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The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology

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Abstract

Background: The test-negative design is an increasingly popular approach for estimating vaccine effectiveness (VE) due to its efficiency. This review aims to examine published test-negative design studies of VE and to explore similarities and differences in methodological choices for different diseases and vaccines.

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POTENTIAL CONFLICTS OF INTEREST

BJC has received honoraria from Sanofi Pasteur and Roche. The authors report no other potential conflicts of interest.

Methods: We conducted a systematic search on PubMed, Web of Science, and Medline, for studies reporting the effectiveness of any vaccines using a test-negative design. We screened titles and abstracts, and reviewed full texts to identify relevant articles. We created a standardized form for each included article to extract information on the pathogen of interest, vaccine(s) being evaluated, study setting, clinical case definition, choices of cases and controls, and statistical approaches used to estimate VE.

Results: We identified a total of 348 articles, including studies on VE against influenza virus (n=253), rotavirus (n=48), pneumococcus (n=24), and nine other pathogens. Clinical case definitions used to enroll patients were similar by pathogens of interest but the sets of symptoms that defined them varied substantially. Controls could be those testing negative for the pathogen of interest, those testing positive for non-vaccine type of the pathogen of interest, or a subset of those testing positive for alternative pathogens. Most studies controlled for age, calendar time, and comorbidities.

Conclusions: Our review highlights similarities and differences in the application of the test-negative design that deserve further examination. If vaccination reduces disease severity in breakthrough infections, particular care must be taken in interpreting vaccine effectiveness estimates from test-negative design studies.

INTRODUCTION

Vaccines have made major contributions to global health (1). While some vaccines confer strong life-long protection against infections, other vaccines provide more moderate or short-lived protection. Evolution in circulating pathogens can also modify vaccine effectiveness (VE), and some vaccines such as the influenza vaccine need to be updated regularly. Monitoring of VE to confirm continued effectiveness is an essential component of vaccination programmes (2). For reasons of ethics and logistics, observational studies rather than randomized trials are typically used to monitor VE post-licensure (3).

Case–control studies present a particularly efficient approach for monitoring VE because they tend to be faster and cheaper than cohort studies (4). A key design issue in case–control studies is the choice of controls, who should represent the exposure distribution in the source population from which the cases arose (5). Inappropriate control selection can lead to selection bias and, consequently, invalid conclusions (6). When cases have one particular infection or illness that is identified in a medical setting, controls can be selected from the general community, or from among patients with illnesses that are unlikely to be associated with both the disease and exposure of interest. For example, in a case–control study of cholera VE, cases might be selected from patients admitted to hospital with laboratory-confirmed cholera, while controls could be persons from the general community, or persons admitted to hospital with other diagnoses unrelated to cholera and no recent diarrhea or vomiting, to avoid potential misclassification of a case as a control (7).

In some situations, it is possible to draw a causal inference on the effect of particular exposures from observational studies. Because common factors may affect both the receipt of vaccination and the risk of infection, it is typically inappropriate to use the crude exposure odds ratio as a measure of the causal effect of the vaccine on the risk of disease. However, if

these confounding factors are taken into account, for example by statistical adjustment, given certain assumptions one minus the adjusted odds ratio can be used as an estimate of VE (8). Note that the VE is not a measure of the association between vaccination and infection status, but rather is a causal estimate of the effectiveness of the vaccine in preventing the disease. In case–control and test-negative design studies, we adjust the odds ratio for potential confounders, in order to estimate the causal effect of vaccination, i.e. the vaccine *effectiveness* (9, 10).

The "test-negative design" , in which the same clinical case definition is used for enrollment of both cases and controls, and laboratory testing is subsequently used to distinguish which patients were cases and which were controls, is increasingly used in VE studies (11). For example, patients with influenza-like illness could be enrolled in outpatient clinics, demographic information and influenza vaccination history obtained, and specimens collected for testing. Influenza VE can then be estimated by comparing influenza vaccination status in patients testing positive for influenza with those testing negative for influenza. In contrast to the traditional case–control design, controls in the test-negative design would meet the same clinical case definition as cases and are distinguished by laboratory testing results. An important advantage of this approach is the efficiency of enrolling cases and controls in the same location with the same case definition, thereby assuring that they have arisen from the same source population and reducing potential selection biases due to differential healthcare-seeking behavior (8). As with any case–control study, it is crucial to minimize false-positive cases (12) and so the laboratory test used must be highly specific (11, 13). While the test-negative design is typically presented as a variant of the case–control design (14), this study design can also be thought of as a variant of a cohort design where the entire population is the cohort, while the test-negative design includes only members for whom outcomes are ascertained (8, 15).

The test-negative design has been used under a number of different names for different vaccines. One of the earliest examples is the "indirect cohort" or Broome method. Broome *et al.* (16) showed that assuming pneumococcal vaccination did not affect the risk of non-vaccine-type pneumococcal infections among vaccinees (an assumption verified in early randomized controlled trials of polysaccharide vaccines (17, 18)), the odds of vaccination in those infected with non-vaccine-type and vaccine-type disease can be compared to estimate the effectiveness of pneumococcal vaccines. The widest application of the test-negative design has been for assessment of influenza VE, first done by Skowronski *et al.* in Canada, 2004/05 (19), and increasingly used since (11). The study design has been extended beyond vaccine studies, for example to identify risk factors for disease (20), and to improve the efficiency of cluster randomized intervention trials (21, 22). However, in this paper we focus only on vaccine studies.

Whether the application of the test-negative design for the study of VE against different pathogens is appropriate needs further evaluation, and the potential biases affecting VE estimates need to be ascertained within the context of the specific pathogen under study. The objectives of this study were therefore: to review published VE studies employing the test-negative design; to explore choices that have been made in the application of this design to

different vaccines; to explain the rationale for these choices; and to provide recommendations for the continued use of this approach to monitor VE.

METHODS

Search strategy and selection criteria

We followed the PRISMA guidelines in conducting this review. A systematic search was carried out on PubMed, Web of Science (WOS) and Medline, using the following terms on the 24 October 2018:

1. "vaccine" OR "vaccination"
2. "effectiveness" OR "efficacy"
3. #1 AND #2
4. #3 OR "VE"
5. "test-negative" OR "test negative" OR "TND" OR "indirect cohort" OR "quasi-cohort" OR "quasi cohort" OR "case–control" OR "case control" OR "case-referent" OR "case referent"
6. #4 AND #5

Articles published in any languages were considered. We also screened the reference lists of retrieved articles to identify any additional eligible studies.

Screening

We first screened the list of titles returned from the search strategy to eliminate duplicates. HC and BJC independently screened all remaining titles. We defined test-negative design studies as those where all participants met the same clinical case definition (or the same set of syndromes), and cases and controls were discriminated by laboratory test results. Studies were eligible for inclusion if they reported results of a test-negative design to estimate the effectiveness of any type of vaccine for any pathogens in a defined population or population segment.

We excluded studies that did not use a test-negative design including randomized controlled trials (both conventional trials or trials that use the design to assess endpoints), prospective cohort studies, conventional case–control studies (defined as those enrolling controls not tested for the disease under study), studies that estimated VE using the screening method, and animal studies. We also excluded simulation studies, review articles, commentaries, letters, protocols, abstracts and book chapters. We excluded mid-season (interim) VE reports if they had been superseded by an end-of-season report and studies that re-analyzed data published by included studies. In the case where a study has been extended or followed up, we included only the more recent published article.

Data extraction and analysis

Data were extracted from included articles using a standardized form in an electronic database created in REDCap (23). HC and SF independently extracted information on each

pathogen of interest, study setting, clinical case definition, choices of cases and controls, type(s) of vaccine being evaluated, and the statistical model used, including the variables included, to estimate VE.

A key characteristic of the test-negative design is the use of a control group with the same clinical presentation but testing negative for the pathogen of interest. This group of individuals may either be positive for alternative pathogens or negative for all pathogens (pan-negative or undiagnosed). As with any case–control study, the selection of controls should be made independently of exposure status to avoid selection bias. A situation where this assumption may be violated is the presence of viral interference, where vaccinated individuals may be more likely to be infected by alternative pathogens (24-26). Using such a group may inflate vaccination coverage among controls, misrepresenting the underlying population. While a meta-analysis showed no difference in VE estimates between choices of control groups among influenza VE studies, this is uncertain for non-influenza VE studies. It is also uncertain if the choice of non-vaccine type as controls is appropriate. We therefore categorized patients into six categories: tested-positive, vaccine type, non-vaccine type, tested-negative, alternative pathogens, and undiagnosed, according to the pathogen of interest and vaccine component (Table 1). To simplify comparisons between pathogens and vaccines, here the word “type” is used in a broad sense to refer also to subtype, genotype, serotype, species, subspecies, or strain of the pathogen of interest, depending on the specific pathogen (Table 1). If individuals were test-positive for the pathogen of interest, they may be further categorized as being matched to the vaccine type (i.e. tested-positive for a type that was a component of the vaccine) or non-vaccine type. For example, for pneumococcus, those serotypes covered by vaccine (PCV7, PCV10, PCV13, PCV14, PPV23) were defined as vaccine type and those not covered were defined as non-vaccine type. Similarly, when estimating influenza VE against influenza A(H1N1)pdm09 for the monovalent influenza A(H1N1)pdm09 vaccine in 2009/10, influenza subtype A(H1N1)pdm09 was defined as vaccine-type while pre-pandemic influenza A(H1N1), influenza A(H3N2) and influenza B were defined as non-vaccine type. If individuals were test-negative for the pathogen of interest, they may be categorized as positive for alternative pathogen (i.e. patients whose specimens tested positive for pathogen species other than the one of interest), or undiagnosed (i.e. patients whose specimens tested negative for all suspected pathogens).

RESULTS

Included studies

Our search on PubMed, Web of Science and Medline identified a total of 1976 unique articles, and we identified an additional 26 publications from reference lists of published articles. After screening, we identified 348 full text articles that met the criteria for inclusion in our review (Figure 1). We identified test-negative studies estimating VE for a total of 12 different pathogens, including influenza virus (n=253; inactivated=196; live-attenuated=2; both=28; unknown=27) (19, 27-275)(276-278), rotavirus (n=48; live-attenuated=48) (279-326), *Streptococcus pneumoniae* (n=24; conjugate=12; polysaccharide=12) (16, 327-349), *Bordetella pertussis* (n=6; toxoid=6) (350-355), *Vibrio cholerae* (n=4; inactivated=4) (356-359), poliovirus (n=4; live-attenuated=4) (360-363), *Neisseria*

meningitidis (n=3; conjugate=1; polysaccharide=2) (364-366), measles virus (n=2; live-attenuated=2) (367, 368), *Salmonella* Typhi (n=1; polysaccharide=1) (369), *Neisseria gonorrhoeae* (n=1; outer membrane vesicle=1) (370), human papillomavirus (HPV) (n=1; recombinant=1) (371), and *Haemophilus influenzae* (n=1; conjugate=1) (372). Figure 2 shows the number of test-negative design articles by type and year. The majority of the studies were published since 2010, and the earliest study that we identified was a study that estimated the effectiveness of pneumococcal vaccine published in 1980 (16).

Settings and clinical criteria

Study populations were recruited from outpatient settings including emergency department (n=117), inpatients including those with short-stay (n=108), or both outpatient and inpatient settings (n=114) (Figure 3). Nine studies that did not specify patient recruitment settings were based on either statutory databases or laboratory-based surveillance systems. While influenza studies were often conducted in outpatient settings (45%), studies for other pathogens recruited mostly inpatients alone (e.g. 88% for pneumococcus) or both inpatients and outpatients (e.g. 58% for rotavirus).

The choices of case definition depended on the pathogen of interest (Table 2). For influenza studies, the commonly used clinical case definitions were influenza-like illness (n=143), acute respiratory infection for outpatients (n=47), severe acute respiratory infection for inpatients (n=9), febrile respiratory illness (n=4) and pneumonia (n=4). In eight studies, the above choices were not explicitly provided; study eligibility was nonetheless based on manifestation of systemic and/or respiratory symptoms (n=12). In 26 studies, any of the above-mentioned syndromes or influenza-associated complications were considered such as sepsis, exacerbation of underlying asthma, chronic obstructive pulmonary disease, stroke, etc.

We observed similarities across studies in the set of symptoms that defined these standard clinical case definitions (Figure 4). Most influenza studies included fever and various respiratory symptoms. Among 19 pneumococcus studies recruiting invasive pneumococcal disease patients, case definitions were based on laboratory test results detecting the pathogen in normally sterile sites (e.g. blood, cerebrospinal fluid) by culture (n=8) and various other tests (n=11) (Figure 4, panel B). Studies recruiting patients with pneumococcal pneumonia based the case definitions on radiologic findings as well as the presence of respiratory symptoms. Of 48 rotavirus studies that recruited patients with gastroenteritis, 21 considered occurrences of loose stools alone, 19 considered vomiting, and one dehydration besides loose stools, and seven studies did not clearly define gastroenteritis (Figure 4, panel C). None of the four *V. cholerae* studies adopting gastroenteritis as clinical case definition considered vomiting, but loose stools with (n=2) or without dehydration (n=2). Other studies (n=10) defined case definitions based on diagnostic test results or disease-specific symptoms, such as rash (measles virus, n=2) or acute paralytic illness (poliovirus, n=2). Occasionally, positive contact history were also considered (three influenza virus, one measles virus and one poliovirus studies).

Classification of cases and controls

Specimens collected from patients who met case definitions were tested by various laboratory methods. Based on laboratory test results, the choices of cases and controls were divided into four categories: pathogen of vaccine type, non-vaccine type, alternative pathogens and undiagnosed (Figure 5, Table 1). The distinction of cases and controls varied substantially by pathogen of interest (Figure 5). Cases were defined as vaccine-type infections in 305 (88%) test-negative design studies focusing on influenza virus (n=253), pneumococcus, (n=23), rotavirus (n=10), *B. pertussis* (n=6), *V. cholerae* (n=4), poliovirus (n=4), *N. meningitidis* (n=3), HPV (n=1) and *H. influenzae* type b (n=1). Of 50 (15%) test-negative design studies that selected patients who tested-positive for the pathogen of interest (including both vaccine-type and non-vaccine-type strains) as cases, most were for rotavirus (n=47, 89%); in addition, three included patients with any pneumococcal strain, two addressed measles virus, and one addressed influenza virus.

We also identified 11 rotavirus studies assessing the effectiveness of vaccines against non-vaccine-type cases (Figure 5). These cases may include G9P or G12P if the vaccine assessed was pentavalent rotavirus vaccine (RV5), and may include G2P[4], G3P[8], G4P[8], G1P[8], G9P or G12P if the vaccine assessed was monovalent rotavirus vaccine (RV1) (Table 1). An unusual scenario was observed in a *N. gonorrhoeae* study where the effectiveness of outer membrane vesicle meningococcal B vaccine (MenZB) was evaluated. In this study, non-vaccine-type cases diagnosed positive for gonorrhea were compared to controls diagnosed with *Chlamydia trachomatis*, an alternative pathogen.

Almost all influenza test-negative design studies (251/253, 99%) defined patients testing positive for influenza virus (i.e. vaccine-type) as cases and used patients who tested-negative for influenza as controls. Occasionally, patients who tested-positive for an alternative pathogen (n=15) or pan-negative (negative for all tested pathogen) (n=8) were also used as controls. Most of the non-influenza test-negative design studies (n=64, 67%) used all patients who tested negative for the vaccine pathogen as controls. These include studies of rotavirus (n=47), *V. cholerae* (n=4), poliovirus (n=4), pneumococcus (n=4), *B. pertussis* (n=2), measles virus (n=2) and HPV (n=1). We also identified five test-negative design studies (of *S. typhi*, rotavirus, *N. meningitidis, N. gonorrhoeae*, and *H. influenzae*) which defined controls as those diagnosed with alternative pathogens. An exception was observed for 21 (88%) pneumococcus, two *N. meningitidis* and one influenza virus studies, where patients infected by non-vaccine-type pathogens were used as controls for estimating VE. Undiagnosed patients were also chosen as the comparison group in four *B. pertussis* studies. In two pneumococcus studies, vaccine-type cases were compared to a control group consisting of both patients who tested-negative for pneumococcus and patients who tested-positive for non-vaccine-type pneumococcus.

Approaches to estimation of VE

Age was the most commonly controlled variable (n=336, 97%) (Figure 6), as the probability of vaccination and the risk of infection can change with age. Studies controlled for the effect of age by adjustment in the statistical model (n=274, 79%), matching (n=29, 8%), restriction to particular age groups at the enrollment stage (n=19, 5%), or stratification (n=14, 4%). Up

to 83% (n=210) of influenza studies, 77% (n=37) of rotavirus studies, 50% (n=12) of pneumococcal studies, and 65% (n=15) of other studies adjusted for age in statistical model. A total of 10 (4%) influenza studies, two (8%) pneumococcal studies, one (17%) pertussis study, and one (33%) meningococcal study controlled for age by stratification. At the study design stage, 18 (7%) influenza studies, 8 (17%) rotavirus studies, two (50%) poliovirus studies, and one (4%) pneumococcal study matched cases and controls by age. Enrollment of study participants was restricted to particular age groups (<5, <18, ≥65) in seven (3%) influenza studies, five (21%) pneumococcal studies, three (6%) rotavirus studies, (50%) two poliovirus studies, one (17%) pertussis study, and one (100%) HPV study. Among studies that failed to control for age (n=12, 3%), three (25%) used other methods to examine the potential effect of age, such as by using stepwise regression (371).

How age was incorporated into VE models varied substantially, with most specifying a categorical variable (n=142, 52%; 132 were influenza studies). Age was also specified as a continuous variable in 46 (17%) studies. Of these, age was modeled using birth month alone (n=11) or along with birth year (n=9) as a continuous variable in rotavirus studies. A pneumococcal study and 24 influenza studies modeled age as a cubic spline variable. Other test-negative design studies failed to specify how age was modeled (n=57).

Calendar controlled for in 293 (84%) studies. The rationale for including this variable is that the probability of vaccination and risk of infection may change over time (8). Calendar time was most often controlled for by adjustment as a covariate in a statistical model (n=212/293, 72%), particularly in influenza virus studies (n=180, 71%). Adjustments were also made in 20 (42%) rotavirus studies, eight (33%) pneumococcal studies, one (25%) *V. cholerae* study, one (33%) meningococcal study, one (50%) measles virus study, and one (100%) S. Typhi study. We also identified three (1%) influenza virus studies, three (50%) pertussis studies and one (2%) rotavirus study which conducted time-stratified analyses, 34 (13%) influenza virus studies, four (8%) rotavirus, one (4%) pneumococcus study, one (25%) poliovirus study, and one (17%) pertussis study matched cases and controls by calendar time, while 27 (11%) influenza studies, five (10%) rotavirus studies, and one (25%) *V. cholerae* study also controlled for time by restricting patient recruitment to epidemic periods.

Among studies that controlled for the effect of time, calendar time was commonly modeled using week (n=76), month (n=72) and 2-weeks interval (n=25). Studies modeling time using week (n=43), month (n=63) or 2-weeks interval (n=6) often did not specify how these time units were modeled. Wherever this information was available, week was most commonly modeled as a matching (n=13), spline (n=11), categorical (n=5), or continuous variable (n=4); month was modeled as a categorical (n=4), matching (n=3), or stratifying variable (n=2); while 2-weeks interval was modeled as a matching (n=10) or categorical variable (n=9). Three studies used 15-days (n=1), 2-months (n=1), or 3-months intervals (n=1) as a matching variable. Two studies controlled for time using 3 weeks without specifying how these were modeled. Occasionally, timing of symptom onset was modeled as a cubic spline (n=6) or matching variable (n=2), time of presentation was modeled as a matching (n=4), cubic spline (n=1) or continuous (n=1) variable, and time since study began was modeled as a cubic spline (n=1) variable. Studies that covered a time period over more than one season also controlled for the effect of calendar time by stratification or adjusting for season (n=19)

or year (n=12). In the remaining 36 studies, it was unclear what time intervals were used or how time was modeled.

Around half of all eligible studies controlled for comorbidities (n=187, 54%) and sex (n=150, 43%). A total of 40 (21%) also considered obesity and 26 (14%) considered pregnancy. We identified a total of 50 influenza studies that controlled for previous vaccination in their statistical models. Prior infection was not commonly examined; however, we identified five studies that considered prior infection by statistical adjustment (n=4) or restriction (n=1) (167, 218, 240, 254, 273). The majority of studies (n=236) controlled for time intervals from disease onset to laboratory testing. Among these, 53 (22.5%) used statistical adjustment while the remainder used restriction to delays of one week or less (n=144, 61%), two weeks or less (n=36, 15.3%) or one month or less (n=3, 1.3%).

DISCUSSION

We identified and reviewed the methodologic approaches of 348 published test-negative design studies for 12 different pathogens. We identified a rapid increase in the use of the test-negative design for studying VE in recent years, with 90% of studies published since 2011 (Figure 2). Studies share a number of similarities. Case definitions and study sites were generally similar between studies examining the same pathogen. Approaches to the distinction between cases and controls were mostly consistent among studies of the same pathogen, but differed among pathogens (Figure 5). We identified common covariates included in statistical models to estimate VE, i.e. age, calendar time, sex, and comorbidities, but the way covariates were controlled for varied between studies of different and same pathogens.

Potential limitations of the test-negative design study have previously been discussed and examined by a number of authors (8, 13, 373-378). Simulation studies have shown that biases may arise under several circumstances, including if the study fails to adjust for calendar time (373), if vaccination affects the probability of non-influenza infections (374), if vaccination affects the probability of seeking care between cases and controls (375, 376), if healthcare-seeking behavior differs substantially between cases and controls (377), and if misclassification bias is present (13, 378). The ability of the test-negative design to recover accurate VE estimates under a scenario of “leaky” protection has also been questioned (381), although similar biases may be present under other designs as well (3).

The test-negative design is convenient and efficient, and therefore it has been readily applied to laboratory-based surveillance data and health management data as observed in the studies of *B. pertussis* (351-353), and sometimes with linkage data to obtain vaccination or infection status. However, the importance of clear and specific case definitions should not be overlooked, and prospective test-negative design studies may be the most robust. An important strength of the study design is that, in selecting a group of patients who seek care for specific syndromes, it increases similarity between cases and controls, thus minimizing selection bias. One of the potential limitations of using administrative data for the test-

negative design is that it may not always be clear if patients who were tested actually met the case definition.

The choices of study settings for test-negative design studies depended on the diseases of interest, disease severity, and vaccines. Pneumococcal vaccines were licensed primarily for prevention of severe infection leading to hospitalization (379), in contrast to other vaccines such as rotavirus vaccine and oral cholera vaccine that were recommended as part of a comprehensive strategy of disease control (380). Therefore, patients in pneumococcal VE studies frequently consisted of those severely ill and hospitalized with invasive pneumococcal disease or community-acquired pneumonia. Conversely, for studies of influenza or rotavirus VE, for example, disease outcomes may consist of a broader spectrum of diseases from mild to severe, and patients may be recruited from both inpatient or outpatient settings. Biases could persist under the test-negative design if broad variation in disease manifestation gives rise to differential healthcare-seeking behavior in terms of vaccination and care seeking for symptoms, and affect the probability of being tested (381). A more stringent clinical case definition could be used to reduce this source of bias, for example by recruiting severely ill inpatients as in the case of pneumococcus (381). Because disease severity could vary by setting, it is important to consider carefully the most appropriate setting to monitor VE, and in general it may not be appropriate to pool data from inpatients and outpatients when estimating VE.

There was some variation in the clinical case definitions used to recruit study participants. For example, the definitions for influenza-like illness may or may not include myalgia, definitions for gastroenteritis may include loose stools with or without vomiting. It is not clear if the sensitivity of clinical case criteria biases VE estimates, but modeling studies could provide further insight. The theoretical model shows that although more stringent clinical case definitions are, by definition, less sensitive, less biased VE estimates can be obtained. This may be because health-care seeking is highly likely among individuals with severe presentations, reducing the potential for differential health-care seeking between vaccinated and unvaccinated persons (381). Because the choice of clinical case criteria may depend on healthcare seeking behaviors of the specific population being studied (382), standardizing case definitions across all settings may not be feasible. Nevertheless, the choice of clinical symptoms for enrolled patients should ensure similarity between cases and controls and not be dependent on the vaccination or important confounders of the vaccination-disease relationship. An important consideration, therefore, in the application of the test-negative design is whether the vaccine in question causes there to be a difference in the source populations from which the cases and controls are derived. For example, in the case of rotavirus vaccine, where vaccination can mitigate the severity of disease, the propensity to seek care differs between cases and controls leading to a form of selection (collider) bias that can harm the validity of VE estimates (8, 381). The test-negative design should not therefore be blindly applied to all vaccine-preventable diseases; valid application must consider the biological mechanisms underlying the vaccine’s effectiveness.

In terms of distinguishing cases from controls, most studies defined vaccine-type as cases, where vaccines being evaluated were believed to have protective effect against the strains included in the vaccine. In the scenario where vaccination is thought to provide cross-

protection against non-vaccine-types of the same pathogen, for example in rotavirus studies, cases also included non-vaccine-types or all patients testing positive for the pathogen regardless of type. We also identified a lack of consensus on the choices of controls for each vaccine (Figure 5). We would be particularly cautious over the choice of non-vaccine-type patients as controls for vaccine-type cases, as observed in most of the pneumococcal studies. The reason for this is twofold. First, cross-protection may occur (383-385): Some studies have reported a decline in non-vaccine-type pneumococcal disease progression after vaccine rollout leading to the hypothesis that vaccination may have a secondary effect in preventing non-vaccine-type disease even from serotypes against which no cross-protection is expected (386-388). Second, a basic assumption of the test-negative design is that the risk of infections by non-vaccine-targeted causative pathogens resulting in similar clinical disease does not vary by vaccination status. This assumption may be violated in pneumococcal studies if there is a serotype replacement phenomenon, i.e. an increase in the incidence or proportions of infections caused by non-vaccine-types following vaccine introduction (389). It has been argued that the impact of serotype replacement is minimal compared to the substantial reduction observed in overall invasive pneumococcal disease following vaccination (389, 390). Studies also showed that the magnitude for serotype replacement-associated bias in VE estimated by the indirect cohort method is likely to be small in practice (327). The choice to include vaccine-matched pathogens or not should therefore depend on the public health question to be answered: are we interested in knowing by how much this vaccine will reduce the burden of the clinical disease of interest? Or are we interested in estimating the effectiveness of the vaccine only with respect to the pathogens it specifically targets. From a programmatic, policy and public health perspective the former argument is perhaps more relevant.

Notwithstanding the public health intent of a VE study, measuring vaccine effectiveness implies the intention to assess the strength of a causal effect of vaccination on risk of disease (10). Given that test-negative design studies are observational in nature, causal estimates could be biased due to confounding, underscoring the importance of adequate confounder control. Almost all studies controlled for some potential confounders by adjustment, matching, stratification, or restriction. Age is a common confounder as it is likely to be associated with the odds of being vaccinated (exposure) and infected (outcome). Therefore, almost all VE studies should control for age. How this was done was inconsistent across studies and it is unclear by how much the variation in variable specification can harm estimates. However, categorization of a continuous variable will lead to residual confounding, the importance of which matters in VE studies more when small changes in age correspond to large differences in immunological competence. Calendar time was controlled for in studies spanning several years or diseases that manifest seasonal trends, for example influenza virus and rotavirus. Controlling for calendar time is important in situations when vaccination uptake and risk of disease vary over time. Studies have postulated that VE estimates can be biased when controls are recruited outside of the influenza season because vaccination coverage may not reflect coverage during the influenza season (373, 391). Controlling for calendar time or age is also important when investigating the effect of age or time on waning or persistence of vaccine-induced immunity, particularly for immunization programs targeting specific age groups, e.g. childhood vaccines (381).

Where stratified estimates by age or time periods are provided, meaningful interpretation of stratified estimates requires understanding of the mechanism of vaccine under study, whether vaccine confers protection to a proportion of those vaccinated or reduces the force of infection in those unvaccinated (392). In the latter scenario, a decrease in VE might be truly due to a decline over time in protection, or an artefact of depletion of unvaccinated susceptibles (381, 393). It has also been shown that estimation of VE in the test-negative design requires that vaccine confers "all-or-nothing" protection to those vaccinated, but whether vaccine is "all-or-nothing" or "leaky" is not often known (381).

This systematic review extended previous test-negative design reviews and provided a more comprehensive review of the application of the study design in studying VE (11). For some pathogens, studies were too limited to make a fair evaluation of the appropriateness of the test-negative design. We also treated all studies as equal including mid-season (interim) reports for influenza VE which could be reported less meticulously compared to end-of-season reports. Our inclusion criteria were restricted to studies which distinguished case–control status based on laboratory-confirmed presence or absence of the pathogen of interest. We therefore excluded studies by Crowe *et al.* and Muganga *et al.* which assessed the effectiveness of HPV vaccine on histology-based outcomes, and the effectiveness of Hib on purulent cerebrospinal fluid meningitis respectively (394, 395). While these studies can be considered as variants of the test-negative design, there was not a specific definition for the choice of cases. We also excluded studies that used the test-negative design approach to examine bias and confounders (396). One other notable excluded set of studies were randomized controlled trials of adenovirus vaccine conducted in the 1960s, which used a nested test-negative style analysis to estimate VE (397-399).

The test-negative design serves as an efficient option to estimate the effectiveness of vaccines against various diseases and its use is likely to increase in the near future with the introduction of new vaccines and the re-emergence of vaccine-preventable diseases. Based on our findings, we provided several practical recommendations on the applications of the test-negative design to non-influenza pathogens (Box 1). In the case where vaccination reduces disease severity, application of the test-negative design should not be recommended. Careful consideration should therefore be taken into account before applying the test-negative design to estimate VE. Moving forward, given the prospect of increasing use of the study design for multiple diseases, we would like to introduce the idea of establishing a general test-negative design "platform" to facilitate timely VE estimates. For example, all new pediatric admissions (or a chosen subset) could be assessed against a number of clinical case definitions, tested for relevant pathogens consistent with signs/symptoms, and their vaccine history determined, so that those with influenza-like illness could contribute to monitoring VE for influenza (and, in due course, respiratory syncytial virus), those with fever and rash could contribute to monitoring varicella, measles, or enterovirus EV-A71 VE, etc. Besides facilitating annual surveillance of influenza VE, such a platform could help better planning of public health responses in the event of, for example, the reemergence of measles which requires re-evaluation of the effectiveness of measles-containing vaccines (400). Using a platform approach could be an efficient approach to monitor VE for a range of vaccines on an ongoing basis. Once established, such a platform would also be ideal for timely monitoring of vaccines against emerging or re-emerging infections.

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KEY MESSAGES

- The test-negative design has been increasingly used as an efficient study design to estimate vaccine effectiveness for a range of vaccines and pathogens.
- In our review, we found that clinical case definitions used to enroll patients were similar by pathogens of interest, but the sets of symptoms that defined them varied substantially.
- The test-negative design may be more appropriate for some vaccines and pathogens, but less appropriate in some scenarios for example if vaccination reduces disease severity in breakthrough infections.

Box 1.

Recommendations on the application of the test-negative design for vaccine effectiveness.

Recommendations on the application of the test-negative design on non-influenza pathogens

- Select cases and controls that manifest similar degree of severity

  Patients infected with more severe disease may have higher probability of vaccination and testing compared to those with milder disease. Restricting recruitment criteria to one end of disease spectrum can minimize confounding effect by disease severity. In the case where vaccination affects disease severity, test-negative design may not be appropriate, for example, rotavirus.

- Select controls that are unaffected by vaccination

  Selecting controls that are positive for infection potentially cross-protected by vaccine of interest, or with increased risk associated with vaccination, is common and may bias results. This is a concern particularly in diseases where one type predominates over another, such as pneumococcal disease. While the depth of knowledge on disease epidemiology increases with research, examining component of vaccine of interest before applying test-negative design may minimize the possibility of selecting inappropriate controls.

- Provide clearly defined case criteria

  Application of the test-negative design should not rely merely on the availability of laboratory test results. Recruitment of cases and controls based on clearly defined case criteria allows assessment of potential biases, ensures transparency and allows comparison between studies.

- Make appropriate adjustments for confounding and report VE estimates that reflect the causal effect of vaccination in reducing the risk of disease

  In a VE test-negative design study, unbiased VE estimates can be obtained under the following assumptions:

  1. Vaccination does not affect the probability of becoming a control.
  2. Vaccination does not affect the probability of seeking medical care.
  3. Absence of misclassification of exposure and outcome status.

     In the scenarios where any of these assumptions is not met, appropriate adjustments or analytic strategies might still be able to correct for bias. Unless eligibility criteria for participants are highly restrictive in terms of their demographics and clinical characteristics, measures of association (for example, odds ratios) unadjusted for any potential confounders such as age, comorbidities etc are unlikely to reflect the causal role of vaccination in preventing outcome of

interest, nullifying the objective of estimating the causal effectiveness of vaccination.

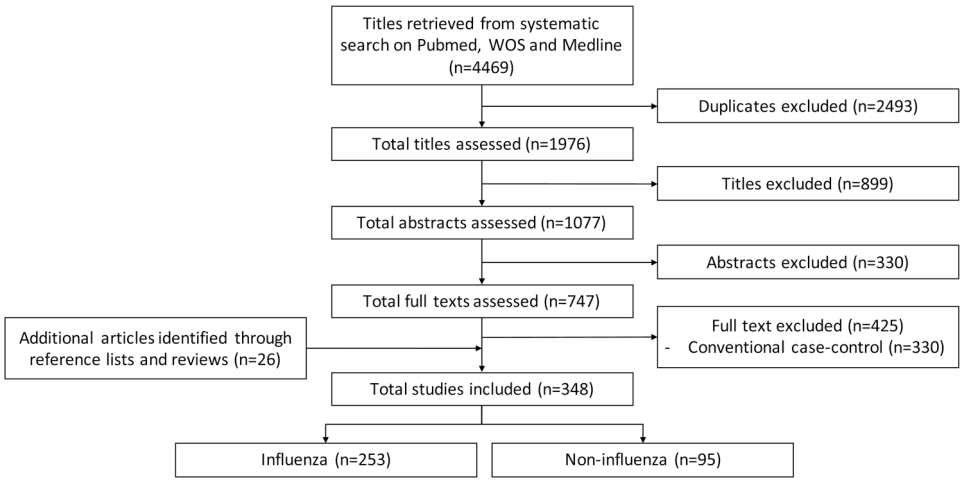

Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the process and results of study screening.

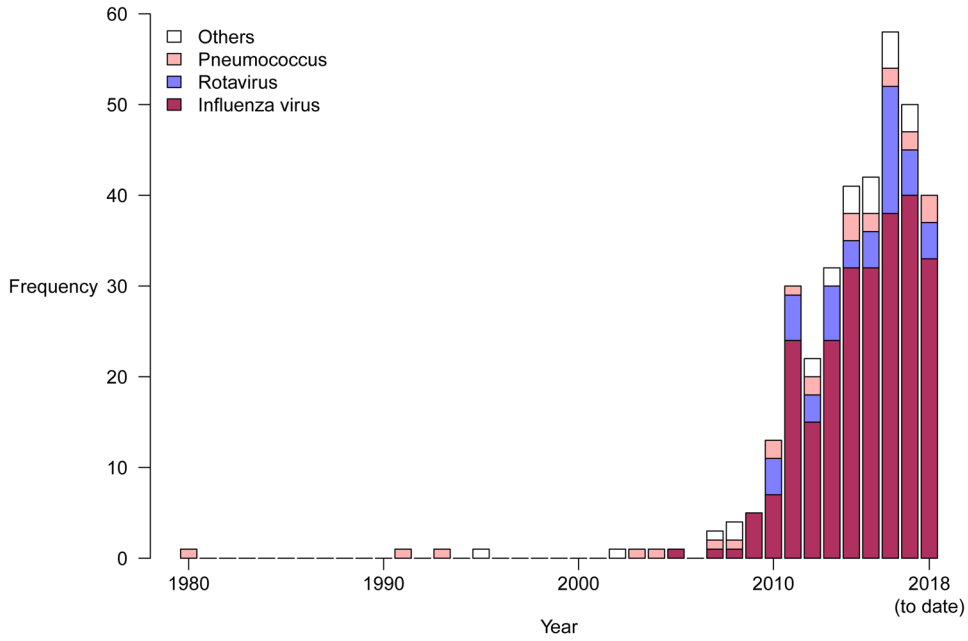

Figure 2.

Number of included studies by year. Most of the studies identified were of influenza virus. The first eligible study was published in 1980 (16).

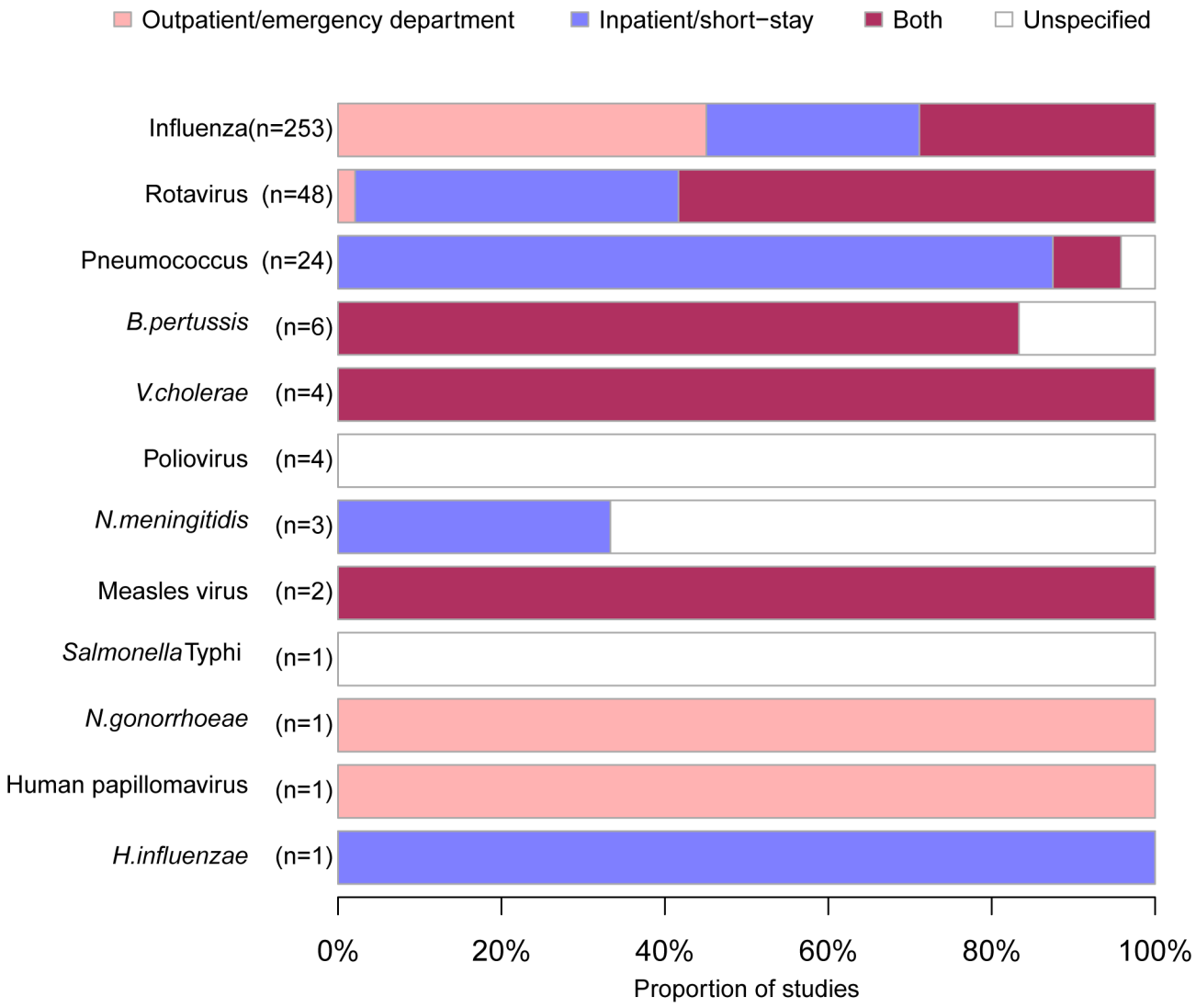

Figure 3.
Study setting by pathogen. Patients could be recruited from outpatient/emergency department, inpatient, or both outpatient and inpatient setting.

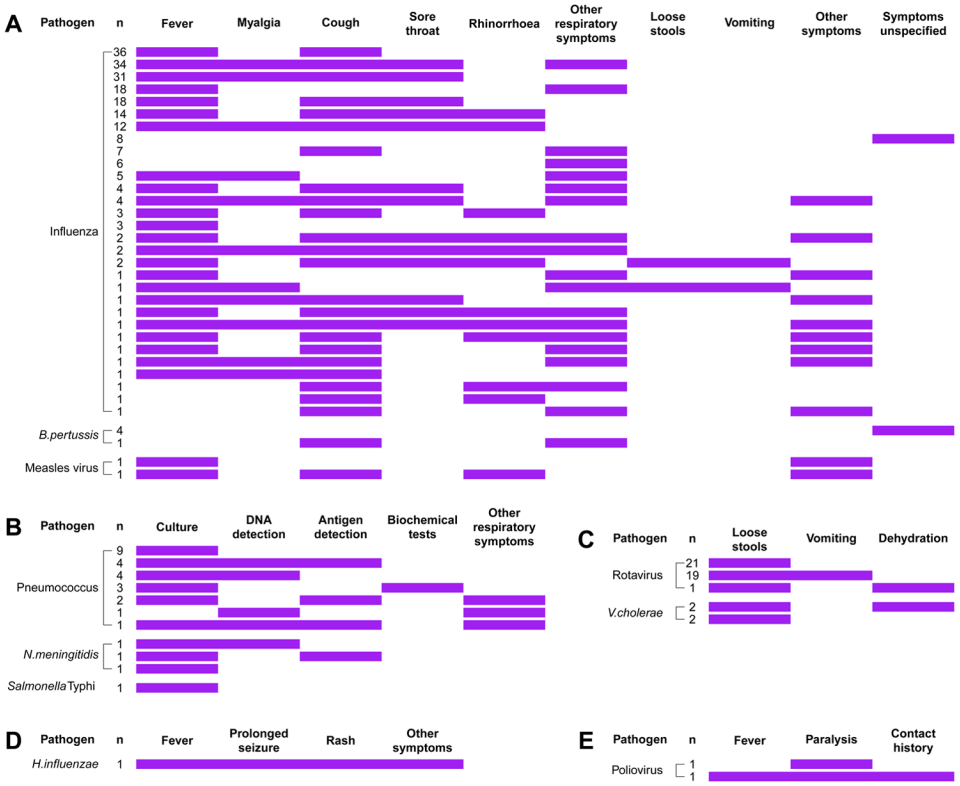

Figure 4.

Choices of clinical case definition by pathogen. Studies that reported recruitment of patients meeting certain clinical case criteria without clarifying specific symptoms were excluded from this figure, including 32 influenza studies (recruited influenza-like illness patients), seven rotavirus studies (recruited gastroenteritis patients), two poliovirus studies (recruited acute flaccid paralysis patients), and one *B. pertussis* study (recruited pertussis-like-illness patients). Human papillomavirus and *N. gonorrhoeae* studies which recruited patients from routine testing were also excluded. Panel A: Other respiratory symptoms include wheezing, whooping cough, apnea, dyspnea, shortness of breath, bronchitis, pharyngitis, pneumonia etc. Other symptoms include complications such as sepsis, stroke, acute exacerbations of chronic respiratory conditions, contact history, etc, or for the case of measles virus, rash, dermal eruption etc. Panel B: Clinical case definition by culture-positive include eight studies which recruited patients with invasive pneumococcal disease and one with acute otitis media. DNA detection may include polymerase chain reaction, or multilocus sequence typing wherever specified. Biochemical tests include bile solubility and optochin susceptibility test. Panel D: Other symptoms include neck stiffness, altered consciousness, other meningeal signs.

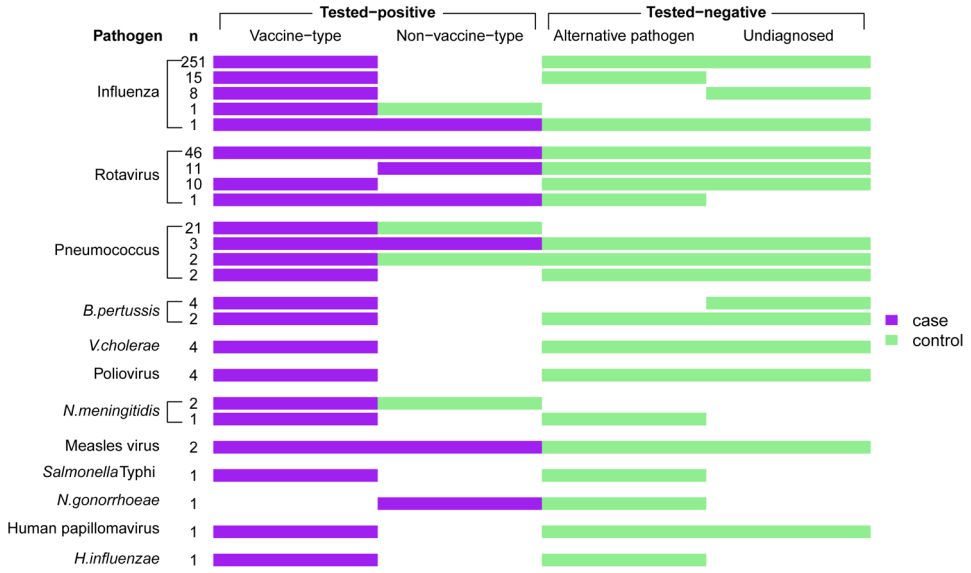

Figure 5.

Choices of cases and controls by pathogen. Purple indicates cases and light green indicates controls. If patient samples were tested-positive for pathogen of interest, patient samples may be further tested to identify whether they were infected by vaccine-type or non-vaccine-type. If patients' samples tested negative for the pathogen of interest, samples may be further tested. Alternative pathogens may be identified or patient samples may be undiagnosed or pan-negative (i.e. negative for all tested pathogen). Studies can be counted more than once when there was more than one choice of cases or controls.

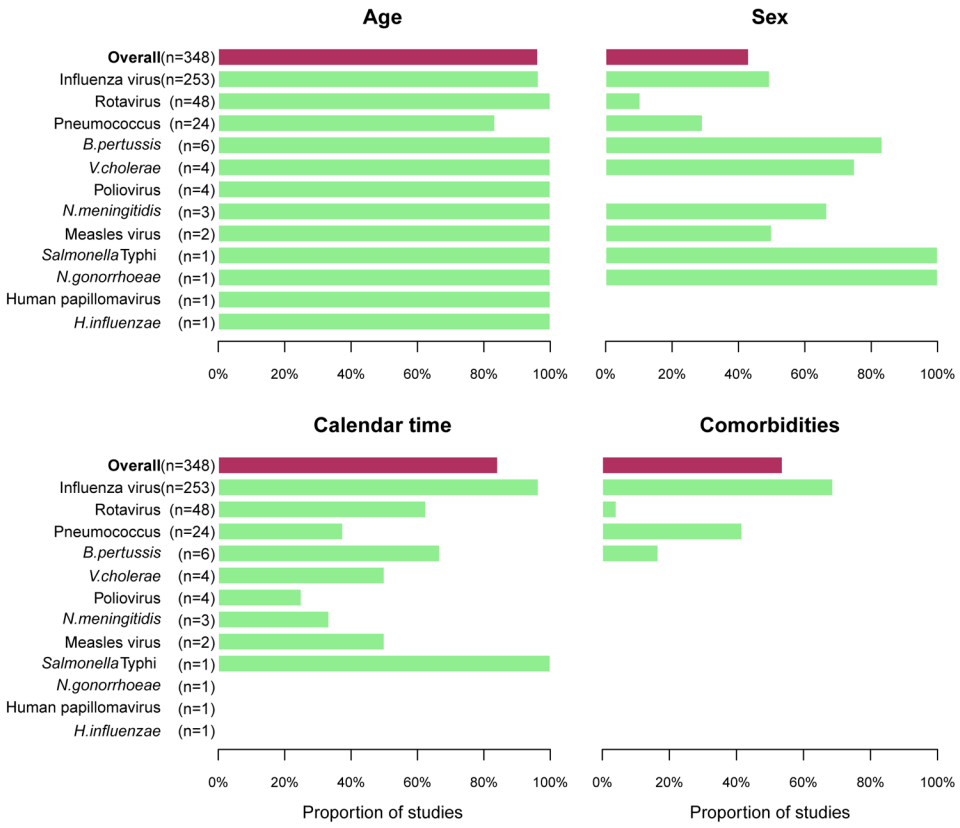

Figure 6.

Proportion of studies that included age, sex, calendar time, or comorbidities in statistical model to estimate VE.

Table 1.

Definitions of vaccine-type, non-vaccine type, and alternative pathogens according to included studies.

Pathogen of interest	Type of vaccine	Vaccine-type	Non-vaccine type	Alternative pathogens
Influenza virus	Trivalent (TIV), Quadrivalent (QIV) influenza vaccine, Live-attenuated influenza vaccine (LAIV)	Influenza A(H1N1), A(H3N2) and B		Rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), parainfluenza virus (PIV), bocavirus (BoV), coronavirus (CoV), adenovirus (AdV), enterovirus (EV) and others
	Monovalent influenza vaccine (MIV)	Influenza A(H1N1)pdm	Influenza A(H1N1)seasonal, A(H3N2) and B	
Rotavirus	Pentavalent rotavirus vaccine (RV5)	G1P[8], G2P[4], G3P[8], G4P[8], G1P[8]	G9P, G12P	AdV, norovirus, *Campylobacter*, *Salmonella*, *Aeromonas*, *Yersinia enterocolitica* and others
	Monovalent rotavirus vaccine (RV1)	G1P[8]	G2P[4], G3P[8], G4P[8], G1P[8], G9P, G12P	
Pneumococcus	7-valent pneumococcal conjugate vaccine (PCV7)	Serotypes 4, 6B, 9V, 14, 18C, 19F, 23F	Other serotypes than included in the vaccine	Unspecified in included studies
	10-valent pneumococcal conjugate vaccine (PCV10)	Serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F		
	13-valent pneumococcal conjugate vaccine (PCV13)	Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F		
	14-valent pneumococcal conjugate vaccine (PCV14)	Serotypes 1, 3, 4, 5, 6B, 7F, 9N, 9V, 15B, 14, 18C, 19A, 19F, 22F, 23F, 33F		
	23-valent pneumococcal polysaccharide vaccine (PPV23)	Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F		
Bordetella pertussis	Whole-cell vaccine and acellular vaccine			Parapertussis
Poliovirus	Monovalent type 1 oral poliovirus vaccine (mOPV1)	Type 1	Type 2 and 3	EV
	Bivalent oral poliovirus vaccine (bOPV)	Type 1 and 3	Type 2	
Vibrio cholerae	Oral cholera vaccine (OCV)	O1, O139		Unspecified in included studies
Measles virus	Measles-containing vaccine (MCV) (e.g. measles, mumps and rubella (MMR))	Genotype A	Genotype B2, B3, C1, C2, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, G2, G3, H1, H2	Unspecified in included studies
Neisseria meningitidis	Serogroup C contained (e.g. bivalent A, C; tetra(quadri)valent A, C, Y, W-135)	Serogroup C	Serogroup B	*Haemophilus influenzae*, *Streptococcus pneumoniae*, etc.
	Serogroup B. C	Serogroup B and C	NA	
Human papillomavirus (HPV)	Bivalent vaccine	Type 16, 18	Other serotypes than included in the vaccine	Unspecified in included studies; test-negative or pan-negative?
	Quadrivalent vaccine	Type 6, 11, 16, 18		
	Nonavalent vaccine	Type 6, 11, 16, 18, 31, 33, 45, 52, 58		

Pathogen of interest	Type of vaccine	Vaccine-type	Non-vaccine type	Alternative pathogens
Neisseria gonorrhoeae	Outer membrane vesicle meningococcal B vaccine (MeNZB)	*N. meningococcal* serogroup B	*N. gonorrhoeae*	*Chlamydia*
Haemophilus influenzae type b (Hib)	Hib conjugated vaccine	Type b	NA	Pneumococcal meningitis
***Salmonella* Typhi**	Typhoid Vi vaccine	*S.* Typhi	NA	*Salmonella* Paratyphi

Table 2.

Clinical case definitions and clinical samples evaluated for each pathogen.

Pathogen of interest	Clinical case definitions	Number of studies	Clinical samples
Influenza virus	Influenza-like illness (ILI)	143	NP swab, NP aspirate, N swab, T swab, P swab, OP swab
	Acute respiratory illness	47	NP swab, NP aspirate, N swab, T swab, OP swab, N wash, N aspirate
	Severe acute respiratory illness	9	NP swab, NP aspirate, N swab, T swab, N wash, N aspirate, OP swab, P washes
	Pneumonia	4	Sputum, NP swab, OP
	Febrile respiratory illness	4	NP swab, NP aspirate, N swab, N wash, T swab,
	Others *	40	NP swab, NP aspirate, OP swab, N swab, T swab, N aspirate
	Unspecified	6	
Rotavirus	Gastroenteritis	48	Stool, rectal swab
Pneumococcus	Invasive pneumococcal disease (IPD)	19	Normally sterile sites including blood, CSF and pleural fluid
	Pneumonia	4	Blood, urine, sputum, pleural fluid, bronchoalveolar lavage
	Acute otitis	1	Otic fluids
Bordetella pertussis	Pertussis-like-illness	2	NP swab, unspecified
	Unspecified	4	NP swab, unspecified
Poliovirus	Acute flaccid paralysis	4	Stool
Vibrio cholerae	gastroenteritis	4	Stool, rectal swab
Measles virus	Measles-like-illness	2	Blood
Neisseria meningitidis	Meningitis	1	CSF, normally sterile sites
	Unspecified	2	
Human papillomavirus (HPV)	Unspecified	1	Cervical smear
Neisseria gonorrhoeae	Unspecified	1	Unspecified
Haemophilus influenzae type b (Hib)	Meningitis	1	CSF
***Salmonella* Typhi**	Enteric fever	1	Stool

* Included more than one clinical case definition.

Note: NP: Nasopharyngeal; N: Nasal; T: Throat; P: Pharyngeal; OP: Oropharyngeal; CSF: Cerebrospinal fluid.