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Hilary Placzek
University of Massachusetts Medical School

Lawrence C. Madoff
University of Massachusetts Medical School

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Review

The use of immunization registry-based data in vaccine effectiveness studies

Hilary Placzek[a,*], Lawrence C. Madoff[b,c,1]

[a] Clinical and Population Health Research, University of Massachusetts Medical School, 55 Lake Ave North, Worcester, MA 01655-0002, United States
[b] Division of Epidemiology and Immunization, Massachusetts Department of Public Health, William A. Hinton State Laboratory Institute, 305 South Street, Jamaica Plain, MA 02130, United States
[c] Department of Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655-0002, United States

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ABSTRACT

Vaccine effectiveness (VE) studies provide a measure of population-based vaccine performance by combining immunization history data with rates of disease incidence. This review assessed the feasibility of using electronic immunization registry data sources in VE studies. Electronic databases were searched through January 31, 2010. Out of 17 studies, only one paper assessed data accuracy (71%), and three papers assessed population coverage of the registry (estimates ranged from 25% to 90%). This review shows that registry-based data sources can be used to conduct VE studies in a variety of settings and populations. However, we found little information regarding the quality of this data source in VE studies and future evaluations should investigate their reliability, accuracy, and potential bias.

Contents

1. Introduction

In the United States, national recommendations provide guidance for use of vaccines to reduce, eliminate, or eradicate 17 vaccine-preventable diseases. Recent reports indicate that the number of cases of most vaccine-preventable diseases (VPD) is at an all-time low. Hospitalizations and deaths attributable to VPD have also decreased [1]. Other estimates indicate that vaccination

* Corresponding author. Tel.: +1 413 427 6662; fax: +1 508 856 3659.
E-mail addresses: hilary.placzek@umassmed.edu, hplaczek@gmail.com (H. Placzek), larry.madoff@state.ma.us (L.C. Madoff).
[1] Tel.: +1 617 983 6803; fax: +1 617 983 6840.

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with 7 of the 12 routinely recommended childhood vaccine prevents an estimated 33,000 deaths and 14 million cases of disease in every birth cohort, and saves society an additional $33 billion in costs including disability and lost productivity [2].

However, despite their goal of providing safe, effective disease prevention, vaccines do not guarantee complete protection. Recently published literature has re-examined epidemiological concepts surrounding two study designs used to determine how well a vaccine performs [3]. Pre-licensure, experimental vaccine efficacy trials represent how well the vaccine performs under controlled conditions, and are best measured by double-blind, randomized, clinical control trials [4]. This paper will focus on population-based vaccine effectiveness (VE) studies. Evaluations of VE occur after vaccine efficacy has been established, and assess how well a vaccine performs under natural field conditions rather than in a controlled clinical trial. VE studies take into account vaccine potency, how well target groups are immunized, and can control for the complexities of immunization practices and transmission dynamics such as exposure to disease, or individual response to particular vaccines. Measures of VE can also assess the benefits and effects of a vaccination program or identify previously unknown factors related to vaccine failure, and are critical to ensure that a licensed vaccine is working within a population.

Several study designs can be used to evaluate VE: (1) retrospective case control studies compare vaccination rates among infected cases and controls. This type of study expresses VE as a rate difference by calculating an odds ratio (OR) for developing infection despite vaccination; (2) an indirect cohort study examines individual protective responses by comparing vaccine-serotype infection rates with nonserotype-infection rates within a diseased population [5]; (3) case-coverage studies compare vaccination rates among cases with those of a similar cohort over a defined period of time, or (4) observational studies examine the change in disease burden and impact of a vaccine within a population over time [3]. Observational studies are often designed to measure the impact of a vaccine program by studying the effect of disease incidence in a population before and after program implementation [6], and to determine the relative risk of disease among the vaccinated groups compared to the unvaccinated [7,8].

In the U.S., VE studies have utilized population-based data by measuring immunization rates by telephone surveys, school- and practice-based assessments, and insurance claims information, among others. These methods can be time-consuming, expensive, and biased [9]. In response, an increasing number of resources, including immunization registries, maintain immunization records for infants, children, adolescents, and adults. These immunization information systems (IISs) are repositories of immunization data within specified geographic areas. IISs collect and consolidate records of vaccinations from multiple health care providers and across care settings. These surveillance systems have been shown to provide better immunization delivery by assisting in medical decision-making, reminder recall, determining coverage levels, and identifying pockets of need [10–15]. IISs can be used in VE studies to measure the degree of vaccine uptake in a variety of settings and populations by identifying confirmed VPD cases and/or confirming immunization history. Investigators then use this information to calculate vaccine performance [16–19].

Using IIS data can offer several methodological advantages over traditional observational studies. First, registries may allow more rigorous research methods to be used: in population-based studies, IISs provide individual-level information that can be matched with VPD morbidity data and could be used to conduct large cohort studies more efficiently. One benefit of cohort studies is that they are less prone to bias than case–control studies, a widely used design in populations lacking registries. In case–control studies, IISs can also provide a uniform method of determining vaccination status for cases or controls, and can reduce bias due to differential ascertainment of vaccination status. VE studies using IIS data can use case–control or population-based study designs such as prospective or retrospective cohort, or cross-sectional study design. Since registries contain population-based data for large numbers of people, extracting immunization information from a registry means that cohort studies could be conducted in populations with low incidence of disease, or in other low-risk populations since there is a larger sample from which to draw [20]. In addition, centralized data sources can allow researchers to measure the impact of vaccination in populations precisely by defining the base population more clearly. This population-based approach can prevent the introduction of socioeconomic or demographic biases that may be present in other data sources such as HMO-based data [21].

There is also evidence that the use of registry-based data is a developing field. Many immunization registries are currently operating all over the world. The US government, through CDC goals of expanding registries and financial incentives for fulfilling meaningful use objectives for electronic health records (EHRs), is instrumental in the promotion of IISs [22]. Furthermore, the Health Information Technology for Economic and Clinical Health Act (HITECH) Provisions within the ARRA were enacted in February 2009 [23]. As a result, there is an emphasis on improving health information technology in the US, and an increasing number of registries at state, city, and regional levels [12,24]. Centralized statewide registries are currently operating in 48 of 50 states, as well as several cities [21,25,26]. In one recent study, IIS data from eight states and one city (representing approximately 10% of the U.S. population) was used in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) study identifying adverse events from the H1N1 vaccine. PRISM represents a novel way of linking IISs and heath plan data to assess population-based immunization coverage and outcomes data on a nationwide basis.

However, considerable gaps exist in the literature detailing precisely how registries can facilitate more accurate, population-based vaccine effectiveness studies. In addition, harnessing IISs is a new and expanding field, and methodological limitations such as missing, inaccurate, or the potential for biased data have not been fully explored. Observational studies of vaccine effectiveness at the population level depend on accurate data [27], and recent studies have found that vaccination studies relying on electronic records may misclassify vaccinated individuals as unvaccinated, thereby producing inaccurate estimates of vaccine effectiveness [28]. This systematic review will determine how registries have been used to conduct VE studies, and if data contained in the registry is accurate and generalizable through the following aims: (1) to assess if an individualized, centralized system for tracking immunization rates can be utilized in vaccine effectiveness studies, (2) to describe reported estimates and methods to measure accuracy of registry data in VE studies, and (3) to describe reported results and methods to measure base population coverage of registry data in VE studies.

2. Methods

We conducted a systematic review of all available medical literature through January 31, 2010 that referred to or established the use of registry-based data sources to evaluate vaccine effectiveness.

2.1. Search strategy

We searched the electronic databases PubMed, MedLine, EMBASE, MeSH, ISI Web of Science, and the CDC immunization information system (IIS) Database. The following terms were used: ‘registry-based vaccine effectiveness’, or key words ‘immunization registry or register and vaccine effectiveness’;

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'immunization information system and vaccine effectiveness' (PubMed; MedLine; EMBASE); 'vaccination registry'; or 'coverage'; or 'registries/standards'; or 'registries/statistics and numerical data'; or 'vaccination/statistics and numerical data'; or 'immunization programs/standards'; or 'immunization programs/statistics and numerical data' (MeSH); 'vaccin*; registr* and effective*' (ISI Web of Science); and 'vaccination registry' (CDC IIS search). This strategy was supplemented by searching the reference lists of included articles to identify additional papers. Two authors of included studies provided supplemental materials; and two authors were contacted for recently published article content that was not available during the initial search attempt.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) researchers extracted registry-based immunization data to conduct vaccine effectiveness study in a human population; (2) study utilized any population-based, centralized (national, statewide, countywide, etc.) immunization registry data as a main source of vaccination status information; and (3) studies were published in English.

Exclusion criteria were as follows: (1) review papers; (2) studies published in a language other than English; (3) studies that included HMO-based or hospital-registry-based data only, without population-based data; (4) studies that did not address vaccine effectiveness; (5) studies with poor quality rating scores defined as <7 points out of a possible 14 points.

2.3. Definitions

'Registry-based' was defined as any population-based data source maintained at the local, regional, or national level that systematically collects immunization history information. Institutional- or HMO-based data did not meet review criteria in this context. The 'reference data source' refers to a demographic, census, or other population-based data source researchers used to validate population-based registry data utilized in the study (if applicable). 'Population coverage estimates' are the reported percentage of the source population included in the IIS. 'Accuracy' reported is the percentage of data that was consistent between the registry information and a validated measure (i.e. provider records, parent recall, or manual validation). In addition, 'VPD data sources' are the data sources used to provide a measure of VPD to calculate rates of vaccine effectiveness.

2.4. Data abstraction

We conducted a preliminary review by scanning article titles and abstracts; papers were then retrieved, and study text was scanned to determine if all inclusion criteria were met. To systematically collect data from included studies, we developed a data abstraction form that was pilot-tested prior to data collection (Appendix A).

2.5. Quality rating scores

A modified Downs and Black quality rating scale was used to rate the studies (Appendix B) [29]. We modified some text of the checklist and removed questions related to randomized case–control and intervention studies since these were not appropriate in this context. We then abstracted data from the selected papers, rated the studies independently, and compared our quality rating scores. Discrepancies in quality rating were discussed and addressed to reach study quality consensus between reviewers.

2.6. Analyses

We determined the number of studies using registry-based data to conduct VE studies. We then determined the distribution of rates for population coverage estimates, reported accuracy, and described this range using descriptive statistics.

3. Results

3.1. Search results

Two hundred ninety-three papers were identified as fulfilling the initial search criteria.

After application of the inclusion and exclusion criteria, 280 of the studies were discarded (Fig. 1), and we included 13 articles for final review. The main reason for exclusion was that the study did not use registry-based data to calculate VE (137 papers, 49% of excluded studies). No studies were dropped because of poor study quality.

Through direct systematic personal communication with included authors, we obtained four additional papers and included them in the final review.

Table 1 describes basic characteristics of included articles. The year of publication ranged from 1997 to 2010, and 13 of the 17 papers (76%) were published during or after 2004. Included studies utilized four types of study design, and occurred in nine countries focusing on ten vaccine-preventable diseases. Registry types included citywide, countywide, regional, statewide, and national IIS systems. Studies used VPD data collected from healthcare providers [30,31], linked notification reports systems and hospital discharge diagnosis data [32,33], or other national/regional disease surveillance systems [34]. Information related to matching IIS data with incident disease data at the individual-level is also included.

Table 2 contains information from the included studies highlighting specific IIS details. Results of the modified Downs and Black checklist to assess study quality indicate that out of a possible fourteen points, all included studies scored at least 7 points, with a mean study score of 11, and a range from 7 to 14 points. This table also lists population-based data sources used for reference purposes, study contexts, as well as accuracy and source population coverage rates.

3.2. Use of registry data in VE studies

Reviewed VE studies demonstrated three unique contexts in which registry-based data sources could identify immunization history data:

1. *Responding to an outbreak*: Three studies responded to epidemiological data showing an alarming increase in incidence for a particular type of vaccine-preventable disease. These studies used IIS-based data to identify outbreak cases and determine immunization history of these cases. Studies were retrospective in nature [30,31,35].
2. *Assess how vaccination affects incidence of disease*: Eight studies sought to measure the impact of vaccination programs by comparing population-based immunization data with incident rates of disease before and after implementation of vaccine programs. Study results were reported as changes in rates of incident disease as a result of implementation of vaccination or another intervention. Studies were retrospective if authors assessed or evaluated a vaccine program following its implementation [6,36–40]. One paper prospectively monitored the impact of a vaccine intervention at the beginning of program implementation [8].

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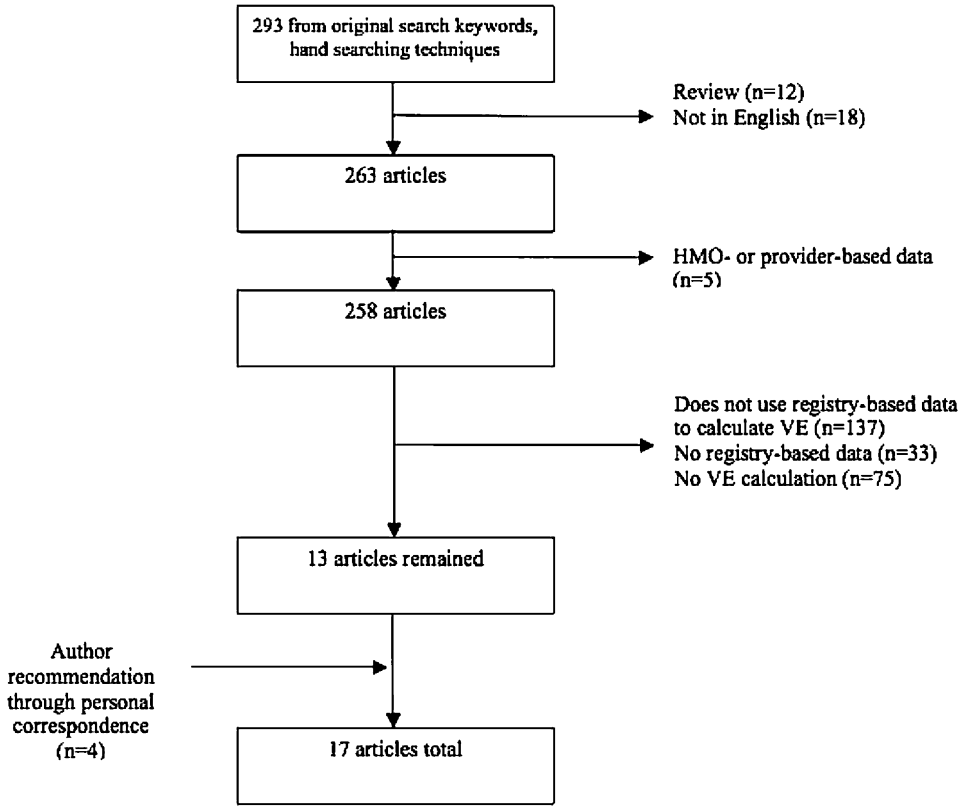

Fig. 1. Flow chart of included and excluded articles.

3. *Estimate vaccine effectiveness for a specific vaccine using population-based data:* Six studies monitored how effectively vaccines could prevent VPD. Of these, two studies matched cases with controls to conduct case–control evaluations of VE [41,42]. Three studies utilized a population-based data source to calculate risks of infection in vaccinated compared to unvaccinated groups, and expressed VE as an odds ratio (OR) [19,33,34]. One paper conducted serological testing of possible influenza cases, and compared vaccination rates between laboratory-confirmed and -unconfirmed cases [12]. In these studies, authors calculated VE by comparing immunization history data with incident cases of disease.

3.3. Accuracy in IISs

Only one of the 17 papers (6%) addressed accuracy of information contained in the IIS (Table 2). In this study, researchers found 65–77% accuracy of IIS data.

In this instance, Boom et al. assessed the effectiveness of pentavalent rotavirus vaccine (RV5). They also sought to validate immunization data from the Houston-Harris County Immunization Registry (HHCIR) against provider records to assess the utility of an IIS in evaluating VE. Results showed that registry data were the same as the provider record for 71% of patients. These authors also found that VE calculated using IIS data (VE for RV5 was 89% [CI]:70–96% and 85% [CI]:55–95%) was similar to estimates using a manually validated control group based on provider records (82% [CI]: 19–96%) [42].

3.4. Population coverage in IISs

While there are different methods of comparing or defining a base population, of the 17 papers included in this review, only three (18%) reported how many of the source population were included in the registry. Population coverage estimates encompassed a wide range of target population coverage estimates ranging from 25% to 90%.

For example, Fu et al. determined the effectiveness of the mumps vaccine against clinical mumps in outbreak cases. Cases were identified from physician-based surveillance data, and only cases whose information was found in the IIS were included in the study. Of the 1849 children in Guangzhou identified with mumps between Sept 1, 2004 and March 31, 2005, 1380 (74.6% of the total) were excluded because their records were not found in the system [35].

4. Discussion

This review shows that registry-based data have been used to evaluate VE in a variety of settings, contexts, and populations. We have found studies that matched registry-based immunization history data and measures of incident disease to assess VE in population-based settings. In order for IISs to provide accurate calculations of VE, however, two major assumptions should be satisfied:

Assumption 1: Data contained in the IIS accurately report who has or has not received a vaccine. This assumes that all IIS information is correct, and requires validation of accuracy, or matching of information from a reference data source. In this review, some papers indicated a need for establishing more accurate data, but did not conduct data validation [36]. Authors also noted that their registry data source might have underestimated current coverage due to incomplete reporting of vaccination status which may cause an underestimation of VE [19].

Assumption 2: Immunization data contained in the registry are representative of the general population. This assumes that the IIS in

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Table 1
Basic characteristics of articles included in the review ($n = 17$).

	First author	Title	Year	Study design	Vaccine type	Sample size	Study setting	IIS type	VPD data source	IIS data matched to individual-level[a]
1	Van Alphen	Effect of nationwide vaccination of 3-month-old infants in the Netherlands with conjugate Haemophilus influenzae type b vaccine: high efficacy and lack of herd immunity	1997	Case–control	Haemophilus influenzae type b	1.6 million	Netherlands	National	National Reference Lab for Bacterial Meningitis	Yes
2	Anonymous	Measles outbreak – Netherlands, April 1999–January 2000	2000	Retrospective cohort	Measles	2,907	Netherlands	National	National routine surveillance data	Yes
3	Markey	The effectiveness of Haemophilus influenzae type b conjugate vaccines in a high risk population measured using immunization register data	2001	Retrospective cohort	Haemophilus influenzae type b	119	Australia	National	Regional Hospital laboratory/Infection Control data	N/A
4	Averhoff	Control of hepatitis A through routine vaccination of children	2001	Prospective cohort	Inactivated hepatitis A	29,789	US: Butte County, CA	Countywide	Enhanced regional surveillance	Yes
5	Torvaldsen	Effectiveness of pertussis vaccination in New South Wales, Australia 1996–1998	2003	Retrospective cohort	Pertussis	1,278	South Wales, Australia	National	Notifiable Diseases Database of the NSW DoH	Yes
6	Hviid	Impact of routine vaccination with a conjugate Haemophilus influenzae type b vaccine	2004	Retrospective cohort	Haemophilus influenzae type b	758,988	Denmark	National	National Hospital Discharge Registry	Yes
7	Hviid	Impact of routine vaccination with a pertussis toxoid vaccine in Denmark	2004	Retrospective cohort	Pertussis	541,525	Denmark	National	National Hospital Discharge Registry and national reporting data	Yes
8	Barricarte	Effectiveness of the 7-valent pneumococcal conjugate vaccine: a population-based case–control study	2007	Case–control	7-valent pneumococcal conjugate (PCV7)	510	Navarra, Spain	Regional	Regional hospital laboratory data	Yes
9	Kelly	A Prospective Study of the Effectiveness of the New Zealand meningococcal B vaccine	2007	Prospective cohort	Meningococcal B	1,190	New Zealand	National	National surveillance (EpiSurv) combined with lab data	Yes
10	Ortqvist	Influenza vaccination and mortality: prospective cohort study of the elderly in a large geographical area	2007	Prospective cohort	Trivalent split-virion influenza	260,000	Stockholm County, Sweden	National	Weekly surveillance, Swedish Institute for Infectious Disease Control	Yes
11	Fu	Matched case–control study of effectiveness of live, attenuated S79 mumps virus vaccine against clinical mumps	2008	Case–control	Live, attenuated S79 mumps virus	938	Guangzhou, China	Citywide	Guangzhou Center for Disease Control and Prevention (Guangzhou CDC)	Yes
12	Anonymous	Interim within-season estimate of the effectiveness of trivalent inactivated influenza vaccine-Marshfield, WI 2007–2008 influenza season	2008	Case–control	Trivalent inactivated influenza	616	US: Marshfield, WI	Regional	Regional/statewide laboratory data	Yes
13	Adamkiewicz	Effectiveness of the 7-valent pneumococcal vaccine in children with sickle cell disease in the first decade of life	2008	Retrospective cohort	7-valent pneumococcal conjugate (PCV7)	1,247	US: Metro Atlanta, GA	Regional	Pop-based surveillance from Georgia Emerging Infections Program (EIP)	Yes
14	Bialek	Impact of routine hepatitis B immunization on the prevalence of Chronic hepatitis B virus infection in the Marshall Islands and the Federated States of Micronesia	2009	Retrospective cohort	Hepatitis B	1,171	Micronesia	National	Laboratory confirmation from serosurvey samples	N/A
15	Fu	Evaluation of live attenuated S79 mumps vaccine effectiveness in mumps outbreaks: a matched case–control study	2009	Case–control	Live, attenuated S79 mumps virus	388	Guangzhou, China	Citywide	Guangzhou Center for Disease Control and Prevention (Guangzhou CDC)	Yes
16	Galloway	Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccine in children	2009	Retrospective cohort	Meningococcal B	258,421	New Zealand	National	Surveillance data from Institute of Environmental Science & Research	Yes
17	Boom	Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States	2010	Cross-sectional	Pentavalent rotavirus (RV5)	285	US: Houston-Harris County, TX	Countywide	Surveillance data, Texas Children's Hospital	Yes

[a] 'N/A' indicates VPD data not matched to individual-level IIS data.

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Table 2
Key IIS components and study characteristics.

	First author	Year	Quality rating	Study context	Accuracy reported[a]	Reference population-based data source	Source population coverage[b]
1	Van Alphen	1997	10	Monitor incidence of disease	N/A	Central Bureau of Statistics	N/A
2	Anonymous	2000	7	Responding to an outbreak	N/A	N/A	N/A
3	Markey	2001	13	Monitor incidence of disease	N/A	Australian Bureau of Statistics	90%
4	Averhoff	2001	12	Monitor incidence of disease	N/A	State of CA, Dept. of Finance, Demographic Research Unit	N/A
5	Torvaldsen	2003	14	VE	N/A	N/A	N/A
6	Hviid	2004	12	Monitor incidence of disease	N/A	Central Registration System	N/A
7	Hviid	2004	14	Monitor incidence of disease	N/A	Danish Civil Registration System	N/A
8	Barricarte	2007	11	VE	N/A	N/A	N/A
9	Kelly	2007	13	Monitor incidence of disease	N/A	Statistics New Zealand	N/A
10	Ortqvist	2007	13	VE	N/A	Stockholm County Population Register	N/A
11	Fu	2008	11	Responding to an outbreak	N/A	N/A	25.4%
12	Anonymous	2008	9	VE	N/A	N/A	N/A
13	Adamkiewicz	2008	10	Monitor incidence of disease	N/A	National Immunization Survey	N/A
14	Bialek	2009	7	Monitor incidence of disease	N/A	N/A	N/A
15	Fu	2009	11	Responding to an outbreak	N/A	N/A	N/A
16	Galloway	2009	12	VE	N/A	Statistics New Zealand	N/A
17	Boom	2010	13	VE	71%	N/A	44%

[a] 'N/A' indicates no reported measure of accuracy in study results.
[b] 'N/A' indicates no reported measure of source population coverage in study results.

question is representative of the entire denominator of the source population, and requires validation by comparing IIS data to census results or other population-based data sources.

In countries that have linked census, healthcare utilization, and health outcome data, confirming population coverage is more manageable, for example, by using a unique identification number to link all national registries [33,38]. However, in countries without integrated national registries, there are no centralized linked statistical bureaus with demographic, healthcare, and utilization data. Without linkage capabilities, it can be challenging to conduct large population-based VE studies. Reference population data used in U.S. studies included National Immunization Survey data [8], or census data from the State of California [6]. These data sources can be limited by low participation rates and selection bias, and may not provide individual-level information.

Individual-level IIS data provide the level of detail required to conduct rigorous VE studies [43], and most population-based VE studies included in this review provide VPD incidence data linked to individual-level immunization data. However, some authors noted that, because of poor quality registry data, precise rates of vaccine coverage could not be determined [6,36], and two studies calculate VE based on aggregate coverage and/or disease levels. In one paper, authors indicated that poor quality IIS data could not be used to calculate immunization history, therefore mean vaccine coverage statistics were used to determine the denominators for VE calculations, rather than using IIS data directly [36]. Another study used IIS data to generate vaccination rates for the population, but applied these rates to mean disease levels to conclude that implementation of vaccination had decreased incidence of disease [37].

4.1. Conclusions

This is the first systematic review that has assessed the use of registry-based data in vaccine effectiveness studies. This review has shown that central immunization registries can be useful tools for evaluating the impact of immunization programs by measuring VE as a response and preventive measure in a variety of populations, study contexts, and diseases. It also demonstrates the potential utility of an immunization registry to conduct future VE studies and highlights future potential applications of registry-based data.

However, this review found that the quality of information may vary between registries, and much work remains to be done validating the accuracy and precision of immunization registry information. Standards and regulations do exist on issues surrounding costs, access and provider matters, validation methods, technical design considerations, and legal environment [12]. It is also true that other literature has addressed accuracy and generalizability of registry-based data [20,44,45], which indicates that validation methods for registry-based data have been developed and tested. In this review, only one study assessed accuracy of IIS data, and three papers assessed source population coverage rates. Because of the limited information available, IIS data quality, inherent bias, and population coverage can be difficult to assess, and

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drawing conclusions about the impact of validation techniques is difficult.

Studies also defined the base population differently, or had limited access to the base population information due to technological or financial limitations. Thus, even if consistent validation methods have been defined and tested elsewhere, technological or financial limitations can be considerable, and researchers may not have the resources to apply consistent validation measures in their studies.

In addition, reliable estimates of VE depend on accurate measures of disease incidence data, and require validated methods to match disease and immunization history data at the individual-level. This review did not assess the quality of incident disease data, but this should be addressed in future work.

Finally, improvements in the quality of individual-level immunization history data would strengthen VE studies using IISs by providing more precise information about who has or has not received a particular vaccine during a specified time period. These data could allow researchers to understand responses to current vaccines and better prepare for future pandemics. Higher quality individual-level data could also help us monitor the impact of the change of vaccines as well as shifts in VE attributable to other factors such as shifts in prevalent strains of pathogens, or herd immunity in the general population. Responding to today's changing and emerging vaccine-preventable diseases, more attention must be paid to the development of registry-based data sources to conduct population-based vaccine effectiveness studies.

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Appendix A. Abstraction form for a systematic review: immunization registry data as a method of surveillance in a pediatric population

Number of the study:
Study title:
First author of the study:
Year of publication:

1. Inclusion and Exclusion Criteria:
Is the study being included?
1. Yes
2. No

2. Reason(s) for inclusion/exclusion (check the following items that apply from the inclusion and exclusion criteria): Inclusion Criteria:
1. Focus of the study is vaccine effectiveness in a specified population
2. Study utilizes any population-based, centralized (statewide or citywide) immunization registry data as a main source of vaccination status information
3. Studies were published in English.

3. Exclusion criteria:
1. Review papers
2. Study does not include population-based registry-based data.
3. Study does not focus on vaccine effectiveness.
4. Studies published in language other than English
5. Studies have poor quality rating score

Reference:
Study type:
a. Clinical trial
b. Observational study
c. Cohort: prospective or retrospective
d. Case–control
e. Cross-sectional
f. Survey
g. Other

4. Background/study aims:
5. Study objectives:
6. Study population:
a. Inclusion criteria:
b. Exclusion criteria:
c. Sample size: Total: Male: Female:
d. Mean age ± SD or CI:
e. Age groups:
f. Gender distribution: Male(%): Female(%):
g. Control or comparison groups, if applicable: Yes No
h. SES Information available:
i. Race/ethnicity information
j. Other immunization/anti-viral hx information:

7. Study setting:

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Study location: - Urban - Rural - Mixed

8. Assessment of exposure:
- Registry (is self-report included?) How is immunization status determined?
  - Method of validation?

9. Assessment of outcome:
How was timing of disease season determined?
How is VE calculated/defined?
How is VE measured?

10. Study time period:

11. IIS Specifics:
- What is specific role of IIS in this study?
- What type of data is contained in the immunization information system (IIS)?
- Is there an indication of accuracy?
- How is the registry system organized and maintained? Who funds this system?
- Was a reference data source used to assess the source population coverage?
- Is this a cross-sectional estimate, or conducted over a period of time?
  - Is there a method of tracking immunization rates in order to compare annual rates?
- How is the registry tied into public health efforts?
- Other?
  - Is there evidence of increased immunization/utilization among target populations?
  - Address size of target and enrolled populations: high-risk groups, SES, race-ethnicity

12. Results:
Is a change in disease incidence reported?
Are figures reported for VE? If so, list them here:

13. Study design characteristics:
Types of bias addressed:
- Selection
- Detection
- Report
- Attrition
- Other

Residual confounding addressed?
Confounders:
a. Adjusted for potential confounders:
   i. Yes
   ii. No
b. List of confounders:

14. Appropriate statistical analysis?
15. Limitations:
16. Main findings:

17. Other notes:

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Appendix B. MODIFIED Downs and Black checklist

Reporting
Total:

1. ***Is the hypothesis/aim/objective of the study clearly described?***

Yes	1
No	0

2. ***Are the main outcomes to be measured clearly described in the Introduction or Methods section?***
If the main outcomes are first mentioned in the Results section, the question should be answered no.

Yes	1
No	0

3. ***Are the characteristics of the patients included in the study clearly described?*** In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

Yes	1
No	0

4. ***Are the interventions of interest clearly described?*** Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	1
No	0

5. ***Are the distributions of principal confounders in each group of subjects to be compared clearly described?*** A list of principal confounders is provided.

Yes	2
Partially	1
No	0

6. ***Are the main findings of the study clearly described?*** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions (This question does not cover statistical tests which are considered below).

Yes	1
No	0

7. ***Does the study provide estimates of the random variability in the data for the main outcomes?*** In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be

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assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1
No	0

8. ***Have actual probability values been reported (e.g. 0.035 instead of 0.05) for the main outcomes except where the probability value is less than 0.001?***

Yes	1
No	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.

9. ***Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*** The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	1
No	0
Unable to determine	0

10. ***Were the staff, places, and facilities where the patients were treated, representative of the treatment of the majority of patients receive?*** If yes, the study should demonstrate that the intervention was representative of that in use in the source population. The answer should be no if the intervention was undertaken in a specialist center unrepresentative of the hospitals most of the source population would attend.

Yes	1
No	0
Unable to determine	0

Internal validity – bias

11. ***Were the statistical tests used to assess the main outcomes appropriate?*** The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1
No	0
Unable to determine	0

12. ***Were the main outcome measures used accurate (valid and reliable)?*** For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrate the outcome measures are accurate,

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the question should be answered as yes.

Yes	1
No	0
Unable to determine	0

13. ***Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*** This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

Yes	1
No	0
Unable to determine	0

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