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Abstract: Background
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Methods
Four participating databases retrieved data from primary care (PC) setting: (BIFAP: Spain), THIN and RCGP RSC: UK) and PEDIANET: Italy); the fifth SIDIAP (Spain) from both PC and hospital settings. The algorithms were defined by setting, data domain (diagnoses, drugs, or tests) and concept sets (specific or unspecified pertussis). BorPer IRs were estimated in children aged 0-14 years enrolled in 2012 and 2014 and followed up until the end of each calendar year and compared with IRs of confirmed pertussis from the ECDC surveillance system (TESSy).
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The number of cases and the estimated BorPer IRs per 100,000 person-years in PC, using data representing 3,173,268 person-years, were 0 (IR=0.0), 21 (IR=4.3), 21 (IR=5.1), 79 (IR=5.7), and 2 (IR=2.3) in BIFAP, SIDIAP, THIN, RCGP RSC and PEDIANET respectively. The IRs for combined specific/unspecified pertussis were higher and were comparable with data from TESSy, except PEDIANET. In SIDIAP the estimated IR was 45.0 when discharge diagnoses were included. The sensitivity and positive predictive value of combined PC specific and unspecific diagnoses for BorPer cases in SIDIAP were 85% and 72%, respectively, based on overlap between hospital and PC diagnoses (adjusted IR=35.5).
Conclusion

This study demonstrated the value of quantifying the impact of different event-finding algorithms across databases and the possibility of benchmarking with disease surveillance data as well as assessing validity estimates when data from different settings can be linked.

Dr Gregory A Poland
Editor-in-Chief, Vaccine

18 January 2019

Dear Dr Poland

We are pleased to submit our paper '*Quantifying outcome misclassification in multi-database studies: the case study of pertussis in the ADVANCE project*' to your Journal, Vaccine, for the ADVANCE supplement. This paper describes the analyses we have performed to quantify the impact of different event-finding algorithms across databases on outcome misclassification. It is the 8th of the series of 10 papers that will be included in the supplement.

On behalf of all co-authors

Dr Rosa Gini

***Author Agreement**

I, Dr. Rosa Gini, declare that all authors have seen and approved the final version of the manuscript being submitted. We warrant that the article is our original work that has not been previously published and is not under consideration for publication elsewhere

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***Declaration of Interest Statement**

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Rosa Gini, Caitlin Dodd, Kaatje Bollaerts, Claudia Bartolini, Giuseppe Roberto, Consuelo Huerta-Alvarez, Elisa Martín-Merino, Talita Duarte-Salles, Gino Picelli, Lara Tramontan, Giorgia Danieli, Ana Correa, Chris McGee, Benedikt Becker, Charlotte Switzer, Jorgen Bauwens, Nicoline van der Maas, Gianfranco Spiteri, Emmanouela Sdona declared no conflicts of interest. Sonja Gandhi-Banga declared that she works for Sanofi Pasteur and holds company shares. Daniel Weibel declared that he has received personal 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.

Abstract

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Quantifying outcome misclassification in multi-database studies: the case study of pertussis in the ADVANCE project

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Abbreviations used

BorPer: Bordetella pertussis

B/R: benefit-risk

ECDC: European Centre for Disease Prevention and Control

IR: incidence rate

PC: primary care

PPV: positive predictive value

Abstract

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1. Introduction

ADVANCE is a public-private collaboration aiming to develop and test a system for rapid benefit-risk (B/R) monitoring of vaccines using existing healthcare databases in Europe [1] (see Appendix for list of consortium members). These databases have proven very useful for studying drug effects and are commonly used in pharmacoepidemiology [2].

Identifying events, such as vaccine-preventable diseases, adverse events of interest, co-morbidities and exposure to vaccination, is a pivotal first step in vaccine B/R studies. Since there is limited or no control over the primary data collection when using existing healthcare databases, event retrieval is usually not perfect. Individuals who experienced the event might not be retrieved, for example if an individual is admitted to hospital for the event but no primary care (PC) diagnosis is recorded, the event will not be retrieved from PC databases and some individuals might be identified as having the event when in fact they did not. In a PC database, this typically happens when the physician had only a suspicion, or if it was a ruled-out diagnosis.

Researchers who access these databases usually develop their own methods to identify events of interest, which are not always fully transparent [3, 4]. Events may be retrieved by combining information from different settings (e.g., PC and hospital) and data domains, for example diagnostic codes, drugs as proxies (e.g. in the case of diabetes), or laboratory measurements. Use of information from more than one data domain, compared with using diagnoses information only, can alter the sensitivity and positive predictive value (PPV) of the event-finding algorithm. This alteration may happen differently in different databases, due to the local characteristics of the database, the population, or the healthcare system.

It is well established that misclassification of events (false positives or false negatives) can introduce bias in epidemiological studies, which can be corrected, to some extent, using statistical methods [5-7]. However, to correct this bias, some validity parameters such as

sensitivity and PPV are required [8]. For this a gold standard and chart reviews are required, which generally make it costly and time-consuming.

In an attempt to develop a systematic approach to quantifying the impact of using different event identification algorithms in multi-national, multi-database studies, the *component algorithm* strategy was developed (Roberto 2016): a set of standardized algorithms, called *components*, are defined and applied in each database. The impact of different algorithms on the resulting estimates of disease occurrence is subsequently measured [9]. In this study we aimed to refine this strategy by further standardizing the process, by developing and applying novel formulas, by using benchmark data from another source and by using a data source which had data from two settings. Since the proof-of-concept studies of ADVANCE focused on pertussis, we used this event as case study.

2. Methods

2.1. Bordetella pertussis disease information

Bordetella pertussis causes pertussis, a vaccine-preventable infectious disease of the respiratory tract. Symptoms include paroxysms of cough typically lasting from 1 to 6 weeks or more and these may be milder in adolescents or immunised children [10, 11]. Several tests are available to confirm *Bordetella pertussis* infection, including culture (which takes up to 14 days), serology and nucleic acid amplification tests. Pertussis is a notifiable infectious disease and cases should be reported to the national surveillance system in all the countries involved in ADVANCE. European Union member states are required to report available data on pertussis cases to the European Centre for Disease Prevention and Control (ECDC). A standardised case definition is used which classifies cases based on clinical, epidemiological and laboratory criteria [12]. All national reports are submitted to the European Surveillance System database (TESSy) managed by the ECDC [13].

2.2. Data sources

We assessed the impact of different event-finding algorithms using five databases that participated in the ADVANCE proof-of-concept studies: BIFAP and SIDIAP (Spain), PEDIANET (Italy) and RCGP RSC and THIN (United Kingdom). All databases were population-based with data from electronic medical records in the PC setting. In SIDIAP, the analyses were restricted to the population in this PC database that could be linked to hospital discharge records. Surveillance data on pertussis were obtained from the TESSy surveillance system through ECDC, a partner of ADVANCE.

2.3. Study population and study design

We used a dynamic cohort study design to study the impact of different event-finding algorithms on the estimated pertussis IRs. Due to the methodological nature of this study, to enable us to explore in more detail a number of strategies, we included a larger cohort in the study population than that in the other ADVANCE studies. Therefore, children aged 0 to 14 years who were registered in the participating databases entered the study cohorts on 1st January 2012 and 1st January 2014, and were followed up during 2012 and 2014, respectively. Children who were born during 2012 or 2014 were followed up from birth until the end of the calendar year. Children who were older than 14 years at any point in the follow-up were excluded. To exclude any previous cases that had been notified before the start of the study period, children who had a record of one of the components of pertussis during the two years prior to one of the cohort entry dates were excluded, unless the component referred to the data domain of drugs (see below for more details on the component definition).

2.4. Selection of component algorithms

A component algorithm is a standardised event-finding algorithm specified by three characteristics: the *setting* of primary data collection (PC or hospital), the *data domain* involved in the algorithm, and the *set of concepts* used to find the codes used to query the

database [9]. The sets of concepts were created by aggregating the codes that were obtained from an initial proposed list, completed with a literature review and pertussis case definitions [2, 13]. The CodeMapper tool was used to support the process [14]. Labelling and classification of identified concepts, as well as the construction of the components, were conducted by one of the authors who is a pertussis expert (NvdM). As a result, seven concept sets were created (**Table 1**) [15, 16]. In particular, two sets of concepts belonged to the diagnoses data domain: the set labelled '(*Bordetella pertussis*)' included three concepts which specifically indicated *Bordetella pertussis* as the causative agent of the infection, while the set labelled '(pertussis unspecified)' included five concepts indicating unspecified pertussis. The corresponding codes and free text keywords are given in **Supplementary Table 1**.

The primary components associating concepts with settings (PC and hospital) are described in **Table 2**. Some secondary components, combining primary components in pre-defined temporal relations (e.g., symptoms in the presence of a drug prescription in the previous 30 days) were also created.

2.5. Analysis

Each database manager received an R-coded programme (quality checked by double-coding against Stata) which was programmed using the pre-specified common data model [1]. These programmes produced aggregated outputs, which were then transferred to the remote research environment. Event-finding algorithms were created as logical combinations of individual components using Boolean operators. For example, the two components 'PC diagnosis, specific' and 'PC diagnosis, unspecified' were combined in one component: 'PC specific OR unspecified diagnoses', which detected all individuals that were positive for either of the original components. Based on the different event-finding algorithms, incidence rates (IRs) were estimated using the number of persons retrieved with the respective events as numerator and the follow-up person-time as denominator (see **Supplementary File 1**).

Age and country-specific incidences per 100,000 person-years of confirmed BorPer for both 2012 and 2014 were calculated for children aged 0-14 years. The calculations used the reported confirmed cases in the TESSy surveillance system in 2012 and 2014 as the numerator, and person-time from population distributions in EUROSTAT for 2012 and 2014 as the denominator [17]. Exact Poisson confidence intervals (95% CI) were calculated [18].

Some formulae link the true proportion of BorP and/or validity indices with each other and with the observed proportion of the component algorithms (**Table 3**). These formulas are explained in **Supplementary File 2**.

In this study we considered Π = IR (see **Supplementary File 1**) and we assumed that for all algorithms A and B, the proportion of true positives among those detected by both algorithms (PPV of A **AND** B), was the same as the PPV of A OR B, whichever was the highest, which may be considered the most conservative assumption.

Since the concept set labelled '*Bordetella pertussis*' was composed of codes explicitly mentioning the bacterium, we considered that components based on this had a high likelihood of extracting true cases. Therefore we considered it was conservative to assume that the PPV for 'PC diagnosis, specific' and for 'inpatient diagnosis, specific' was 90%. We explored two scenarios for the cases extracted by the components associated with the concept set labelled 'pertussis unspecified', assuming that the PPV was 70% or 50%. The PPV for the component 'positive laboratory results' was assumed to be 100%. Finally, we assumed that all true cases in SIDIAP were recorded in at least one of the diagnosis or laboratory-based components: this assumption may overestimate sensitivity. Based on this and on the formulae in Table 3, we derived sensitivity and PPV estimates for the algorithm 'PC specific OR unspecified diagnosis' in SIDIAP, and the adjusted IR of BorPer in the study population.

3. Results

3.1. Study population

We followed 3,173,268 person-years of children during the study period: 488,847 from the SIDIAP database, 796,324 from BIFAP, 88,754 from PEDIANET, 1,387,939 from THIN and 411,404 from RCGP RSC (**Table 4**). The percentages of children aged 0 or 1 years in the population aged 0-14 years in Spain were 12.1% and 16.1% in SIDIAP in BIFAP, respectively, compared with 13.5% in the EUROSTAT Spanish population. In the UK the percentages were 15.1% and 14.8% in RCGP RSC and THIN 13.0%, respectively, compared with 14.3% in the EUROSTAT UK population and in PEDIANET (vs 12.9%); in (vs 14.3%).

3.2. Incidence rates estimated by the algorithms

The IRs for the component and composite algorithms, as well as the benchmark IRs from the TESSy surveillance system are illustrated in Figure 1 and documented in **Table 4**. The IRs estimated from the TESSy surveillance system in 2012 and 2014 for children aged 0-14 years were 21.2 (95% CI: 20.5; 22.0) for Spain, 13.4 (95% CI: 13.0; 13.9) for the United Kingdom, and 5.4 (95% CI: 5.1; .8) for Italy. The number of cases of 'PC diagnosis, specific' (and IRs per 100,000 PY) were 0 (0.0), 21 (4.3), 21 (5.1), 79 (5.7), and 2 (2.3) in the BIFAP, SIDIAP, RCGP RSC, THIN and PEDIANET databases, respectively. The component 'PC diagnosis, unspecified' had a higher IR in all databases, and combining the two components (one OR the other) increased the number of cases detected and the IRs to 135 (IR=17.0), 194 (IR=39.6), 39 (IR=43.9), 246 (IR=17.7), and 91 (IR=22.1), respectively. In BIFAP, SIDIAP, RCGP RSC and THIN, when taking into account that the unspecified component may have captured some false positives, the IRs were comparable with the corresponding IR from the TESSy surveillance system (17.0 vs 21.2; 39.6 vs. 21.2; 22.1 vs. 13.4; 17.7 vs. 13.4, respectively). In PEDIANET the composite IR was much higher than the IR from the TESSy database (43.9 vs 5.4).

SIDIAP was the only database in which data from both the PC and hospital settings could be linked. The total number of cases in 'PC OR inpatient diagnosis' in SIDIAP was 220 (IR=45.0), including 26 (12%) that had not been identified in the PC setting. Unlike in the PC setting, where most of the diagnoses were unspecified, in the inpatient setting there were around half specific and half unspecified diagnoses.

In BIFAP, the 'symptoms and drugs within 30 days' component identified 122 cases with an IR of 15.3 per 100,000 PYs. When this component was combined with PC diagnoses, the IR increased to 32.0, which was higher than the reference IR which was 21.2. Almost none of the children aged 0 or 1 year old in 'symptoms in infants' in any database had a corresponding prescription or dispensing of macrolides in the 'symptoms in infants and drugs within 30 days' component.

The 'test' component was available in all databases and had a relatively high IR (from 4.8 in BIFAP to 42.8 in PEDIANET). 'Positive laboratory results' were only available in SIDIAP and THIN, with only 19 and 3 cases, respectively. In SIDIAP, 3 of the 19 cases were not captured by a diagnosis in either primary care or hospital settings.

In **Supplementary Figure 1** and **Supplementary Table 2**, the analysis was repeated for infants (children aged 0 or 1). The IRs in this subpopulation were around three times higher than the IRs in the overall study population. The findings confirmed the relationship between components observed in the general study population, with the exection of 'PC OR inpatient diagnosis' in SIDIAP (n=98), where 25.5% (n=25) were not retrieved from the PC setting, vs 11.8% in the overall study population.

In SIDIAP we explored two scenarios, corresponding to different assumptions for PPV of 'PC diagnosis, unspecified' and of 'inpatient diagnosis, unspecified': in the first, this was 70%, in the second 50%. As a consequence, in the first scenario 'PC specific OR unspecified diagnosis' had a PPV of 72% (or, in the second: 54%) and a sensitivity of 85% (or, in the

second: 83%). Based on this estimate, the adjusted IR of BorPer in the SIDIAP study population was 35.5 per 100,000 PY (or, in the second scenario: 25.9) vs the TESSy surveillance system IR 21.2.

4. Discussion

We assessed several algorithms as potential strategies to detect cases of pertussis and thus estimate the IR in five European healthcare databases. The IRs estimated by these algorithms were heterogeneous within and between databases. However, there was at least one IR estimated by the algorithms in each database that was comparable with the reference value from the TESSy surveillance system, although some false positives were probably included. Based on a few assumptions, that may have overestimated sensitivity, it was estimated that the PPV and sensitivity of the algorithm detecting PC diagnoses in SIDIAP ranged from 54% to 72% and from 83% to 85%, respectively, and that the IRs of *Bordetella pertussis* in the corresponding population ranged from 25.9 to 35.5 per 100,000 person-years, against the TESSy surveillance system estimate of 21.2.

4.1. General comments

Three components were expected to have a high PPV: PC and inpatient specific diagnoses, and positive laboratory results. Two were expected to have lower PPV (PC and inpatient unspecified diagnoses). One was expected to be sensitive (prescription of a laboratory test), two were very unspecific (symptoms and symptoms in infants) and were planned to be used only in combination with the last component (prescription or use of macrolides) in a 30-days window of time.

In all the databases, at least one composite algorithm estimated a number of cases that was compatible with the number expected from the TESSy surveillance system, but this was not with the combination of the components which was expected to have a high PPV (specific diagnoses and laboratory tests) in any of the databases. One possible explanation could be that

it takes several days to confirm the diagnosis of pertussis after the disease is suspected, and there may be no opportunity for the specific diagnosis to be recorded if the patient does not return to the healthcare facility. Another possible explanation may be that the medical personnel may not see the need to update the record for the purposes of clinical care. This attitude may be influenced by the level of awareness of possible reuse of electronic records for research purposes. These potential explanations may have varying levels of impact in the different databases. For example, in some databases we observed that among the cases detected by a diagnostic component (unspecified or specific), the specific diagnosis was more frequent, indicating that some clinicians might have been more aware about potential research uses of the databases and therefore entered specific diagnoses rather than free text, which was common for unspecified diagnoses.

Based on the results of this study, in all the databases it is now possible to design sensitivity analysis using a more specific (but less sensitive) definition of pertussis. In case of heterogeneity in the results of a study on pertussis, designing such sensitivity analyses should be considered as a valid option. On the other hand, in all the databases there is now a possible choice among different sensitive algorithms: we explored several of them, among which 'unspecified diagnoses' (the most conservative) and 'test' (the least conservative). Even though these algorithms are likely to have lower PPVs, they may still be useful for sensitivity analyses, especially if there are reasons to think that a specific algorithm could be affected by differential misclassification. For example, pertussis may be more readily suspected and tested for in unvaccinated children, and therefore would be recorded in a more accurate manner.

We developed a component for infants that we though would be sensitive and, although it was likely to have a low PPV, it was less prone to differential misclassification, because it captured symptoms that physicians may not think of as being related with pertussis. However

this component proved to be unusable; in reality, when we added a secondary component for concurrent macrolide use there were very few cases that would have been expected to be found in infants with an infection. In contrast, we developed a component specifically for the symptom 'pertussis-like cough' *(tos pertusoide* in Spanish language) that was apparently specific for pertussis cases that were only found in the BIFAP database. Not only did the majority of cases have a concurrent record of prescription of macrolides, but a manual review of a sample of 100 records including physician free text comments, found 2 cases of unspecified pertussis and 2 cases of suspected pertussis. Therefore, this component may be considered for sensitivity analysis.

4.2. Compatibility with TESSy and seroprevalence surveys

In this study we were able to compare the IRs estimated for paediatric cohorts in five databases using the various algorithms with the national IR estimates from ECDC's TESSy surveillance database. The cases captured by the two types of systems were expected to be slightly different, for various reasons. First, TESSy provides estimates at the national level using census denominators, while three of the databases participating in this study had a regional/multiregional scope (SIDIAP, BIFAP and PEDIANET) and two were based on a representative sample of the national population (THIN, RCGP RSC). Therefore it is possible that some clusters of the infectious disease might be under or over-represented in these database. Second, we collected only confirmed cases from TESSy, while some true cases captured by a PC database with a sensitive algorithm may never be confirmed (under ascertainment), or may never be notified (underreporting) [19, 20]. Thus the databases may be a complementary source of true cases which are not notified, while adding potentially false positive cases. Finally, the TESSy data for pertussis may also be affected by under ascertainment and underreporting.

The IR found for PEDIANET, which was much higher than the IR estimate from TESSy for Italy (43.9 vs 5.4), may be explained by a combination of both phenomena discussed above. PEDIANET collects data from PC physicians working in the Italian region Veneto, in the North East of the country. The Regional Office for Infectious Diseases of the Veneto Region provided an estimated IR of 10.0 to the data custodians of PEDIANET. This shows that the region had a higher pertussis notification rate than at the national level for 2012 and 2014, although almost all the diagnoses in PEDIANET were unspecified. However, the regional estimate could be underestimated because of under ascertainment. Finally, as in the other databases, many cases in PEDIANET could be false positives. In general, if estimates of the PPV of the diagnoses are available, the estimated IR from databases can provide a quantitative estimate of under ascertainment and under notification in TESSy. Vice versa, if under notification to TESSy is known to be small, estimates of the PPV for the algorithm can be obtained.

Results from seroprevalence surveys have provided estimates for the incidence of *Bordetella pertussis* infection [21-23]. These have provided prevalence estimates beyond those of the surveillance systems, partly as they also capture asymptomatic or mildly symptomatic infections. On the contrary, in this study, we observed that estimates of incidence obtained from databases are roughly comparable with those of TESSy.

4.3. Scope of the component strategy

The scope of this component strategy goes beyond ADVANCE and has the potential of being a comprehensive tool to address heterogeneity and disease misclassification in databases, particularly in multi-database pharmacoepidemiology studies, when the characteristics of the databases affect the operational definition of the outcomes and benchmarking.

Inspection of components can provide knowledge that can inform the interpretation of the heterogeneity of the study results. The component strategy can support quantitative bias

analysis. In this study, we first developed a set of components with increasing sensitivity and decreasing PPVs. We explored several scenarios for possible PPVs of the components, but in many European databases, estimating directly the PPV of simple algorithms such as components is feasible in a relatively timely and inexpensive way [24-26]. If this is possible, then a consequence of our formulas in Table 3 is that the only value needed to obtain a complete estimate of validity is the sensitivity of the composition of the algorithms, as the rest can be analytically derived. In many cases, sensitivity of the composition could be argued to be very high. In the case of pertussis, we can speculate for instance that cases that were missed from SIDIAP were either seen in a hospital outside of the network that transmits their data to the database, or were very mild and did not require medical attention. The percentage of cases with those characteristics may be estimated from external sources. If estimating this quantity is not possible, then the formulas of Table 3 can still be applied, and they can provide an upper limit for the sensitivity of all the components, that is, the maximum possible sensitivity: to obtain this, it is sufficient to make an assumption on the sensitivity of the *composite* algorithm.

If the validity of the variables that enter the analysis can be convincingly proven to be high, this analysis provides evidence that the study results are robust to misclassification. If not, comparing the distribution of components across exposure strata can indicate if differential misclassification is to be suspected. If it is suspected, it can be an important source of bias, as shown by the simulations we report here, as well as in other studies [5, 6]. Components with different validity can, thus, be used to design sensitivity analyses of the study results, applying repeated adjustments for validity to check if the result is robust. If both the PPV and sensitivity are suspected to be non-differential, then the estimate may be unbiased, but the confidence intervals of the estimate need to be adjusted for validity [8]. In future work, the estimates provided by the component strategy could be validated against actual validation

studies. Moreover, the components could be analysed using latent class modelling, which enables to estimate the validity conditional on various covariates, e.g., age [27].

4.4. Strengths and limitations

In this study, we used standardised component algorithms as a transparent way of documenting the data extraction process across multiple databases. At the same time, we could also perform a qualitative evaluation of the expected validity of each component Bordetella pertussis, based on its specified semantics and setting. Quantitative scenarios for the validity of each component can also be made using the same approach. We showed that estimates of the validity of various composite algorithms can then be derived in a purely algebraic manner. We could use the incidence estimates based on data from the TESSy surveillance system, which is where European Union member states are required to report pertussis cases, as a reference value, although we cannot exclude the possibility that they may also be subject to under ascertainment and underreporting.

The estimates of sensitivity that we obtained for SIDIAP cannot be generalised to the other PC databases. The sensitivity of the PC databases depends on how often a person with the disease symptoms would seek attention in a PC practice. Although in all the databases, the PC physicians have a gatekeeper role, emergency care can be sought without PC referral, and PC practices may not be accessible at night or weekends. Referrals from other settings may be recorded in the PC practice, but no automatic mechanism is in place. In the absence of a database-specific estimate, estimates from another database are a realistic alternative to assuming that sensitivity is 100%.

5. Conclusions

This study demonstrated the value of quantifying the impact of different event-finding algorithms across databases and the possibility of benchmarking with disease surveillance data as well as assessing validity estimates when data from different settings can be linked.

405 The validity parameters could be used to correct disease IR estimates from healthcare
406 databases.
407

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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 relate solely to the methodological testing 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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Declaration of potential conflicts of interest

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Figure caption

Figure 1: Study results for the incidence of tested component and composite algorithms. For each component algorithm the incidence rate per 100,000 person-years is shown. For the composite algorithms, the incidence rates were stratified per type of case: cases detected only by the left-hand component (indicated in the label before the Boolean operator 'OR'), cases detected by both components, and cases detected by the right-hand component (indicated in the label after the key Boolean operator word 'OR'). The dashed line represents the national incidence rate per 100,000 person-years based on data from the TESSy surveillance system. Data for years 2012 and 2014 were pooled.

Appendix: Members of ADVANCE consortium (October 2018)

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)

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)

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

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

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

592 WUM: Polish Medicines Agency - Warszawski Uniwersytet Medyczny

593 (https://wld.wum.edu.pl/)

594

Table 1: Sets of concepts selected for the component algorithms

Each set of concepts can contain one or more concepts, each described and, if available, with a Concept Unique Identifier of the Unified Medical Language System.

Concept set label	Concept set description	Concept	Concept Unique Identifier
(*Bordetella pertussis*)	Concepts referring to diagnoses specifically mentioning pertussis induced by an infection of *Bordetella pertussis*	*Bordetella pertussis*	C0043167
		Whooping cough due to *Bordetella pertussis* without pneumonia	C2887068
		Whooping cough due to *Bordetella pertussis* with pneumonia	C2887069
(Pertussis unspecified)	Concepts referring to diagnoses which refer to pertussis, but without a specific indication that *Bordetella pertussis* is responsible for the infection	Whooping cough due to unspecified organism	C0043168
		Bordetella infections	C0006015

Concept set label	Concept set description	Concept	Concept
		Whooping cough-like syndrome	C0343485
		Notification of whooping cough	
		Pneumonia in pertussis	C0155865
(Symptoms compatible with pertussis)	This set of concepts was introduced because the Spanish translation of 'whooping cough' was found to be considered by physicians as a symptom, not as a diagnosis	Concept of 'tos pertusoide' in Spanish general practice	
		Apnea	C0003578
(Symptoms in infants)		Cyanosis	C0010520
	Concepts referring to symptoms that were found to be predictive of pertussis in infants [13, 14]	Post-tussive vomiting	C1740793
		Paroxysms of coughing	C0231911
(Macrolides)	Use of macrolides	Macrolides	
		Polymerase chain reaction test	
(*Bordetella pertussis* test)	The concepts listed in this set indicate the prescription of tests that are considered to be confirmatory of a *Bordetella pertussis* infection	Culture or serology	
		Isolation of *Bordetella pertussis* from a clinical specimen	

Concept set label	Concept set description	Concept	Concept
(Positive result from a *Bordetella pertussis* test)	The concepts listed in this set indicate a positive result from a tests confirmatory of a *Bordetella pertussis* infection	Positive polymerase chain reaction test Positive culture or serology Positive isolation of *Bordetella pertussis* from a clinical specimen	

Table 2: Components for pertussis

The concept sets referred to by the words in round parentheses can be found in Table 1.

Name	**Setting**	**Data domain**	**Concept set**
PC diagnosis, specific	Primary care practice	Diagnosis	(*Bordetella pertussis*)
Inpatient diagnosis, specific	Hospital	Diagnosis	(*Bordetella pertussis*)
PC diagnosis, unspecified	Primary care practice	Diagnosis	(Pertussis unspecified)
Inpatient diagnosis, unspecified	Hospital	Diagnosis	(Pertussis unspecified)
Symptoms	Primary care practice	Diagnosis or signs/symptoms	(Symptoms compatible with pertussis)
Symptoms in infants	Primary care practice	Diagnosis or signs/symptoms	(Symptoms in infants)

Name	Setting	Data domain	Concept set
Test	Any setting where a test can be prescribed, or facility where the test is administered	Laboratory test	(*Bordetella pertussis* test)
Positive laboratory results	Any setting where a health professional records the results of a test, or facility where the results of the test are generated	Results from laboratory test	(Positive result from a *Bordetella pertussis* test)
Drug use	Facility dispensing medications or primary care practice issuing prescriptions	Drug	(Macrolides)
Secondary components			
Symptoms and drugs within 30 days	A patient is positive if they have both a record of symptoms and of drug use, and the interval between the dates is less than 30 days		
Symptoms in infants and drugs within 30 days	A patient is positive if they are 0 or 1 and has both a record of symptoms in infants and of drug use, and the interval between the dates is less than 30 days		

Table 3: Analytic formulae linking the true proportion of pertussis and validity indices of one or two algorithms

In the formulas, Π is the true proportion of cases of pertussis, P is the proportion of cases detected by the algorithm, SE is the sensitivity and PPV is the positive predictive value of the algorithm.

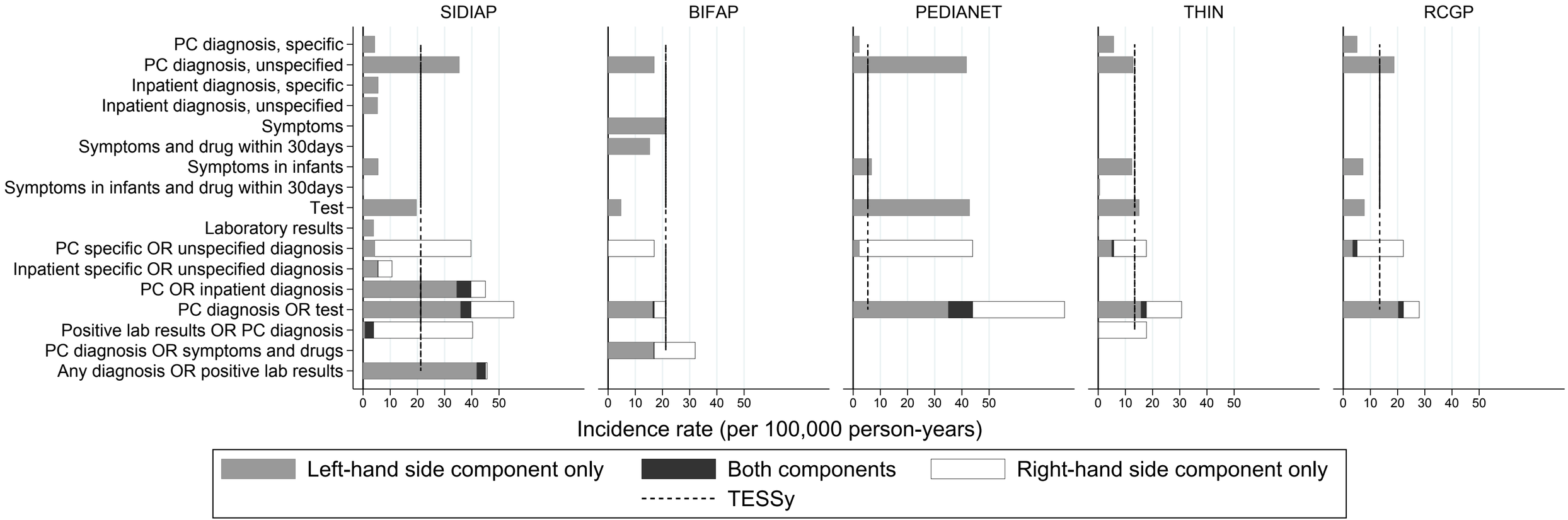
Known parameters	**Formula to derive another parameter**
One algorithm	
PPV and SE	$\pi = \frac{P \times PPV}{SE}$
PPV and Π	$SE = \frac{P \times PPV}{\pi}$
SE and Π	$PPV = \frac{SE \times \pi}{P}$
Two algorithms A and B	
SE of A, of B, and of A **AND** B	$SE_{A\ \mathbf{OR}\ B} = SE_A + SE_B - SE_{A\ \mathbf{AND}\ B}$
Π and PPV of A, of B, and of A **AND** B	$SE_{A\ \mathbf{OR}\ B} = \frac{P_A \times PPV_A}{\pi} + \frac{P_B \times PPV_B}{\pi} - \frac{P_{A\ \mathbf{AND}\ B} \times PPV_{A\ \mathbf{AND}\ B}}{\pi}$
SE of A **OR** B, and PPV of A, of B, and of A **AND** B	$\pi = \frac{P_A \times PPV_A + P_B \times PPV_B - P_{A\ \mathbf{AND}\ B} \times PPV_{A\ \mathbf{AND}\ B}}{SE_{A\ \mathbf{OR}\ B}}$
PPV of A, of B, and of A **AND** B	$PPV_{A\ \mathbf{OR}\ B} = \frac{P_A \times PPV_A + P_B \times PPV_B - P_{A\ \mathbf{AND}\ B} \times PPV_{A\ \mathbf{AND}\ B}}{P_{A\ \mathbf{OR}\ B}}$

Table 4

Table 4: Study results. Number of person-years (PYs) entering the study in each database. Incidence rates of pertussis per 100,000 children aged 0-14, with 95% confidence interval (CI), from the TESSy surveillance system in the corresponding country and the estimate incidence rate per 100,000 for each component algorithm are shown. In composite algorithms, the incidence rates were stratified per type of case: cases detected only by the left-hand component (indicated in the label before the keyword 'OR'), cases detected by both components, and cases detected by the right-hand component (indicated in the label after the keyword 'OR'). Data for years 2012 and 2014 were pooled.

DB	SIDIAP (Spain)				BIFAP (Spain)				PEDIANET (Italy)				THIN (United Kingdom)				RCGP (United Kingdom)			
Person-years	488,847				796,324				88, 754				1,387,939				411,404			
TESSy (IR and 95% CI)	21.2 (20.5-22.0)				21.2 (20.5-22.0)				5.4 (5.1-5.8)				13.4 (13.0-13.9)				13.4 (13.0-13.9)			
Component algorithms (N and IR per 100,000 PYs)																				
PC diagnosis, specific	21 (4.3)				0 (0.0)				2 (2.3)				79 (5.7)				21 (5.1)			
PC diagnosis, unspecified	173 (35.4)				135 (17.0)				37 (41.7)				178 (12.8)				77 (18.7)			
Inpatient diagnosis, specific	27 (5.5)																			
Inpatient diagnosis, unspecified	26 (5.3)																			
Symptoms					166 (20.8)															
Symptoms and drug within 30days					122 (15.3)															
Symptoms in infants	27 (5.5)								6 (6.8)				172 (12.4)				30 (7.3)			
Symptoms in infants and drug within 30days	1 (0.2)												8 (0.6)							
Test	96 (19.6)				38 (4.8)				38 (42.8)				209 (15.1)				32 (7.8)			
Positive laboratory results	19 (3.9)				0 (0.0)								3 (0.2)							
Composite algorithms																				
	N (IR)	N (IR) in left-hand component only	N (IR) In both components	N (IR) In right-hand component only	N (IR)	N (IR) in left-hand component only	N (IR) In both components	N (IR) In right-hand component only	N (IR)	N (IR) in left-hand component only	N (IR) In both components	N (IR) In right-hand component only	N (IR)	N (IR) in left-hand component only	N (IR) In both components	N (IR) In right-hand component only	N (IR)	N (IR) in left-hand component only	N (IR) In both components	N (IR) In right-hand component only
PC specific OR unspecified diagnosis	194 (39.6)	21 (4.3)	0 (0.0)	173 (35.4)	135 (17.0)	0 (0.0)	0 (0.0)	135 (17.0)	39 (43.9)	2 (2.2)	0 (0.0)	37 (41.7)	246 (17.7)	68 (4.9)	11 (0.8)	167 (12.0)	91 (22.1)	14 (3.4)	7 (1.7)	70 (17.0)
Inpatient specific OR unspecified diagnosis	52 (10.6)	25 (5.1)	1 (0.2)	26 (5.3)																
PC OR inpatient diagnosis	220 (45.0)	168 (34.3)	26 (5.3)	26 (5.3)																
PC diagnosis OR test	271 (55.4)	77 (15.8)	19 (3.9)	175 (35.8)	168 (21.1)	33 (4.1)	5 (0.6)	130 (16.3)	69 (77.7)	30 (33.8)	8 (9.0)	31 (34.9)	426 (30.7)	181 (13.0)	29 (2.1)	217 (15.6)	115 (28.0)	24 (5.8)	8 (1.9)	83 (20.2)
Positive lab results OR PC diagnosis	197 (40.3)	3 (0.6)	16 (3.3)	178 (36.4)	135 (17.0)	0 (0.0)	0 (0.0)	135 (17.0)					247 (17.8)	1 (0.1)	2 (0.1)	244 (17.6)				
PC diagnosis OR symptoms and drugs					255 (32.0)	133 (16.7)	2 (0.3)	120 (15.1)												
Any diagnosis OR positive lab results	223 (45.6)	204 (41.7)	16 (3.3)	3 (0.6)																

Figure 1


SIDIAP
BIFAP
PEDIANET
THIN
RCGP
PC diagnosis, specific
PC diagnosis, unspecified
Inpatient diagnosis, specific
Inpatient diagnosis, unspecified
Symptoms
Symptoms and drug within 30days
Symptoms in infants
Symptoms in infants and drug within 30days
Test
Laboratory results
PC specific OR unspecified diagnosis
Inpatient specific OR unspecified diagnosis
PC OR inpatient diagnosis
PC diagnosis OR test
Positive lab results OR PC diagnosis
PC diagnosis OR symptoms and drugs
Any diagnosis OR positive lab results
0 10 20 30 40 50
Incidence rate (per 100,000 person-years)
Left-hand side component only
Both components
Right-hand side component only
TESSy

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Supplemental Figure 1

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