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Title: Characteristics of Vaccine Safety Observational Studies and Authors' Attitudes: A Systematic Review

Running title: Characteristics of Vaccine Safety Observational Studies and Authors' Attitudes

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Abstract

Background: Post-licensure observational studies are the mainstay of vaccine safety evaluation. However, these studies have well-known methodological limitations, rendering them particularly vulnerable to unmeasured confounding. We sought to describe high-impact observational studies of

vaccine safety, investigate the authors' attitudes towards their study's findings and limitations, and report on spin practices.

Methods: We conducted a Pubmed systematic review of comparative observational studies of vaccine safety published in the six top medical journals from inception to March 2024.

Results: Thirty-seven studies were included, spanning publications from 1995 to 2024. Most studies focused on COVID19 and influenza vaccines (n=11, 30%, and n=10, 27%, respectively). Study designs and methodologies varied. Electronic health records (54%), passive surveillance databases (32%) and national registries (27%) were the most common data sources. Negative control outcomes were used in a single study. Residual confounding was conceded in 54% of studies, and an additional 24% did so implicitly. Spin was noted in 48.6% of the studies. This systematic review found that authors of observational vaccine safety studies in high-impact medical journals often acknowledge residual confounding, but rarely use methods like negative control outcomes to better detect unmeasured confounding. Furthermore, spin is common, occurring in approximately 50% of the studies.

Conclusions: Although our findings are somewhat limited by subjectivity in study assessments, they suggest that editors and reviewers of high-impact journals should ensure the language used in reporting observational studies accurately reflects the findings and their limitations.

Keywords: vaccine safety, observational studies, systematic review, spin practices

Introduction

Historically, post-licensure safety monitoring has relied on passive surveillance and ad hoc epidemiological studies[1]. Because pre-licensure clinical trials primarily focus on efficacy and often lack the power to detect rare, delayed, or subpopulation-specific adverse reactions, observational studies have become the mainstay of post-licensure vaccine safety evaluations. Recently, pre-established large-linked databases, and less frequently Phase IV trials, have increased the ability to study rare adverse events[2].

Passive surveillance systems play an important role in post-licensure safety monitoring due to their relatively low operational costs[3]. For instance, in the United States (US), the Vaccine Adverse Events Reporting System (VAERS) was implemented in 1990 by the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) as a passive reporting system to provide a unified national system for collecting all reports of clinically significant adverse events[4]. In Europe, the passive surveillance system EUDRAVIGILANCE has been operating since 2001[5]. Several individual countries also have substantial experience with passive surveillance for immunization safety[1], and the WHO-Uppsala Monitoring Center compiles data from multiple countries[6].

However, observational studies based on passive surveillance data suffer from several methodological limitations, which may hinder the ability to draw reliable conclusions[1]. These include under- or overreporting, selective reporting, and incomplete reporting. Most significantly, passive reporting systems do not allow for comparisons between vaccinated and unvaccinated persons. These systems lack data on the total number of people vaccinated and on the corresponding numerator and denominator for the unvaccinated. When data is available, event rates are calculated using the number of doses of vaccine administered, distributed or vaccine coverage data as the denominator.

In view of these limitations, other approaches gained popularity. Large-linked databases, such as the Vaccine Safety Datalink (VSD) in the US and the Vaccine Adverse Event Surveillance and

Communication (VAESCO) in Europe, have allowed for large population-based studies to be conducted, with as many as hundreds of thousands of people included[1]. These databases often include thousands to millions of individuals, who are commonly members of managed care organizations or integrated healthcare systems, and link computerized vaccination data and medical outcome records. One alleged advantage is their cost-effectiveness for conducting safety studies[1]. Yet, vaccine coverage rates are high in the VSD database, which leaves few unvaccinated control subjects available for comparative analyses. As a result, VSD studies often employ risk-interval study designs, such as self-controlled case series, which focus exclusively on vaccinated individuals and are mainly useful for detecting acute and severe adverse events[1]. Some countries, such as the Nordic countries, have national registries that enable nationwide vaccine safety assessments[7]. Mass immunization campaigns have also provided opportunities to implement active surveillance networks and conduct prospective studies[1].

While post-licensure observational studies of vaccine safety are of critical importance to public health by generating evidence on incidence, prevalence, associations and prognosis of certain conditions, their nonexperimental nature renders them particularly susceptible to unmeasured confounding and different kinds of bias[8]. Specifically, differential health-seeking behaviors between vaccinated and unvaccinated individuals often give rise to the healthy vaccinee effect – a situation when patients, who are in better health conditions, are more likely to adhere to the vaccination[9]. A major objective of vaccine safety evaluations is to determine whether certain events occurring after vaccination are truly caused by the vaccine. In that respect, results from observational studies should be interpreted with caution. Some methods, such as negative control outcomes, can improve the methodological robustness of observational studies by detecting unmeasured confounding – a recognized challenge in causal inference[10–14].

Here we sought to describe high-impact observational studies of vaccine safety, investigate the authors' attitudes towards their study's findings and limitations, and report on spin practices. We systematically reviewed studies published in six top medical journals from their inception through March 2024.

Materials and Methods

Search strategy and selection criteria

We systematically searched Pubmed from inception to March 19, 2024 for relevant observational studies published in 6 top medical journals according to google Scholar excluding those focusing on basic science[15] – *New England Journal of Medicine* (NEJM), *Journal of the American Medical Association* (JAMA), *The BMJ*, *Lancet*, *Nature Medicine* and *PlosOne*. We used the search term "vaccine safety" and excluded certain article types such as clinical trials, reviews and comment (the detailed search strategy can be found in the Appendix).

Our inclusion criteria were specific to primary comparative observational studies focusing on vaccine safety evaluation in humans. We excluded all interventional studies, non-comparative studies, meta-analyses, reviews, decision and cost-effectiveness analyses, animal or laboratory experimental studies, studies whose main data were derived from modeling, commentary pieces, protocols and studies that did not evaluate vaccine safety. One reviewer screened, abstracted, and appraised articles (M.B.).

Data extraction and analysis

We extracted study-level information, including year of publication, study design, vaccine or exposure of interest, setting, study population, sample size, study duration, source of data, duration of observation, industry funding and potential conflicts of interest with the industry (more details are given in the Supplement). Data sources were classified into the following types: passive surveillance database (e.g. VAERS or VSD), active surveillance database, national registries, administrative database, interviews, electronic health records, healthcare organization integrated data, trial database.

Additionally, we assessed whether studies reported negative control outcomes, all-cause mortality and vaccine effectiveness. We also recorded whether the authors commented on the similarity at

baseline between groups, whether the authors conceded residual confounding and, more specifically, whether they explicitly considered or conceded the presence of the healthy vaccinee effect.

Verbatim was recorded for author statements indicative of spin. For our purposes, spin refers to practices that distort the interpretation of results and mislead readers to view the results in a more favorable light[16]. Spin was classified into one of four categories derived from one systematic review[17]: Cat. 1) “Reporting practices that distort the presentation and interpretation of results, creating misleading conclusions”, Cat. 2) “Discordance between results and their interpretation, with presentation of favourable conclusions that are not supported by the data or results”, Cat. 3) “Attribution of causality when study design does not support this”, and Cat. 4) “Over-interpretation or inappropriate extrapolation of results”.

Finally, we recorded “caution statements”, defined as author statements alerting the reader for a cautious interpretation of the study findings. We present simple descriptive statistics to provide an overview of the features of the eligible studies. Descriptive statistics were done using Microsoft Excel for Microsoft 365.

Results

Out of 711 studies yielded in the Pubmed search, 37 studies were included for analysis (the references for all the included studies are available in the Supplement). Figure 1 shows the process of study selection and a description of the vaccine/exposure studied in included studies. These 37 articles are prominent vaccine safety studies that appear in the top medical journals.

The five most common vaccines/exposures studied were COVID19 vaccines (n=11, 30%), influenza vaccines (n=10, 27%), Diphtheria-Tetanus-Pertussis (DTP) vaccines (n=4, 11%) rotavirus vaccines (n=3, 8%) and Measles, Mumps, and Rubella (MMR) vaccines (n=2, 5%). The 37 studies were published between 1995 and 2024, and most studies (n=29; 78%) were published in or after 2010

(Figure 2). The duration and time span of each study (i.e. the period of time during which the study population was studied) is represented in Figure 3.

Most studies were cohort studies (n=17, 46%): ten retrospective and seven prospective. Other study designs included self-controlled case series (n=8, 22%), case-control (n=5, 14%; four retrospective and one prospective), case-centered approach (n=1, 3%), case-cohort (n=1, 3%), case series (n=1, 3%), case cross-over (n=1, 3%), emulated trial (n=1, 3%), ecological study (n=1, 3%), and sequential approach (n=1, 3%). In 8 (22%) studies, the design was not clearly stated and was determined by our judgment (4 cohort, 1 self-controlled case series, 1 case-control, 1 ecological and 1 sequential approach study).

The most common study setting (n=15, 41%) was the US. Two (5%) studies were conducted in each of the following settings: UK, Canada, Denmark, Israel, Italy, Sweden and Norway (together), and Taiwan. The eight studies left were each conducted in a different setting (eTable 1 in the Supplement).

Figure 4 shows the distribution of sample sizes in included studies by study design. Of note, the sample size was not clearly stated in 8 studies and was determined by our assessment of data.

Thirteen (35%) studies included children, 5 (14%) included children and adults, 4 (11%) included adults and adolescents and 3 (8%) included adults only. Among studies in special populations, 7 (19%) included pregnant women, and 1 (3%) each included healthcare workers, elderly people, individuals with end-stage renal disease on hemodialysis, women aged 15 to 59 serotested for rubella, and patients aged 60 or older with certain immune-mediated diseases. The median time of observation after vaccination was 2.8 months (IQR 1.2-11.3) for 36 studies, since one study did not report observation time.

Each study could have more than one source of data. Electronic health records were used in 20 (54%) studies, passive surveillance databases in 12 (32%) studies, national registries in 10 (27%) studies, administrative databases in 9 (24%) studies, interviews in 3 (8%) studies, active surveillance

databases in 3 (8%) studies, healthcare organization integrated data in 1 (2%) study, and trial data in 1 (2%) study. Of the 10 studies using national registries, 7 were conducted in Nordic countries, and the other 3 in France, Israel, and Taiwan.

Two (5%) studies had industry funding and one study did not disclose sources of funding. In 10 studies (27%), at least one author publicly disclosed a relationship with one or more pharmaceutical companies.

In Table 1, we describe the authors' attitudes towards reporting selected parameters of study robustness and limitations, as well as spin. One study (out of 37) reports negative control outcomes and most (n=31, 84%) do not report all-cause mortality. All the six studies that we considered that reported all-cause mortality were conducted in pregnant women and assessed outcomes such as stillbirth, spontaneous abortion, fetal death and neonatal mortality.

Four (11%) studies reported vaccine effectiveness. The authors conceded residual confounding in 20 (54%) studies. Authors implicitly conceded residual confounding in 9 (24%) additional studies. In 13 (48%) studies, the authors commented that groups were different at baseline and similarity status was deemed unknown in more than a third of studies (n=11, 41%). The healthy vaccinee effect was explicitly considered or recognized in 11 (31%) studies, 6 of which were cohort studies, 3 were self-controlled case series, 1 was the emulated trial and 1 was the case-crossover study. Regarding spin practices, approximately half the studies (n=18, 49%) had any sort of spin present. Caution statements were present in 13 (35%) studies. All author statements considered indicative of spin are reported in the eTable 2 in the Supplement.

Discussion

We examined 37 studies on vaccine safety which appeared in the top medical journals between 1995 and 2024. These studies concerned a variety of products for children and adults. All the 37 included

studies focused on vaccines for the prevention of infectious diseases. Unsurprisingly, a large number of studies (30%) focused on COVID19 vaccines. Otherwise, influenza vaccine studies (27%) have also been a prominent focus of observational research.

These two vaccines have been widely used across populations and in mass vaccination campaigns, often repeated annually, which may explain the interest in studying a myriad of safety concerns. In contrast, studies of rotavirus vaccines have focused on one specific safety signal – the association between the vaccine and intussusception in children[18]. We found a median observation time of 2.8 months, reflecting the focus of many studies on short-term safety concerns (e.g. thrombotic events, myocarditis, and neurological events such as seizures and Guillain-Barré Syndrome).

We noted an increase in publication in top journals after 2010, with 8 articles appearing before and 29 appearing after. This has several possible explanations – the increasing number of vaccines available, the proliferation of observational research over the years[19], the development of nationwide and international monitoring networks, and the growing variety of study designs for vaccine safety surveillance[8]. Self-controlled and risk-interval designs are now widely used in vaccine safety[8]. In our review, 22% studies were self-controlled case series and the case-centered and case cross-over studies used risk-interval designs. Neither study design, whether traditional cohort and case-control or more specialized types, is inherently superior to the other, and all have important limitations[8]. It is worth noting that most cohort and case-control studies in our review were retrospective, which are typically inferior to prospective ones[20].

Notably, most studies (41%) were conducted in the US. Only two studies were industry-funded, despite industry ties in about a quarter of studies, meaning that the vast majority are supported by national research institutions, and/or the manufacturers of products are reluctant to conduct such research or submit it for publication in high-impact journals. In the US, the CDC leverages various monitoring systems, namely VAERS and VSD, for ongoing observational research[21]. Several of the non-US studies in our review were conducted in countries that either had large vaccine safety surveillance networks, large-linked databases and/or national registries, such as the UK, Canada, Israel, and the Nordic countries. In fact, many of our included studies used more than one source of

data. Electronic health records, passive surveillance databases and national registries were used most often (in 54%, 32% and 27% of studies, respectively), whereas active surveillance with prospective data collection was used in only three (8%) studies. About a quarter of studies used nationwide registry data, most of which were conducted in Nordic countries. All Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) have data on virtually every individual residing in those countries (thus minimizing selection and participation biases[22]), and the similarities between registries in those countries allow for the combination of data and joint analyses[23], which is why they are deemed valuable for research[24].

A considerable number of our included studies focused on vaccine safety in children (35%) and pregnant women (19%). Safety standards for pharmaceutical products given to healthy people (e.g. vaccines) are higher than those for therapeutic agents given to ill people[25], but this is especially true for vulnerable groups, such as children and pregnant people. Moreover, the exclusion of pregnant women from pre-licensure vaccine clinical trials[1] explains post-licensure safety evaluations.

We found that only one study used negative control outcomes, even though the literature on how to leverage negative controls has significantly expanded over the last fifteen years[13]. Negative control outcomes, also called falsification testing, are useful to identify spurious correlations in observational datasets[10]. In these cases, outcomes that cannot plausibly be linked to vaccination are examined for imbalance, and if present this suggests residual confounding and/or time-zero biases. All-cause mortality may serve as one such endpoint if it is implausible that vaccination for a condition (e.g. shingles) would result in all-cause mortality benefits that exceed the annual risk of death from that condition (e.g. shingles) or that exceed vaccine effectiveness. Except for studies in pregnant women, in which fatal events to the fetus/newborn were recorded, none of our included studies evaluated all-cause mortality.

Despite the lack of negative control outcomes, which would allow for better detection and quantification of unmeasured confounding, approximately half the included studies ultimately conceded residual confounding, and nearly a quarter more did so implicitly. This means that at least three quarters of the studies had important methodological limitations, despite the myriad of study

designs employed. In a significant percentage of studies (48%), comparison groups showed significant differences at baseline with respect to measured variables, and in another 41% baseline group characteristics were unknown, increasing the potential for unmeasured confounding. Therefore, it is not surprising that nearly a third of the studies acknowledged the healthy vaccinee effect as a source of potential bias in their results.

Despite these limitations, spin was found in over 50% of the studies, most commonly of the type "over-interpretation or inappropriate extrapolation of results" (category 4), and that appeals to cautious interpretations were only made in a third of cases. This is noteworthy because we exclusively assessed studies published in high-impact medical journals, where, theoretically, the highest standards of quality and scrutiny are upheld.

Our study has limitations. First, data extraction and analysis was done solely by one reviewer, which likely introduces an element of subjectivity in the assessment of studies. Second, the publication patterns of high-impact journals may differ from those of lesser impact. In leading journals, authors may feel compelled to show the impact of their study and thus over-interpret their findings. But it could also be the case that observational studies are more scrutinized for overinterpretation during peer review given the high impact of the journal.

Conclusion

In this systematic review of 37 comparative observational studies of vaccine safety published in six high-impact medical journals, we found that most studies focused on influenza and COVID19 vaccines, study methodologies varied, and the most common data sources were electronic health records, passive surveillance databases and national registries. Only one study used negative control outcomes, and about three quarters of the studies conceded residual confounding (explicitly or implicitly). Finally, spin was found in approximately 50% of studies. While our review is limited by an element of subjectivity in the assessment of studies, our findings suggest that observational studies could more often use accurate methods to detect confounding, and that editors and reviewers of high-

impact journals should ensure that the language used in reporting observational studies accurately reflects the study findings and their limitations.

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Tables

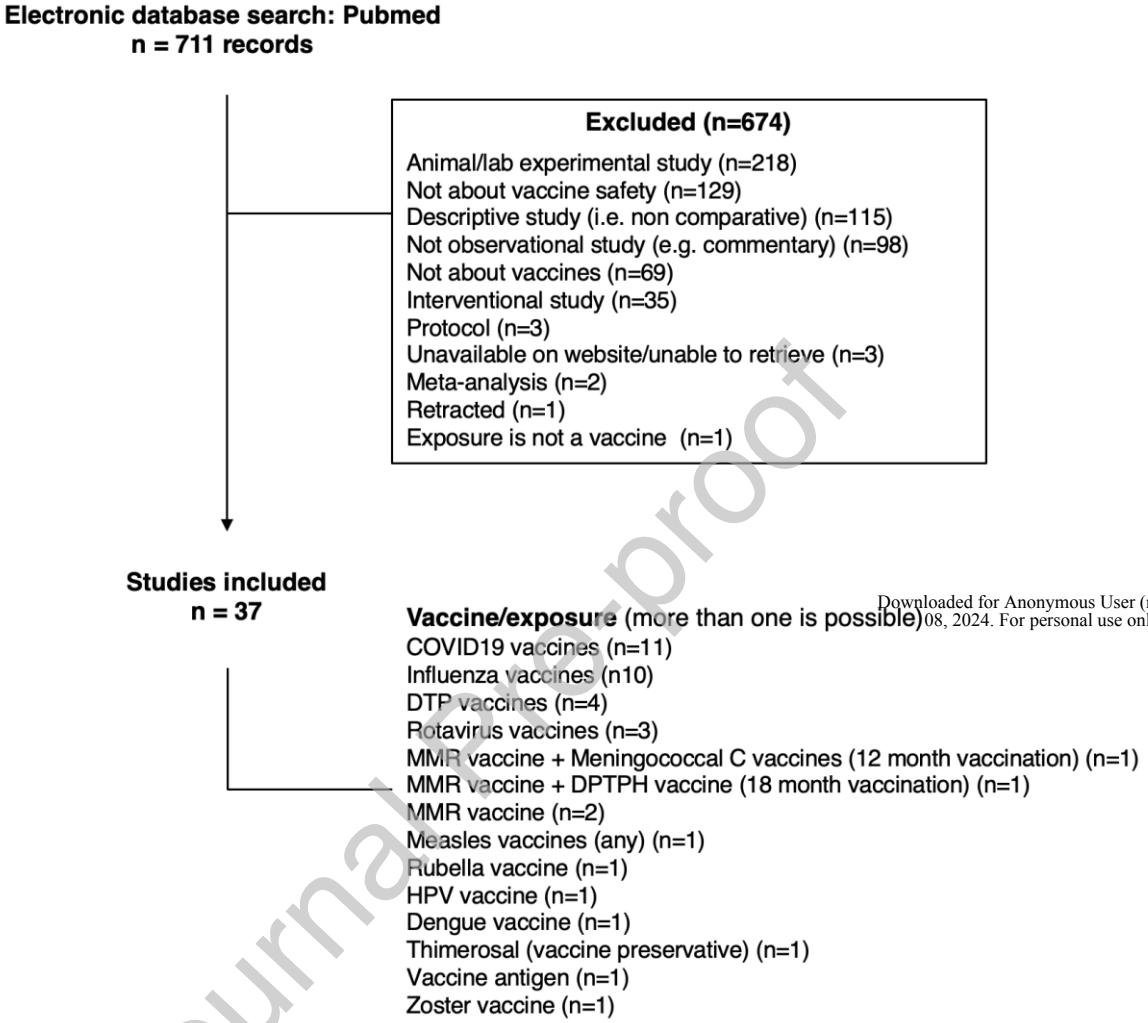
Table 1. Reporting of selected parameters of study robustness and limitations and practices in included studies.

Parameters assessed	No. (%) studies
Negative control outcomes	1/37 (3%)
All-cause mortality [a]	6/37 (16%)
Vaccine effectiveness [b]	4/37 (11%)
Authors concede residual confounding	
Yes	20/37 (54%)
Implicitly	9/37 (24%)
Authors comment on the similarity at baseline between groups (n=27) [c]	
Groups similar [d]	3/27 (11%)
Groups different	13/27 (48%)
Unknown [e]	11/27 (30%)
Authors explicitly consider or recognize healthy vaccinee effect [f] **(n=36)**	11/36 (31%)
Spin present	18/37 (49%)
(more than one category possible)	
Cat. 1: Distortion of results and interpretations, creating misleading conclusions	1/37 (3%)
Cat. 2: Discordance between results and their interpretation, with presentation of favorable, yet unsupported, conclusions	7/37 (19%)
Cat. 3: Unwarranted attribution of causality	6/37 (16%)
Cat. 4: Over-interpretation or inappropriate extrapolation of results	10/37 (27%)
Spin in the abstract (n=36)[g]	10/37 (27%)
Caution statements	13/37 (35%)

[a] All the six studies here considered were conducted in pregnant women and assessed outcomes such as still-birth, spontaneous abortion, fetal death and neonatal mortality.
[b] In one study (zoster vaccine), the safety and effectiveness outcome was the same (zoster diagnosis).
[c] Similarity considerations generally focused on demographics and, occasionally, other potential confounders that the authors measured. For simplicity, self-controlled case series, case-cross over and case-centered studies (a total of 10 studies) were not here considered, as in these studies each subject serves as his/her own control, eliminating differences in time-invariant factors between the comparators.
[d] One study did not measure baseline characteristis and simply assumed similarity.
[e] Meaning that the study either did not report it or only 1 or 2 variables were considered.
[f] One study not included here because it used randomized data with regards to vaccination.
[g] One study did not have an abstract.

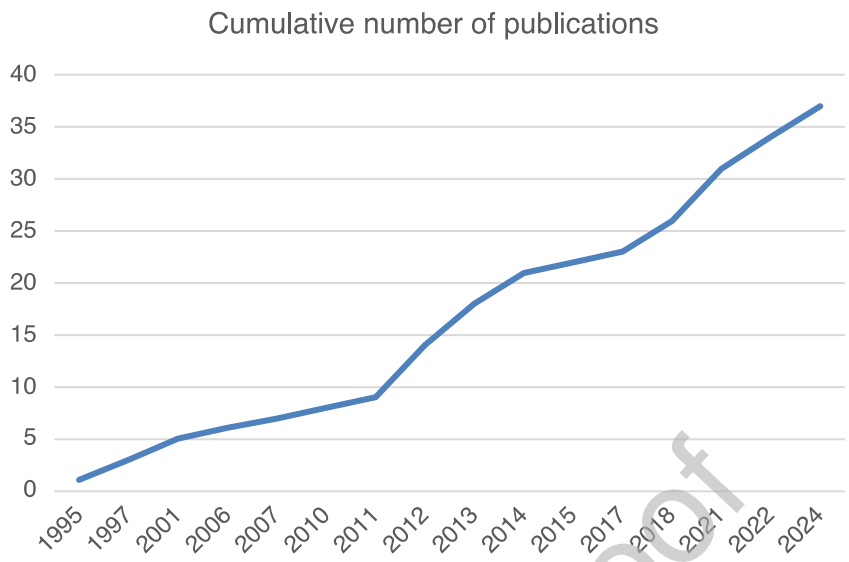
Figures

Figure 1. Study selection and description of vaccine/exposure studied in included studies (n=37).



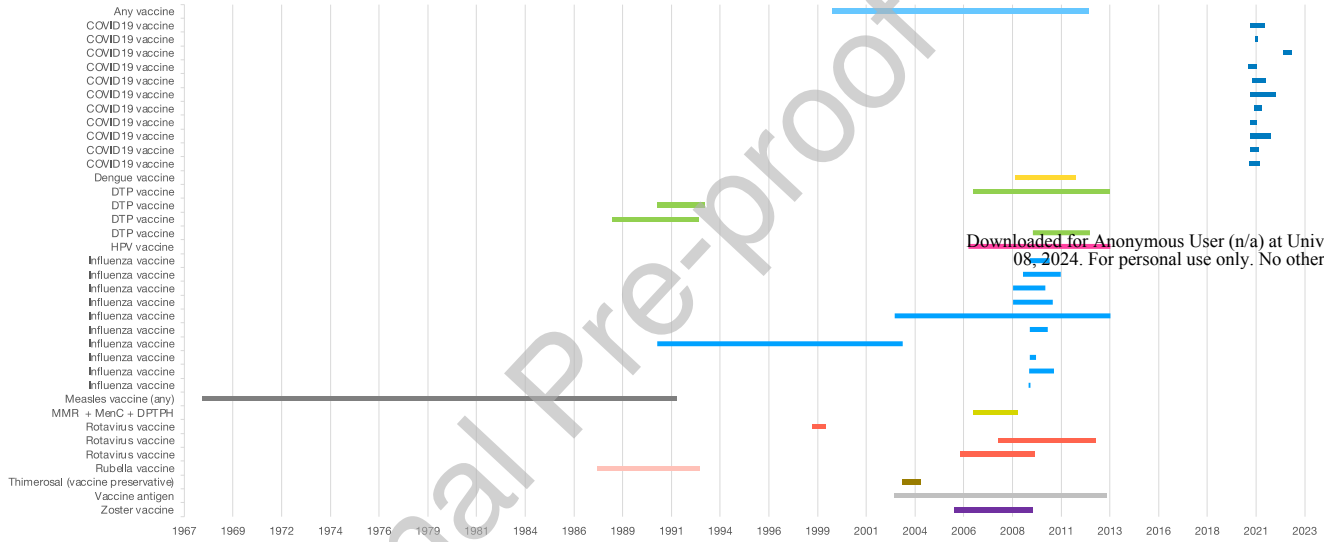
Legend: DTP: Diphtheria-Tetanus-Pertussis, MMR: Measles, Mumps, and Rubella, DPTPH: Diphtheria, acellular Pertussis, Tetanus, Polio and Haemophilus influenzae type b, HPV Human papilloma virus.

Figure 2. Cumulative distribution of published studies over time.



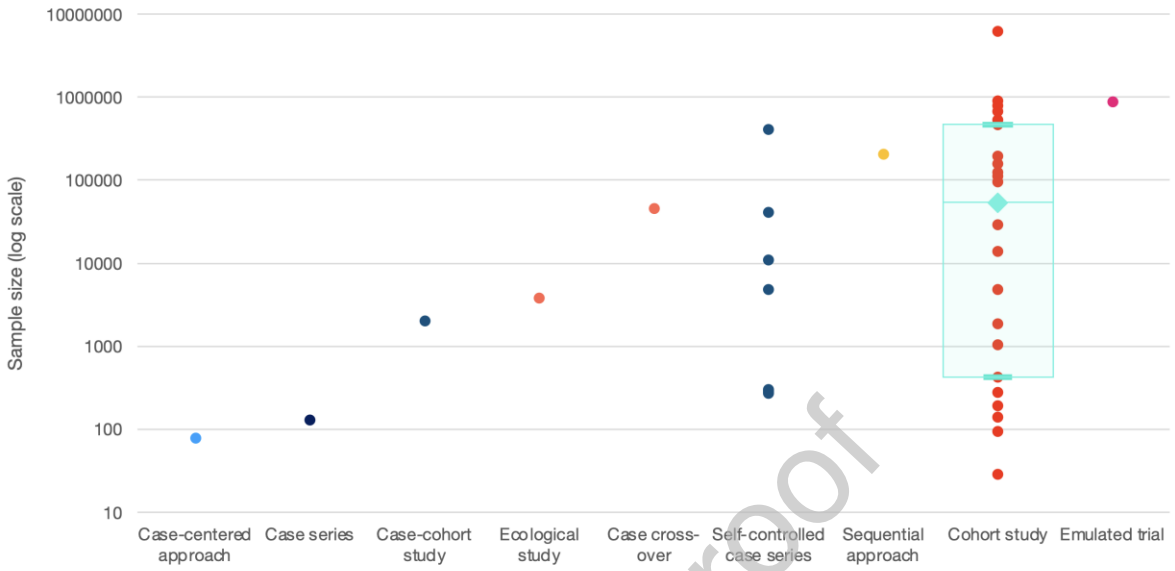
Legend: The year 2024 was only assessed until March 19, 2024.

Figure 3. Duration and time span of included studies.



Legend: Each vaccine/exposure is represented in a different color. DTP: Diphtheria-Tetanus-Pertussis, MMR: Measles, Mumps, and Rubella, DPTPH: Diphtheria, acellular Pertussis, Tetanus, Polio and Haemophilus influenzae type b, HPV Human papilloma virus.

Figure 4. Sample size distribution by study design (log scale).



Legend: Most cohort studies included samples of vaccinated individuals only. Pregnancy studies were the exception, including all pregnant individuals or births. The case cross-over study is here analyzed together with cohort studies because, in terms of sample size, the study behaved like a cohort study. The same occurred for one cohort study, which was here analyzed as a case-control study.

Clinical Significance