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Brief report

Use of the state immunization information system to assess rotavirus vaccine effectiveness in Connecticut, 2006–2008

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ABSTRACT

Immunization information systems (IIS) contain individual vaccination records and have potential use for evaluating post-licensure vaccine effectiveness (VE). A matched case–control study was performed by using the Connecticut state IIS to calculate rotavirus VE against hospitalization; results were compared with pre-licensure efficacy and with estimates previously obtained by traditional case–control methods using matched controls from medical sources and medical chart abstracted data. Case–patients ($n = 54$) were vaccine-eligible children with IIS entry and hospitalized for rotavirus gastroenteritis during July 2006–December 2008; each was matched to five control subjects ($n = 270$) who were randomly selected from IIS based on case-patient's birth date and town of residence. VE of at least one dose was 90.6%, comparable to the pre-licensure efficacy of 96% and to the unadjusted 83.5–90.7% estimates by using traditional case–control methods. IIS can be a convenient and potentially accurate tool for calculating VE.

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1. Introduction

Population-based immunization information systems (IIS) are electronic registries that consolidate vaccination records from multiple sources for persons residing in a geographic area [1–4]. The participation rate and data accuracy and completeness of IIS have improved since standards were set in 2001, although variations in data quality still exist [2,5–7]. IIS with a high rate of participation and data completeness have potential use for rapidly conducting post-licensure vaccine effectiveness (VE) studies, which traditionally have relied on a time- and labor-intensive method of finding suitable control subjects, conducting patient and control subject interviews, contacting providers for immunization data, and reviewing medical charts. A limited number of studies have used IIS as alternative data sources to traditional VE case–control methods [7–10], although vaccination data from IIS have been used to determine vaccine effectiveness in outbreak situations (e.g., identifying cases and their immunization history and population vaccination rates), to assess the impact of vaccination programs on incidence of disease, and to evaluate the effectiveness of a specific vaccine in preventing disease by using population-based data [7].

The IIS in Connecticut, the Connecticut Immunization Registry and Tracking System (CIRTS), authorized by state statute [11], was implemented statewide in 1998, and contains electronic entries of individual vaccinations and dates and demographic data for children aged <5 years [12]. Enrollment of children born and residing in Connecticut is automatic unless parents choose not to participate (in 2007, approximately 9% opted-out, another 6% were lost to follow-up after birth and before age 2 years) [13]. The accuracy of CIRTS immunization data has not been formally assessed. However, because of the relatively high participation rate and active efforts to ensure that all routine childhood immunizations are reported, CIRTS was previously used to calculate pneumococcal conjugate VE, demonstrating its utility for this purpose [9]. To assess CIRTS' utility and reliability for evaluating effectiveness of other vaccines, we describe its use in calculating rotavirus VE and compare our results with pre-licensure rotavirus efficacy [14] and with estimates previously obtained by using traditional methods [15].

2. Materials and methods

2.1. Study population and data collection

Connecticut has two pediatric specialty hospitals located in separate geographic regions: Yale New Haven Children's Hospi-

Abbreviations: IIS, immunization information systems; VE, vaccine effectiveness; CIRTS, Connecticut Immunization Registry and Tracking System; YNHCH, Yale New Haven Children's Hospital; CCMC, Connecticut Children's Medical Center; mOR, matched odds ratios; CI, confidence interval.

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tal (YNHCH) and Connecticut Children's Medical Center (CCMC) in Hartford. Case–patients were all infants aged ≥2 months but <3 years who had a positive stool test for rotavirus antigen and were hospitalized (i.e., admitted as inpatients) at YNHCH or CCMC for gastroenteritis any time during July 2006–December 2008. Children who received care in the emergency department but did not require hospitalization were not included. Age 2 months was chosen because rotavirus vaccination is recommended to begin at that age [14,16]. The upper age limit was the oldest a child could be who had received at least one dose of vaccine by July 2006. Because rotavirus was not a reportable disease in Connecticut at the time of this study, cases were identified through a retrospective review of hospital laboratory data beginning in July 2006, when the rotavirus vaccine (RotaTeq®, Merck & Co., Inc., Whitehouse Station, New Jersey) began to be widely distributed throughout Connecticut. Medical charts of all case–patients were reviewed by the study investigators to confirm that clinical symptoms were compatible with rotavirus gastroenteritis.

Using CIRTS, five control subjects were matched to each case-patient by birth date (within 14 days) and town of residence. After matching by town, control subjects were selected using the closest qualifying matches by birth date. In addition, based on review of CCMC and YNHCH laboratory data, controls had not been hospitalized for a laboratory confirmed rotavirus infection during July 2006–December 31, 2008. Control subjects were not contacted to verify absence of rotavirus infection diagnosed elsewhere.

Rotavirus vaccination status for case–patients and control subjects was obtained directly from CIRTS. The CIRTS record of case–patients was identified by searching for an exact match of first and last names and birth date. For the subset of case-patients and matched subjects, the number of rotavirus vaccine doses and exact dates of administration were extracted. A dose of rotavirus vaccine was considered valid if administered at least 7 days before illness onset of the case–patient. Additionally, a dose was considered valid if administered at age-appropriate intervals according to 2006 national recommendations [16]. The majority of our study period occurred before national recommendations were updated in June 2008 to increase the maximum age for the first dose and to extend the interval between subsequent dosing [17]. Case–patients without a CIRTS record (no matching name and birth date) were excluded from analysis.

2.2. Statistical analysis

Descriptive statistics were used to summarize rotavirus immunization information (vaccination with Rotateq®). Matched odds ratios (mOR) of having at least one dose, the partial series (less than three doses), and the full series of Rotateq®, and 95% confidence intervals (CIs) were calculated by using conditional logistic regression. We used the maximum likelihood estimator for receipt of at least one dose and for partial series vaccination. For full vaccination, we used the median unbiased estimator because of the limited number of fully vaccinated children [18]. VE was calculated as $(1 - \text{mOR}) \times 100\%$. SAS® statistical software, version 9.1.3 (SAS Institute, Inc., Cary, North Carolina), was used for analysis.

2.3. Ethical approval

This study was approved by the institutional review boards at CCMC, the YNHCH, and the Connecticut Department of Public Health. This investigation underwent human subjects review at the Centers for Disease Control and Prevention and was determined to be public health practice, not research.

3. Results

Of 68 case–patients identified, 14 (21%) did not have a CIRTS record. Of the remaining 54 (79%) case-patients, 41 were YNHCH patients and 13 were CCMC patients. Median age at symptom onset for the 54 case–patients was 11 months (range: 2–27 months). Three (6%) of the 54 case–patients had received one dose of rotavirus vaccine; two were considered as having received a valid dose, and one was not (vaccine administered same day as symptom onset). All three vaccinated case–patients were YNHCH patients.

Five matched control subjects were able to be identified for each of the 54 case–patients, resulting in a total of 270 controls. Among these 270 control subjects, 59 (22%) had received at least one valid dose of rotavirus vaccine: 18 (7%) one dose, 16 (6%) two doses, and 25 (9%) all three doses.

The receipt of one or more doses of rotavirus vaccine was 90.6% effective (95% CI: 59.0–97.9) against hospitalization at YNHCH or CCMC for rotavirus gastroenteritis (Table 1). Both vaccinated case–patients were hospitalized at YNHCH. Using only the YNHCH cases and controls, VE calculation of one or more doses was 87.4% effective (95% CI: 41.2–97.3) against hospitalization. VE of partial vaccination and of full vaccination for all cases and controls was 83.6% and 92.2%, respectively (95% CIs: 24.9–96.4 and 48.2–100, respectively).

4. Discussion

The VE estimates found using CIRTS are consistent with those obtained using other methods. We calculated a 90.6% rotavirus VE with a 95% upper confidence interval of 97.9%, which is consistent with the pre-licensure efficacy of 96% of at least one dose of vaccination in preventing hospitalization for rotavirus gastroenteritis [14]. Furthermore, our results are validated by Desai et al. by using an approximately identical case–patient population during an overlapping study period [15]. In both studies, case–patients included hospitalized YNHCH patients, and control subjects were identified from the same geographic region. Whereas we relied only on CIRTS to conduct the case–control study, Desai et al. used the traditional approach of enrolling control subjects and contacting providers for immunization records. Despite different study methodology, we calculated 87.4% effectiveness of at least one dose of rotavirus vaccine against hospitalization at YNHCH for rotavirus gastroenteritis, comparable to the unadjusted 83.5–90.7% estimates obtained by Desai et al. Moreover, without needing to enroll control subjects, obtain consent, and contact individual providers for immunization histories, our study required substantially less time and resources to complete, requiring only approximately 3 weeks with one staff person working part time. Because more information was obtained on control subjects, Desai et al. were able to adjust VE estimates on the basis of such factors as race/ethnicity, child care attendance, and tobacco use; these adjustments increased VE to 94.3–96.9% in their study. Thus, this is the second study using CIRTS that demonstrates that it can be used to generate reliable estimates of VE.

Additional evidence supporting potential use of IIS to traditional VE methods is provided by a rotavirus VE study conducted in Houston, Texas, using a similar methodology [10]. In that study, using only IIS data to obtain vaccination status and to identify control patients provided similar rotavirus VE estimates to using provider-verified data and concurrently enrolled control patients (82% and 82–88%, respectively). Although the authors found significant agreement in immunization data between IIS and provider records, IIS data were less complete overall, and only 49% of case–patients had an IIS record; however, the IIS was not population-based and required parents to elect to participate. In

Table 1
Effectiveness of rotavirus vaccine against hospitalization for rotavirus gastroenteritis among children aged 2 < 36 months, Connecticut, 2006–2008.

	Overall			
	YNHCH and CCMC combined		YNHCH	
	Case–patients	Control subjects	Case–patients	Control subjects
	n = 54 (%)	*n* = 270 (%)	*n* = 41 (%)	*n* = 205 (%)
Unvaccinated	52 (96.3)	211 (78.1)	39 (95.1)	162 (79.0)
Vaccinated[a]	2 (3.7)	59 (21.9)	2 (4.9)	43 (21.0)
Partial vaccination	2 (3.7)	34 (12.6)	2 (4.9)	22 (10.7)
Full vaccination	0 (0)	25 (9.3)	0 (0)	21 (10.2)
Receipt of one or more doses				
Matched OR (95% CI)	0.094 (0.021–0.417)	0.126 (0.027–0.588)		
Vaccine effectiveness (95% CI)	90.6% (59.0–97.9)	87.4% (41.2–97.3)		
Partial vaccination				
Matched OR (95% CI)	0.164 (0.036–0.751)		–	
Vaccine effectiveness (95% CI)	83.6% (24.9–96.4)		–	
Full vaccination[b]				
Matched OR (95% CI)	0.078 (0–0.518)		–	
Vaccine effectiveness (95% CI)	92.2% (48–100)		–	

YNHCH, Yale New Haven Children's Hospital; CCMC, Connecticut Children's Medical Center; OR, odds ratio; CI, confidence interval.

[a] Receipt of valid dose of rotavirus vaccine (Rotateq®).

[b] Although no case–patients had full vaccination, use of the median unbiased estimator resulted in a vaccine effectiveness estimate of <100%.

contrast, CIRTS captures vaccination coverage of children across Connecticut, and enrollment begins automatically at birth unless parents opt out. Although not all case–patients identified in our study were enrolled in CIRTS, 79% had a CIRTS record, a percentage that was similar to the overall 85% participation at the time [13].

Our study and the Houston rotavirus VE study raise the questions, what levels of participation, completeness and accuracy are necessary in order for an IIS to be considered useful by a program for assessing VE using case–control methodology? There is no ready or single answer. It depends in part on the purpose of the VE assessment and whether the program would be comfortable using a simple estimate to compare effectiveness in actual use with pre-licensing efficacy. The critical data in VE calculations is the probability of cases being vaccinated relative to controls. As long as the methodology limits vaccination information to that previously recorded in the IIS for both cases and controls, the main major sources of potential bias are if groups with different risks of getting the disease in question have different chances of getting vaccinated or of having vaccination reported to the IIS. These potential sources of bias can be mostly controlled for by matching cases and controls on these factors or controlling for them in analysis (e.g., town or zipcode of residence, number of other vaccines given, Medicaid eligibity). Once these criteria are met, participation, completion and accuracy rates by themselves in a case–control study have predictable effects on VE estimates. Participation mainly affects generalizability. Under-reporting of vaccination tends to artifactually reduce VE estimates with the effect greater with higher levels of under-reporting and with higher baseline vaccination rates. Accuracy, as long as it applies equally to cases and controls, will result in a net either increase or decrease in the percentage of cases and of controls vaccinated, with an effect similar to under-reporting if the net effect is a decrease in those vaccinated, and an increase in estimated VE if inaccuracies result in a net increase in those vaccinated. The higher the participation, vaccine data completeness and accuracy rates though, the less concern there is about their potential effects and of unrecognized bias. It is clear from the CIRTS studies and from the Houston study that VE estimates can be accurate with markedly different participation rates. More VE studies using IIS in different settings studying the same vaccine are needed, however, to provide the necessary data and experience to determine their usefulness for routinely providing initial data on overall VE of new vaccines. As part of those studies, it will be important to include information on assessments of the completeness and accuracy of the underlying registry vaccination data to understand the magnitude of their possible influence on the resulting VE estimates [7].

Our study has several important limitations. First, we did not validate CIRTS immunization data against provider records. However, we expect inaccuracies to be few (data transcription and data entry) as provider records are the original data source, to be of an equal extent between case–patients and control subjects and thus not likely to overestimate VE. Further, although it is likely that vaccination data may have been incomplete, we expect incompleteness rates to be low and equal between cases and controls. Vaccination data is actively solicited from providers for children who appear behind in vaccines at 7 and 19 months of age, and vaccination completion rates for all vaccines by age two years are high (>80%) and agree with Connecticut-specific estimates produced by the National Immunization Survey [19]. Second, our results might not be representative of VE statewide because case finding was limited to two geographic regions. However, these regions were in different, non-overlapping parts of the state and covered ≥27 different towns combined, thus representing a fairly large area of the state. Also, VE results in each area were similar. Third, while population-based, CIRTS does not include all children born in Connecticut or who move into Connecticut from out-of-state, as exemplified by the inability to include 21% of cases (missing CIRTS record). This could limit the generalizability of our results to all segments of the population of children, particularly if those not included are different with respect to socioeconomic factors such as race/ethnicity or poverty level. Fourth, because of the relatively small number of cases, we did not have statistical power to assess dose specific VE. Fifth, there could be differences in opportunities of case–patients and control subjects to be vaccinated. By matching by town, we minimized that possibility. Finally, misclassification of control subjects might have occurred if they had been admitted for rotavirus gastroenteritis to a hospital outside our study. However, if this happened, it would result in an underestimation of rotavirus VE.

In summary, rotavirus VE calculated by using CIRTS was similar to estimates obtained by using traditional methods for collecting vaccine histories and enrolling control subjects. By saving staff time and resources, IIS can be a useful and potentially reliable tool for rapidly evaluating VE.

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