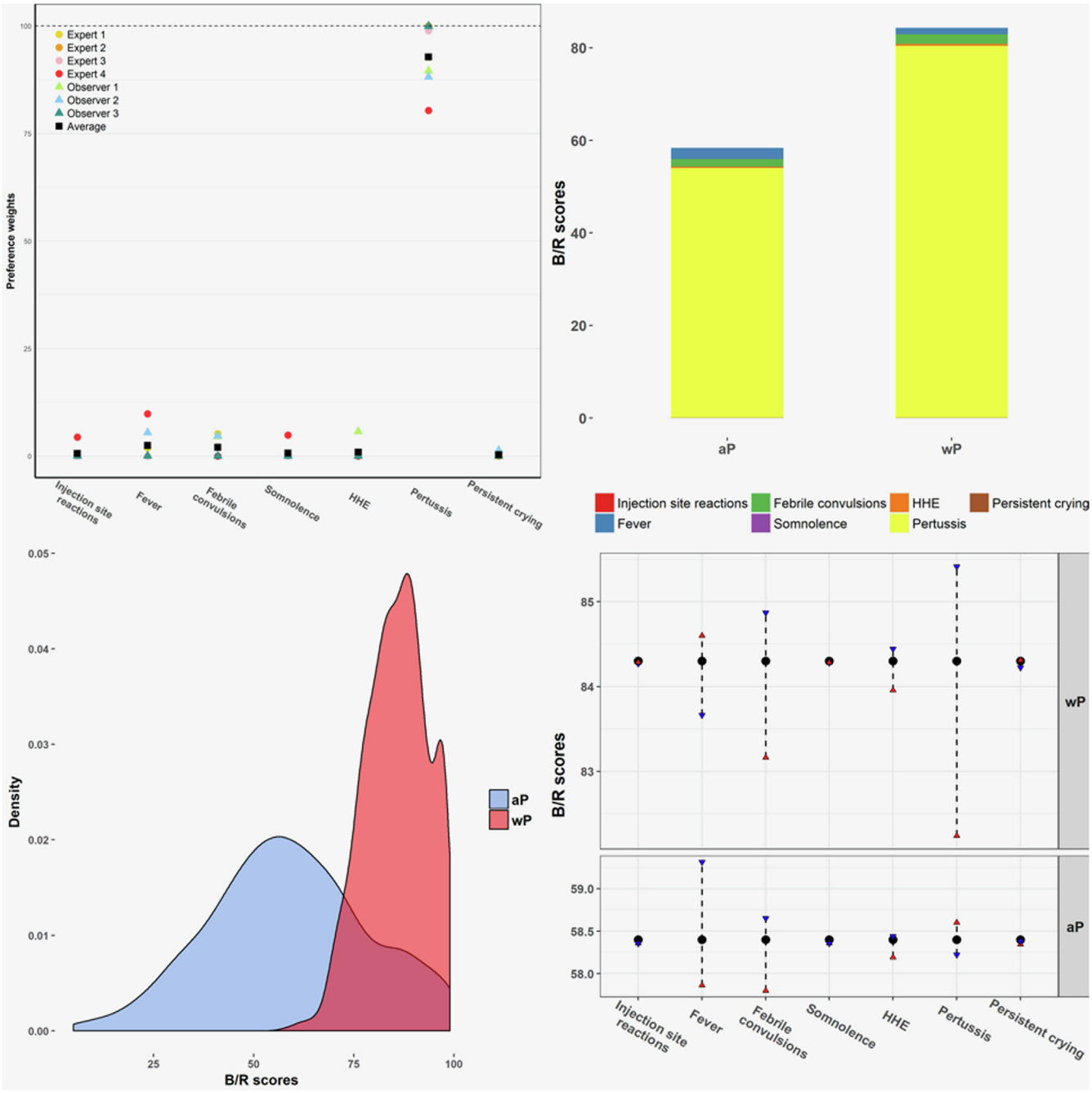

Fig. 5. (a) Individual and averaged preference weights. (b) Overall B/R score and outcome contributions by vaccine formulation (aP vs wP). (c) Impact of data uncertainty: distribution of the overall B/R scores by vaccine type obtained through Monte Carlo simulation. (d) Impact of preference weights: changes in the overall B/R scores when doubling (red arrows) or halving (blue arrows) the preference weights one-at-the-time.

Further discussions on when, from whom and how to elicit preferences regarding vaccination is needed as preference elicitation for vaccines raises many questions. Unlike drugs, vaccines are mostly administered to healthy people, often to children as part of a vaccination programme or mandate. This results in a very low public tolerance for vaccination risks, despite the risks being rare. On the other hand, the benefits of vaccination are often invisible as the incidence of many vaccine-preventable diseases has substantially decreased as a result of vaccination. In addition, some vaccines have the potential to induce herd immunity, whereby unvaccinated individuals are protected indirectly by those vaccinated, implying that the benefits are not necessarily borne by the same individuals who take the risks.

Numerous methods for preference elicitation exist (e.g. time trade-offs, discrete choice experiments, conjoint analyses) and these can be used in diverse settings, such as focus groups or surveys. Alternatively, it would be possible to use composite burden of disease measures such as disability-adjusted life years (DALY) to perform B/R assessments [24]. With this work, we only explored preference elicitation using MCDA swing-weighting. Exploration of different preference elicitation techniques for vaccines is needed as well as more ethical discussions on comparing disease prevented by vaccination and disease induced by vaccination.

In conclusion we have shown that it is feasible to use existing B/R methodology and estimates from eHR databases to assess vaccines B/R successfully. We illustrated how modelling can be used

to build the B/R effects table expressed as the expected number of events in hypothetical populations, which facilitates the comparison of different vaccine effects.

Declaration of Competing Interest

Tom de Smedt, Hanne-Dorthe Emborg, Giorgia Danieli, Talita Duarte-Salles, Consuelo Huerta, Elisa Martin-Merino, Gino Picelli and Lara Tramontan declared no potential conflicts of interest. Kaatje Bollaerts and Daniel Weibel received consultancy fees from GSK for work unrelated to the submitted work. Miriam Sturkenboom declared that she has received grants from Novartis, CDC and Bill & Melinda Gates Foundation, for work unrelated to the submitted work. Edouard Ledent and Vincent Bauchau declared that he is employed by GSK and holds company shares.

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Disclaimer

The results described in this publication are from the proof of concept studies conducted as part of the IMI ADVANCE project with the aim of testing the methodological aspects of the design, conduct and reporting of studies for vaccine benefit-risk monitoring activities. The results presented herein relate solely to the testing of these methodologies and are not intended to inform regulatory or clinical decisions on the benefits and risks of the exposures under investigation. This warning should accompany any use of the results from these studies and they should be used accordingly.

The views expressed in this article are the personal views of the authors and should not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organisations with which the authors are affiliated.

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Appendix A. Members of ADVANCE consortium (October 2018)

A.1. Full partners

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios (www.aemps.es).

ARS-Toscana: Agenzia regionale di sanità della Toscana (https://www.ars.toscana.it/it/).

ASLCR: Azienda Sanitaria Locale della Provincia di Cremona (www.aslcremona.it).

AUH: Aarhus Universitetshospital (kea.au.dk/en/home).

ECDC: European Centre of Disease Prevention and Control (www.ecdc.europa.eu).

EMA: European Medicines Agency (www.ema.europa.eu).

EMC: Erasmus Universitair Medisch Centrum Rotterdam (www.erasmusmc.nl).

GSK: GlaxoSmithKline Biologicals (www.gsk.com).

IDIAP: Jordi Gol Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (http://www.idiapjordigol.com).

JANSSEN: Janssen Vaccines - Prevention B.V. (http://www.janssen.com/infectious-diseases-and-vaccines/crucell).

KI: Karolinska Institutet (ki.se/meb).

LSHTM: London School of Hygiene & Tropical Medicine (www.lshtm.ac.uk).

MHRA: Medicines and Healthcare products Regulatory Agency (www.mhra.gov.uk/).

MSD: Merck Sharp & Dohme Corp. (www.merck.com).

NOVARTIS: Novartis Pharma AG (www.novartisvaccines.com).

OU: The Open University (www.open.ac.uk).

P95: P95 (www.p-95.com).

PEDIANET: Società Servizi Telematici SRL (www.pedianet.it).

PFIZER: Pfizer Limited (www.pfizer.co.uk).

RCGP: Royal College of General Practitioners (www.rcgp.org.uk).

RIVM: Rijksinstituut voor Volksgezondheid en Milieu (www.rivm.nl).

SCIENSANO: Sciensano (https://www.sciensano.be).

SP: Sanofi Pasteur (www.sanofipasteur.com).

SSI: Statens Serum Institut (www.ssi.dk).

SURREY: The University of Surrey (www.surrey.ac.uk).

SYNAPSE: Synapse Research Management Partners, S.L. (www.synapse-managers.com).

TAKEDA: Takeda Pharmaceuticals International GmbH (www.tpi.takeda.com).

UNIBAS-UKBB: Universitaet Basel – Children's Hospital Basel (www.unibas.ch).

UTA: Tampereen Yliopisto (www.uta.fi).

A.2. Associate partners

AIFA: Italian Medicines Agency (www.agenziafarmaco.it).

ANSM: French National Agency for Medicines and Health Products Safety (ansm.sante.fr).

BCF: Brighton Collaboration Foundation (brightoncollaboration.org).

EOF: Helenic Medicines Agency, National Organisation for Medicines (www.eof.gr).

FISABIO: Foundation for the Promotion of Health and Biomedical Research (www.fisabio.es).

HCDCP: Hellenic Centre for Disease Control and Prevention (www.keelpno.gr).

ICL: Imperial College London (www.imperial.ac.uk).

IMB/HPRA: Irish Medicines Board (www.hpra.ie).

IRD: Institut de Recherche et Développement (www.ird.fr).

NCE: National Center for Epidemiology (www.oek.hu).

NSPH: Hellenic National School of Public Health (www.nsph.gr).

PHE: Public Health England (www.gov.uk/government/organisations/public-health-england).

THL: National Institute for Health and Welfare (www.thl.fi).

UMCU: Universitair Medisch Centrum Utrecht (www.umcu.nl).

UOA: University of Athens (www.uoa.gr).

UNIME: University of Messina (www.unime.it).

Vaccine.Grid: Vaccine.Grid (http://www.vaccinegrid.org/).

VVKT: State Medicines Control Agency (www.vvkt.lt).

WUM: Polish Medicines Agency - Warszawski Uniwersytet Medyczny (https://wld.wum.edu.pl/).

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