Vaccine 28 (2010) 6314–6317

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Use of an immunization information system to assess the effectiveness of pentavalent rotavirus vaccine in US children☆

Leila C. Sahni[a,b,*], Julie A. Boom[a,b,c], Manish M. Patel[d], Carol J. Baker[a,c,e], Marcia A. Rench[a,c], Umesh D. Parashar[d], Jacqueline E. Tate[d]

[a] Center for Vaccine Awareness and Research, Texas Children's Hospital, Houston, TX, United States
[b] Immunization Project, Texas Children's Hospital, Houston, TX, United States
[c] Department of Pediatrics, Baylor College of Medicine, Houston, TX, United States
[d] Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States
[e] Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, United States

ARTICLE INFO

Article history:
Received 4 January 2010
Received in revised form 11 June 2010
Accepted 30 June 2010
Available online 15 July 2010

Keywords:
Immunization information system (IIS)
Vaccine effectiveness
Rotavirus vaccine

ABSTRACT

Immunization information systems (IISs) are accessible sources of immunization data. We validated immunization information from a local IIS against provider records and assessed the system's utility in evaluating vaccine effectiveness against rotavirus disease using a case-control study. Among the 91% of case and control patients with immunization records, 49% were in the IIS, and 97% had a provider record. Good agreement was observed across record sources (κ = 0.65). Vaccine effectiveness (VE) was 82% using IIS data compared to 82–88% using provider data. Controls identified through the IIS provided VE estimates similar to hospital control patients. IISs could represent a valuable source of data for effectiveness evaluations.

1. Introduction

Immunization information systems (IISs) are confidential, population-based, computerized systems that contain immunization data for individuals within a geographic area [1–3]. IISs consolidate immunizations administered by multiple public and private providers into one record, thus providing more complete and accurate vaccination histories by reducing immunization record fragmentation. Immunization information can be added into an IIS either by manual data entry from paper records or electronic data transfer [4,5]. Omission of immunizations administered is the most common data entry error, and can result in underestimation of immunization coverage rates [6,7]. As IISs have evolved, data completeness and accuracy have improved, although substantial variations still exist from state to state [8–12].

Concurrent with IIS development, many new vaccines have been added to the childhood immunization schedule. Post-licensure effectiveness studies of these vaccines have typically relied on immunization data obtained from vaccine providers, which is time-consuming and often requires extensive follow-up. To date, the use of IISs in vaccine effectiveness studies has been limited to documentation of immunizations administered and assessments of vaccination coverage [13–15]. More recently, the Boston immunization information system (BIIS) was examined as a possible tool for studying pertussis vaccine effectiveness in adolescents 11 through 17 years of age by comparing provider immunization information to BIIS data. Although a large number of adolescents had an IIS record, discrepancies between provider and IIS data occurred frequently [6]. To our knowledge, IIS data have not been previously used as an alternative source of control group data in vaccine effectiveness studies in the US.

We describe the use of an IIS as the sole source of immunization data for the calculation of pentavalent rotavirus vaccine (RV5; RotaTeq) effectiveness compared to more traditional approaches involving the enrollment of control patients. Our objectives included validating immunization information obtained from an IIS against provider records and assessing the utility of an IIS in evaluating vaccine effectiveness.

2. Methods

2.1. Patient enrollment

Children 15 days through 23 months of age were enrolled as part of a previously described study assessing post-licensure effectiveness of RV5 conducted at Texas Children's Hospital, a

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC).

* Corresponding author at: Immunization Project, 1102 Bates Street Suite 240, Houston, TX 77030, United States. Tel.: +1 832 824 2057; fax: +1 832 825 2103.
E-mail address: lcsahni@texaschildrens.org (L.C. Sahni).

0264-410X/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2010.06.109

582-bed academic pediatric hospital in Houston, TX [16]. In brief, surveillance was conducted for the entire month of June, 2008 among emergency department (ED) patients and inpatients. Fecal specimens were collected from patients with acute gastroenteritis (AGE) and were tested for rotavirus using a commercial enzyme immunoassay (Premier Rotaclone, Meridian Bioscience, Inc., Cincinnati, OH). Case patients with rotavirus-positive AGE and two comparison groups of patients with either symptoms of acute respiratory infection (ARI) or rotavirus-negative AGE were identified and enrolled. .

2.2. Immunization record collection

The names of up to three immunization providers were obtained from the parent/guardian during enrollment, and permission was obtained to contact these providers for immunization information. Immunization providers were contacted and a copy of the patient's immunization record was requested. Permission to search the Houston–Harris County Immunization Registry (HHCIR), the local IIS, for immunization data was also collected. In early 2008, 62% of public and 51% of private providers within the Greater Houston area reported immunizations administered to HHCIR (personal communication, Julie Boom, MD, Medical Director, HHCIR, September, 2008). An HHCIR record was considered to belong to a patient if the name, date-of-birth and sex were the same. HHCIR was queried twice to ensure the capture of all immunization data.

All immunization information for vaccines administered from birth until the day of enrollment was entered into a standardized study database and double-checked for accuracy. Patients for whom an immunization record could not be obtained from either HHCIR or a provider were excluded from analyses.

2.3. Statistical analysis

To assess the agreement between immunization information obtained for each patient from HHCIR and provider(s), comparisons were made between the number of doses of RV5 and diphtheria, tetanus, and acellular pertussis (DTaP) and heptavalent pneumococcal conjugate (PCV7) vaccines recorded in each source. DTaP and PCV7 vaccines were selected as comparison vaccines because they are routinely administered as part of the childhood immunization series and have known high coverage of >90% [17]. Furthermore, the recommended timing of the administration of these vaccines mirrors that of RV5 administration at 2, 4 and 6 months of age. Additionally, PCV7 was selected because it is the only other childhood vaccine not currently available in combination with other vaccines. No distinction between DTaP administered alone or in combination (such as in DTaP-HepB-IPV or DTaP-IPV/Hib) was made.

To measure agreement between HHCIR and provider immunization data, we calculated kappa statistics and Bhapkar's test for marginal homogeneity. Calculations were performed using SAS, version 9.1.

Vaccine effectiveness ($(1 - \text{odds ratio of vaccination}) \times 100$) was calculated using three comparison groups: patients with AGE who tested negative for rotavirus, patients with ARI symptoms, and children selected from HHCIR. Case patients were children with AGE who had laboratory-confirmed rotavirus. Up to 10 children from HHCIR were matched by date-of-birth (+/− 30 days) and zip code of residence. When vaccine effectiveness was calculated using children selected from HHCIR, only HHCIR data were used and provider data were excluded. Rotavirus-positive patients for whom an HHCIR record did not exist ($n = 44$ (49%)) of rotavirus-positive patients) were excluded from the analysis using the HHCIR-selected comparison group. Vaccine effectiveness was also calculated using provider-verified data only, HHCIR data only, and provider and HHCIR data combined for ARI patients and rotavirus-negative AGE patients.

2.4. Ethical approval

Institutional Review Board approval was obtained from Baylor College of Medicine and the Texas Department of State Health Services.

3. Results

A total of 628 AGE and ARI patients were enrolled. Of these, 54 (9%) had no immunization records available from either the HHCIR or a provider. Of the remaining 574 patients, 97% ($n = 555$) had an immunization record available from one or more providers, while 49% ($n = 284$) had a record available from HHCIR.

3.1. Immunization information system data validation

The number of doses of RV5, DTaP and PCV7 administered varied by source of record (Table 1). Combining both sources of immunization information, fewer children received three doses of RV5 than either DTaP or PCV7. However, for any given vaccine (RV5, DTaP or PCV7), the distribution of the number of doses recorded did not vary by source of record.

Of patients for whom immunization information was obtained, 46% ($n = 265$) had both HHCIR and provider records available. Examining the similarity between the number of doses of DTaP, PCV7 and RV5 recorded in each source, there was moderate agreement between sources for DTaP and PCV7 and substantial agreement between sources for RV5 information (Table 2). When records did not agree, the number of doses on the provider record usually, but not always, exceeded the number of doses found in HHCIR.

3.2. Vaccine effectiveness using immunization information system data

The availability of immunization records from providers or the HHCIR was not significantly different by case or control status (Table 3). No significant differences with respect to sex, race/ethnicity, or presence and duration of gastrointestinal symptoms were observed; however, rotavirus-positive case patients with an available IIS record were more likely to be "fussy or irritable" and to have fever during their illness than those without an IIS record (data not shown).

Vaccine effectiveness of a full 3 dose series of RV5 calculated using provider and HHCIR data combined was 85% (95% CI: [55,95]) when ARI patients were used as the comparison group and 89% (95% CI: [67, 96]) using rotavirus-negative AGE patients (Table 4). Vaccine effectiveness calculated using provider data only was 82% (95% CI: [47, 94]) using ARI patients and 88% (95% CI: [66, 96]) using rotavirus-negative AGE patients for comparison. Vaccine effectiveness calculated using HHCIR data only was 81% (95% CI: [−17, 91]) using ARI control patients, 85% (95% CI: [25, 97]) using rotavirus-negative control AGE patients and 82% (95% CI: [19, 96]) using age-matched control children selected from HHCIR.

4. Discussion

To our knowledge, this is the first US study to use immunization data obtained from an IIS in a case-control study of vaccine effectiveness and to validate the results by comparing with effectiveness estimates derived using vaccination data obtained through the traditional approach of contacting health care providers. RV5 vaccine effectiveness calculated using only HHCIR data was similar to estimates obtained using only provider-verified data and using

Table 1
Doses of RV5, DTaP[a] and PCV7 administered through date of enrollment by source ($n = 628$ patients).

	RV5			DTaP[a]			PCV7		
	Provider[b] $n = 555$ (88%)	HHCIR[c] $n = 284$ (45%)	Combined record[d] $n = 574$ (91%)	Provider[b] $n = 555$ (88%)	HHCIR[c] $n = 284$ (45%)	Combined record[d] $n = 574$ (91%)	Provider[b] $n = 555$ (88%)	HHCIR[c] $n = 284$ (45%)	Combined record[d] $n = 574$ (91%)
0 Doses	275 (50)	158 (56)	276 (48)	38 (7)	27 (10)	39 (7)	36 (6)	27 (10)	38 (7)
1 Dose	80 (14)	45 (16)	91 (16)	85 (15)	68 (24)	88 (15)	86 (16)	64 (23)	89 (16)
2 Doses	74 (13)	33 (12)	72 (13)	82 (15)	40 (14)	83 (14)	89 (16)	49 (17)	87 (15)
3+ Doses	126 (23)	48 (17)	136 (24)	350 (63)	149 (52)	364 (63)	344 (62)	144 (51)	360 (63)

[a] Number of doses of DTaP administered alone or in combination with other vaccines.
[b] Immunization history obtained from provider(s) identified by parent during enrollment.
[c] Immunization history obtained from HHCIR.
[d] The number of doses received is the greatest number of doses recorded by either source (provider or HHCIR).

Table 2
Agreement between provider and HHCIR records ($n = 265$).

	RV5	PCV7[a]	DTaP[a]
Provider and HHCIR records agree	206 (78)	186 (70)	187 (71)
Provider doses > HHCIR doses[b]	42 (16)	64 (24)	64 (24)
HHCIR doses > provider doses	17 (6)	15 (6)	14 (5)
K (95% CI)[c]	0.65 (0.58, 0.73)	0.50 (0.42, 0.59)	0.49 (0.41, 0.58)
p-value[d]	0.002	<0.001	<0.001

[a] DTaP and PCV7 comparing 0, 1, 2, and 3+ doses.
[b] The number of doses administered per the HHCIR is greater than the number of doses recorded in the provider record.
[c] Agreement increases with K: K < 0 indicates no agreement; K 0.0–0.19 = poor agreement; K 0.20–0.39 = fair agreement; K 0.40–0.59 = moderate agreement; K 0.60–0.79 = substantial agreement; K 0.80–1.00 = almost perfect agreement [18].
[d] p-value from Bhapkar's test for marginal homogeneity.

Table 3
Availability of vaccine record by source for rotavirus-positive AGE case patients, ARI control patients and rotavirus-negative AGE control patients[a].

	Rotavirus-positive cases	ARI controls		Rotavirus-negative controls	
	$n = 90$ (%)	$n = 228$ (%)	p-value[b]	$n = 115$ (%)	p-value[b]
Provider record available	73 (81)	196 (86)	0.28	102 (89)	0.13
HHCIR record available	44 (49)	96 (42)	0.27	55 (48)	0.88
Either record available	79 (88)	206 (90)	0.50	108 (93)	0.20

[a] AGE cases for whom a stool specimen was not collected were excluded ($n = 195$).
[b] For comparison with rotavirus-positive case patients.

provider and HHCIR data combined when both ARI and rotavirus-negative AGE patients were used for comparison. Furthermore, vaccine effectiveness using children matched from the HHCIR was similar to the vaccine effectiveness calculated in more traditional ways using concurrently enrolled comparison patients. These data, combined with the fact that our effectiveness estimates are comparable to but slightly lower than the pre-licensure RV5 efficacy of 94–96% against ED visits and hospitalizations for rotavirus diarrhea [19], provide reassurance that IIS data could provide a useful tool for post-licensure assessment of vaccine effectiveness.

We found significant agreement between immunization data from the HHCIR and provider records, with higher agreement between RV5 data across sources than for either DTaP or PCV7 data. This higher agreement between RV5 data sources may be because a larger proportion of patients had received no doses of RV5 than had received no doses of DTaP and PCV7. Agreement between number

Table 4
Vaccine effectiveness (VE) (and 95% confidence interval (CI)) against rotavirus disease by type of control and source of vaccination data.

	Source of immunization record								
	Provider and HHCIR records combined[a]			Provider records only[b]			HHCIR records only[c]		
	n 0 doses	n 3 doses	VE[d] (95% CI)	n 0 doses	n 3 doses	VE[d] (95% CI)	n 0 doses	n 3 doses	VE[d] (95% CI)
Cases	67	5	–	61	5	–	38	3	–
ARI controls	88	44	85 (55, 95)[e]	85	44	82 (47, 94)[e]	38	24	81 (−17, 91)[e]
AGE controls	47	32	89 (67, 96)[e]	44	32	88 (66, 96)[e]	21	17	85 (25, 97)[e]
HHCIR controls	–	–	–	–	–	–	260	68	82 (19, 96)[f]

[a] Includes case and control patients who have either a provider record or an HHCIR record or both records. The number of doses was defined as the greatest number of doses recorded in either source.
[b] Includes case and control patients who have a provider record. The number of doses was defined as the number of doses recorded in the provider record. No HHCIR data were included in analysis.
[c] Includes case and control patients who have an HHCIR record. The number of doses was defined as the number of doses recorded in the HHCIR record. No provider data were included in analysis.
[d] Protection conferred against rotavirus diarrhea by 3 doses of RV5 received 14 days or more prior to the hospital visit.
[e] VE adjusted for month and year of birth and age at presentation was calculated using unconditional logistic regression.
[f] VE calculated using conditional logistic regression; age-matched and zip code-matched controls randomly selected from HHCIR.

of doses is more likely to occur when no doses of vaccine have been administered than when one, two or three doses have been administered. Previous studies have suggested that information about newer vaccines in IISs is more likely to be incomplete than information about older vaccines [5]. Although RV5 was a relatively new vaccine at the time of this study, the higher agreement observed between RV5 data than older vaccines across sources suggests that this was not a significant factor.

As rotavirus-positive case patients for whom an HHCIR record could not be obtained were excluded from analysis, our case patient population for calculating vaccine effectiveness using HHCIR data was reduced by 51% from a total of 90 rotavirus-positive children to 44 who had an HHCIR record. However, there was no difference in rotavirus-positive patients with and without HHCIR records with regard to sex, age or zip code of residence. Thus, while the reduced sample size decreased precision (i.e., wide confidence limits), the accuracy of vaccine effectiveness estimates calculated using HHCIR data was not impacted. As previous studies have reported, IIS data vary in completeness and accuracy [4–8,20,21]. It is reasonable to expect that future studies may experience similar difficulties matching enrolled patients to IIS records, and thereby limit the number of case patients available for analysis. Additionally, the record validation demonstrated that the HHCIR data were generally less complete than provider records; thus, using IIS data alone to calculate vaccine effectiveness could result in an underestimation of the number of doses of RV5 administered, and could underestimate vaccine effectiveness.

This study has several limitations. It was conducted using the Houston–Harris County Immunization Registry, an IIS that is unique to the Greater Houston area, is not population-based, and requires parents to elect to participate; thus, the data gathered may not be generalizable to other IISs. The timing of dose administration was not evaluated in this analysis and may have resulted in the inclusion of doses that were administered at invalid intervals for a small number of participants. As previously noted, a low percentage of patients (46%) had both provider and HHCIR immunization records available. In addition, HHCIR data were only available for 49% of case patients. Many of the patients without HHCIR records may be attributed to lack of provider participation, which could be mitigated by the use of population-based IISs in future studies. To minimize these limitations in future vaccine effectiveness studies, the enrollment of large populations of case patients or the use of more heavily-populated IISs will be needed to further reinforce this approach. Furthermore, some IISs have been validated to show good comparability to National Immunization Survey (NIS) results that assess immunization coverage [22–25].

In conclusion, population-based IISs may represent a good source of immunization data for use in vaccine effectiveness studies. Using similar methodology in future studies would eliminate the need for concurrent enrollment of comparison patients, thus reducing study staff time and expenses for completing these tasks. Due to the variability in quality and completeness of IIS data noted in this and other studies, validation prior to use in a vaccine effectiveness evaluation may be needed.

Acknowledgements

The authors wish to thank Lizangela Acevado-Gonzalez, Betsy Mayes, Gabrielle Jackson, Chardria Trotter and Deyanira Verdejo, for their capable work in recruiting patients and collecting data; Maureen Moore and Rose Mata for assistance with data entry; Virginia Moyer, M.D. for editorial comments.

Conflicts of interest: No authors report financial disclosures or conflicts of interest.

Funding: This work was funded by a sole source grant from the Centers for Disease Control and Prevention that was awarded to Houston Department of Health and Human Services and then to Texas Children's Hospital.

References

[1] Centers for Disease Control and Prevention. Vaccines and immunizations: what is IIS? http://www.cdc.gov/vaccines/programs/iis/what-iis.htm. Accessed 19-02-2009.
[2] Horlick GA, Feikema Beeler S, Linkins RW. A review of state legislation related to immunization registries. Am J Prev Med 2001;20(3):208–13.
[3] Urquhart G. National overview of registries, phase II. http://immunizehouston.org/texas-immunization-summit-2008/gary-urquhart. Accessed 19-02-2009.
[4] Boyd TD, Linkins RW, Mason K, Bulim I, Lemke B. Assessing immunization registry data completeness in Bexar County, Texas. Am J Prev Med 2002;22(3):184–7.
[5] Kolasa MS, Cherry JE, Chilkatowsky AP, Reyes DP, Lutz JP. Practice-based electronic billing systems and their impact on immunization registries. J Public Health Manag Pract 2005;11(6):493–9.
[6] Mahon BE, Shea KM, Dougherty NN, Loughlin AM. Implications for registry-based vaccine effectiveness studies from an evaluation of an immunization registry: a cross-sectional study. BMC Public Health 2008;8:160, doi:10.1186/1471-2458/8/160.
[7] Khare M, Battaglia MP, Huggins VJ, Stokley S, Hoaglin DC, Wright RA, et al. Accuracy of vaccination dates reported by immunization providers in the National Immunization Survey. Presented at the American Statistical Association. In: Proceedings of the section on survey research methods. 2000.
[8] Davidson AJ, Melinkovich P, Beatty BL, Chandramouli V, Hambidge SJ, Phibbs SL, et al. Immunization registry accuracy: improvement with progressive clinical application. Am J Prev Med 2003;24(3):276–80.
[9] Samuels RC, Appel L, Reddy S, Tilson M. Tracking of immunizations: computers may not be the magic bullet. In: Presented at annual conference of Ambulatory Pediatric Association. 1996.
[10] Stonehocker-Quick L, Rotharmel P, Webb W, Meagher G, Hoekstra EJ. How valid is registry data for AFIX? Presented at National Immunization Conference. 1997.
[11] LeBaron CW, Mercer JT, Massourdi MS, Dini E, Stevenson J, Fischer WM, et al. Changes in clinic vaccination coverage after institution of measurement and feedback in 4 states and 2 cities. Arch Pediatr Adolesc Med 1999;153(8):879–86.
[12] Adams WG, Conners WP, Mann AM, Palfrey S. Immunization entry at the point of service improves quality, saves time and is well-accepted. Pediatrics 2000;106(3):489–92.
[13] Averhoff F, Shapiro CN, Bell BP, Hyams I, Burd L, Deladisma A, et al. Control of hepatitis A through routine vaccination of children. JAMA 2001;286(23):2968–73.
[14] Piedra PA, Gaglani MJ, Kozinetz CA, Herschler GB, Fewlass C, Harvey D, et al. Trivalent live attenuated intranasal influenza vaccine administered during the 2003–2004 influenza type A (H3N2) outbreak provided immediate, direct, and indirect protection in children. Pediatrics 2007;120(3):e553–64.
[15] Gaglani M, Riggs M, Kamenicky C, Glezen WP. A computerized reminder strategy is effective for annual influenza immunization of children with asthma or reactive airway disease. Pediatr Infect Dis J 2001;20(12):1155–60.
[16] Boom JA, Tate JE, Sahni LC, Rench MA, Hull JJ, Gentsch JR, et al. Effectiveness of pentavalent rotavirus vaccine in a large, urban U.S. population. Pediatrics 2010;125(2):e199–207.
[17] Centers for Disease Control and Prevention. National, state, and local area vaccination coverage among children aged 19–35 months—United States, 2008. MMWR Morb Mortal Wkly Rep 2009;58(33):921–6.
[18] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33(1):159–74.
[19] Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354(1):23–33.
[20] Kempe A, Daley MF, Barrow J, Allred N, Hester N, Beaty BL, et al. Implementation of universal influenza immunization recommendations for health young children: results of a randomized, controlled trial with registry-based recall. Pediatrics 2005;115(1):146–54.
[21] Khare M, Piccinino L, Barker LE, Linkins RW. Assessment of immunization registry databases as supplemental sources of data to improve ascertainment of vaccination coverage estimates in the National Immunization Survey. Arch Pediatr Adolesc Med 2006;160(8):838–42.
[22] Centers for Disease Control and Prevention. Immunization information systems progress—United States, 2006. MMWR Morb Mortal Wkly Rep 2008;57(11):289–91.
[23] Wooten KG, Darling N, Singleton JA, Shefer A. National, state, and local area vaccination coverage among children aged 19–35 months—United States. MMWR Morb Mortal Wkly Rep 2007;56(34):880–5.
[24] Khare M, Piccinino L, Battaglia MP, Linkins RW. Immunization registries as supplemental sources of data for improving vaccination coverage estimates in the U.S. In: Presented at the 2003 Immunization Registry Conference. 2003.
[25] Piccinino L, Khare M, Battaglia MP, Bartlett D, Barker L. Immunization registry and provider-report vaccination histories: assessing missing vaccinations. In: Presented at the 38th annual National Immunization Conference. 2004.