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Leveraging State Immunization Information Systems to Measure the Effectiveness of Rotavirus Vaccine

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KEY WORDS

rotavirus vaccine, vaccine effectiveness, rotavirus, immunization

ABBREVIATIONS

RV—rotavirus vaccine
RV5—pentavalent rotavirus vaccine
IIS—immunization information system
VE—vaccine effectiveness
ED—emergency department
DTaP—diphtheria-tetanus-acellular pertussis
PCV7—7-valent pneumococcal conjugate vaccine
IPV—inactivated polio vaccine
CI—confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: The rotavirus disease burden among US children has declined markedly after the introduction of rotavirus vaccination. Many pediatric providers participate in an immunization information system (IIS), and these systems can be useful for assessing vaccine effectiveness, including that of rotavirus vaccine.



WHAT THIS STUDY ADDS: Vaccine effectiveness of pentavalent rotavirus vaccine was quantitated under routine use in the United States for a 3-dose series during the first 3 years of life and, for partial series using rotavirus cases from 5 hospitals and capitalizing on data from IISs.

abstract

OBJECTIVE: Electronic immunization information systems (IISs) are now established in almost all US states. We used the IIS in Minnesota, Georgia, and Connecticut for immunization data and as the source of 1 of 2 control groups to measure pentavalent rotavirus vaccine (RV5) effectiveness (VE) using case-control methodology.

PATIENTS AND METHODS: Case-subjects were vaccine-eligible children who presented to 1 of 5 hospitals or emergency departments with gastroenteritis and had rotavirus antigen detected in stool during any of 3 rotavirus seasons (2007–2009). Two control groups were used: children with gastroenteritis who tested negative for rotavirus and children from the IIS matched by zip code and birth date. In Minnesota and Georgia, immunization records for rotavirus-positive and -negative children were also obtained from providers.

RESULTS: Overall, 402 (96%) rotavirus case-subjects and 825 (97%) rotavirus-negative controls who met eligibility criteria were found in the IISs. Ten IIS controls were identified for each case. VE estimates for RV5 were similar across control groups, immunization data sources, and states. VE point estimates for 3 vs 0 doses were 89% to 94% among children aged 8 months or older and 86% to 92% among those aged 24 months or older. VE for 2 doses was $\geq 90\%$ among children aged 8 months or older, and VE for 1 dose was 66% among those aged 6 weeks through 5 months.

CONCLUSIONS: Three RV5 doses confer sustained protection against rotavirus disease during the first 3 years of life in US children. Two RV5 doses also seem to provide good protection. IISs can be valuable tools for assessing the effectiveness of vaccines administered to young children. *Pediatrics* 2011;128:e000

Universal rotavirus vaccination was recommended for US infants by the Advisory Committee on Immunization Practices in February 2006 with 3 doses of pentavalent rotavirus vaccine (RV5 [RotaTeq, Merck and Co, Whitehouse Station, NJ]) to be given at ages 2, 4, and 6 months.¹ In June 2008, recommendations were updated to include the monovalent (RV1) 2-dose vaccine (Rotarix [GlaxoSmithKline Biologicals, Rixensart, Belgium]).¹ The first dose of rotavirus vaccine (RV) is to be given at the age of 6 weeks through 14 weeks 6 days and the last dose by the age of 8 months 0 days.

We assessed the effectiveness of RV under routine use in the United States by using case-control methodology and taking advantage of state electronic immunization information systems (IISs).² The use of IISs for assessing vaccine effectiveness (VE), if shown to produce valid results, offers substantial reductions in time and staff effort compared with that expended by contacting individual providers for immunization records. In addition, although each type of control group has advantages and disadvantages, using the IIS itself as a source of controls is a labor-saving approach compared with other methods that require additional steps to obtain immunization information (eg, using birth registries or identifying children seeking hospital care). However, public IISs have been infrequently used in VE evaluations.³ We used IISs from 3 states (Minnesota, Georgia, and Connecticut) in the Emerging Infections Program Network⁴ as a source of immunization data and 1 of 2 control groups, and we compared results with those obtained by using more traditional methods.

PATIENTS AND METHODS

Children With Gastroenteritis: Rotavirus Case-Subjects and Rotavirus-Negative Controls

Data were obtained retrospectively from 2 hospitals in St Paul/Minneapolis,

Minnesota (Children's Hospitals and Clinics of Minnesota), 2 hospitals in Atlanta, Georgia (Scottish Rite Children's Hospital and Egleston Children's Hospital), and 1 hospital in New Haven, Connecticut (Yale-New Haven Children's Hospital), to identify children with gastroenteritis eligible for the evaluation. Eligible children were those who met all of the following criteria: (1) diagnosed with gastroenteritis and managed as an emergency department (ED) patient, short-stay patient, or inpatient per hospital administrative data during any of 3 rotavirus seasons (season 1: December 1, 2006, to June 31, 2007; season 2: December 1, 2007, to June 31, 2008; season 3: December 1, 2008, to June 31, 2009); (2) had results available from a rotavirus antigen immunoassay ordered by the clinician on a stool sample collected within 2 days of presentation; (3) eligible to have received at least 1 RV dose ≥ 14 days before presentation according to birth date (born on or after April 1, 2006) and age at evaluation (≥ 56 days); and (4) lived in the usual catchment area of the hospital (see Supplemental Information). Children met criteria for gastroenteritis diagnosis if they were tested for rotavirus as described above and had either a discharge *International Classification of Diseases, Ninth Revision* (ICD-9) code for gastroenteritis⁵ or documentation of diarrhea or vomiting in the admission note. Children were excluded if any ICD-9 codes for the visit included a severely immunocompromising condition (eg, malignancy, HIV infection). Children who met all of the criteria listed above were classified as either a rotavirus case-subject or a rotavirus-negative gastroenteritis control on the basis of the enzyme immunoassay result.

Vaccination Information and IIS Controls

The public health departments in Minnesota, Georgia, and Connecticut

maintain an IIS, and most pediatric immunization providers in each state participate in the system (see Supplemental Information). Site staff queried the IIS for each rotavirus case-subject and rotavirus-negative control using the child's name and birth date, and the dates and manufacturer of RV doses and dates of diphtheria-tetanus-acellular pertussis (DTaP) vaccine, inactivated polio vaccine (IPV), or 7-valent pneumococcal conjugate vaccine (PCV7) doses administered were obtained; in Connecticut, PCV7 dates were not obtained.

In Minnesota and Georgia, the sites with large case numbers, site staff attempted to obtain immunization records directly from providers of case-subjects and rotavirus-negative controls from seasons 2 and 3 who were aged 6 months or older at rotavirus evaluation and who, according to the IIS, had not received ≥ 3 RV5 doses by the rotavirus evaluation date.

Ten controls per case-subject were selected from the IIS matched by birth date and residence zip code (or Connecticut town) by using a computer program algorithm that selected controls regardless of the child's immunization status. Within the same zip code, controls with the same birth date as the case-subject were selected first, followed by controls with a birth date within 1 day of the case-subject birth date, within 2 days of the case-subject birth date, and so on, until 10 controls were identified (see Supplemental Information).

Analysis

Ages (in days) at the hospital visit and at each vaccine administration were calculated. For analysis, an RV dose was counted if it had been administered ≥ 14 days before the date of the hospital visit or, for IIS controls, ≥ 14 days before the reference age. The reference age for each IIS control was the

age of the respective case-subject at the hospital visit for rotavirus gastroenteritis.

RV effectiveness was calculated as $(1 - \text{odds ratio}) \times 100\%$. Odds ratios for RV dose(s) receipt for case-subjects compared with controls in specific age groups were calculated by using unconditional logistic regression and controlling for site (Minnesota, Georgia, or Connecticut), season (2006–2007, 2007–2008, or 2008–2009), and birth quarter (ie, April 2006 to June 2006). Including birth quarter accounted for increasing RV uptake over time.⁶ Other factors assessed for inclusion in the model were private insurance versus nonprivate/no insurance and specific hospital for Minnesota and Georgia. In almost all children, rotavirus vaccination status did not change after 8 months of age, which indicates that providers were following age recommendations for the last dose. Therefore, overall VE was calculated for children aged 8 months or older. Exact unconditional logistic regression was used for odds ratio measurement in subsets with relatively small case and control numbers. VE estimates were first calculated by using only the immunization information obtained from the IISs and including data from all 3 seasons. For Geor-

gia and Minnesota children from seasons 2 and 3 aged 8 months or older, VE estimates were then calculated by using the maximum number of RV doses from the IIS and provider record combined (see Supplemental Information).

Using the second control group, odds ratios for RV dose(s) receipt for case-subjects compared with IIS controls were calculated by using conditional logistic regression. Analyses were performed by using Stata 11 (Stata Corp, College Station, TX).

RV Doses

It is possible that some children who were considered to have had no RV doses might really have received RV but a true vaccine record covering the early infancy period was not obtained. Therefore, VE estimates were also calculated by using only children who met a vaccine-record “restriction”: available record included 3 doses of at least 1 infant vaccine series (RV, DTaP, IPV, or PCV7) received through 8 months of age, information that parents refused vaccines, or the provider reported that the child was delayed in receiving immunizations. Only RV5 VE could be calculated, because almost all RV doses adminis-

tered during this time period were RV5.

When leftover sample was available, stool samples from case-subjects at the Minnesota and Georgia hospitals during season 3 were sent to the Centers for Disease Control and Prevention (CDC) for strain typing.⁷ This project was reviewed by the human subjects committees at the CDC and the participating institutions.

RESULTS

Overall, 402 (96%) rotavirus case-subjects and 825 (97%) rotavirus-negative controls who met initial eligibility criteria were located in the IISs (Table 1). Sixty-nine percent of the total case-subjects available for analysis had been managed as hospital inpatients (70% in Minnesota, 62% in Georgia, and 100% in Connecticut). Only Minnesota categorized some case-subjects (15%) as short-stay patients. Ninety-eight percent of the case-subjects and 93% of the rotavirus-negative controls had received a gastroenteritis discharge code.

In Minnesota, among children aged 6 months or older who were not up-to-date with RV according to the IIS and for whom a provider record was obtained, 93% of the case-subjects and 70% of the rotavirus-negative controls

TABLE 1 Number of Children Who Tested Rotavirus-positive or Rotavirus-negative, According to Season, Site, and IIS Status

	Season 1: Dec 2006–Jun 2007, n (%)		Season 2: Dec 2007–Jun 2008, n (%)		Season 3: Dec 2008–Jun 2009, n (%)		Seasons 1–3, n (%)	
	In IIS	Not in IIS	In IIS	Not in IIS	In IIS	Not in IIS	In IIS	Not in IIS
Minnesota								
Rotavirus-positive	82 (100)	0 (0)	38 (100)	0 (0)	119 (98)	3 (2)	239 (99)	3 (1)
Rotavirus-negative	75 (99)	1 (1)	153 (100)	0 (0)	178 (99)	1 (<1)	406 (99)	2 (<1)
Georgia								
Rotavirus-positive	63 (95)	3 (5)	21 (88)	3 (12)	54 (95)	3 (5)	138 (94)	9 (6)
Rotavirus-negative	122 (99)	1 (1)	111 (97)	3 (3)	132 (94)	9 (6)	365 (97)	13 (3)
Connecticut								
Rotavirus-positive	11 (100)	0 (0)	9 (82)	2 (18)	5 (83)	1 (17)	25 (89)	3 (11)
Rotavirus-negative	10 (83)	2 (17)	21 (91)	2 (9)	23 (85)	4 (5)	54 (87)	8 (13)
Sites combined								
Rotavirus-positive	156 (98)	3 (2)	68 (93)	5 (8)	178 (96)	7 (4)	402 (96)	15 (4)
Rotavirus-negative	207 (98)	4 (2)	285 (98)	5 (2)	333 (96)	14 (4)	825 (97)	23 (3)

Numbers are based on those children eligible for evaluation (see Children With Gastroenteritis: Rotavirus Case-Subjects and Rotavirus-Negative Controls). “Not in IIS” includes children who were not found in the IIS and those who were found but who were indicated as having opted out of the IIS.

TABLE 2 VE for 3 vs 0 RV Doses Among Children Aged 8 Months or Older

Age ≥ 8 mo	Source of Immunization Data	Minnesota				Georgia				Minnesota + Georgia + Connecticut						
		Cases		Controls		Cases		Controls		Cases		Controls				
		n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)			
Controls: rotavirus-negative	IIS, restricted	170	18 (11)	180	87 (48)	90	80–95	95	4 (4)	135	43 (32)	283	23 (8)	341	141 (41)	89 (81–94) ^a
	IIS, restricted and provider	106	18 (17)	138	87 (63)	93	83–97	66	4 (6)	107	43 (40)	188	23 (12)	265	141 (53)	90 (82–95) ^a
Controls: IIS (matched)	IIS + provider, restricted	120	23 (19)	175	115 (66)	92	84–96	61	5 (8)	105	48 (46)	181	28 (15)	279	163 (58)	90 (84–94) ^b
	IIS + provider, restricted	96	22 (23)	164	115 (70)	93	85–97	47	5 (11)	93	48 (52)	143	27 (19)	257	163 (63)	91 (85–95) ^b
Controls: IIS (matched)	IIS	170	18 (11)	1510	590 (39)	88	79–93	95	4 (4)	836	225 (27)	283	23 (8)	2520	850 (34)	89 (83–93) ^c
	IIS, restricted	106	18 (17)	1114	588 (53)	94	86–97	66	4 (6)	581	225 (39)	188	23 (12)	1847	848 (46)	94 (89–97) ^c

Restricted indicates that analysis was restricted to those children whose IIS record (or provider record, for those with provider records) indicated that the child had received 3 doses of RV, DTaP, IPV, or PCV through 8 months of age, stated that the child was delayed on immunizations, or that the parents had refused immunizations. Eight children were in the last 2 categories combined. Results with only an IIS as the source of immunization data are from seasons 1 through 3 combined. Results with combined IIS and provider as the sources of immunization data are from seasons 2 and 3 combined.

^a VE estimates were the same when the model controlled for specific hospital in Georgia or Minnesota and insurance status (private versus public/none), in addition to site, season, and birth quarter. Therefore, the final model included only site, season, and birth quarter. IIS data from 2 rotavirus-negative controls from Minnesota indicated receipt of 4 RV doses.

^b Overall results using IIS plus provider records are from Georgia and Minnesota combined. IIS data from 2 rotavirus-negative controls from Minnesota indicated receipt of 4 RV doses.

^c Data from 14 IIS controls from Minnesota and 1 from Georgia indicated receipt of 4 RV doses.

had the same number of RV doses in the IIS and provider record (Supplemental Table 5). When restricted to children whose IIS record included 3 doses of a vaccine through 8 months of age, 95% of Minnesota case-subjects and 84% of controls had the same number of RV doses in both data sources. In Georgia, 97% of the case-subjects and 90% of the rotavirus-negative controls on whom a provider record was obtained had the same number of RV doses in both data sources (Supplemental Table 6).

For seasons 2 and 3 children aged 8 months or older at rotavirus evaluation, 162 (78%) of 208 total rotavirus case-subjects had no RV doses, 10 (5%) had 1, 7 (3%) had 2, and 29 (14%) had ≥3 RV doses according to the maximum number of doses from the combined IIS/provider record for Georgia and Minnesota children and IIS record for Connecticut children. Among the rotavirus-negative children aged 8 months or older, 129 (35%) of the total 366 had no RV doses, 22 (6%) had 1, 41 (11%) had 2, and 173 (48%) had ≥3 doses.

VE for 3 RV Doses

Overall, using rotavirus-negative controls, the effectiveness of 3 vs 0 RV doses among children aged 8 months or older was 89% (95% confidence interval [CI]: 81%–94%), and the point estimates in Minnesota and Georgia were virtually identical (Table 2). At both sites with provider records, among children who met the vaccine-record restriction, the within-site VE estimates were virtually identical (93% in Minnesota, 90% and 91% in Georgia) when using RV information from the IIS alone or the maximum doses from the combined IIS/provider record.

Ten IIS controls were located for each case found in the IISs. Overall, 98% of the IIS controls had a birth date within 14 days of the birth date of the respec-

TABLE 3 VE for 3 vs 0 RV Doses, According to Subsets of Age and Hospital Setting Among Children Aged ≥ 8 Months

	Source of Immunization Data	Minnesota + Georgia + Connecticut				VE (95% CI)
		Cases		Controls		
		<i>n</i>	<i>n</i> (%) Vaccinated	<i>n</i>	<i>n</i> (%) Vaccinated	
VE for 3 vs 0 doses, according to age						
Controls: rotavirus-negative						
8–11 mo	IIS + provider	24	4 (17)	92	63 (68)	93 (75–99) ^{a,b}
12–23 mo	IIS + provider	102	21 (21)	147	86 (59)	89 (77–94) ^a
≥ 24 mo	IIS + provider	55	3 (5)	41	14 (34)	91 (62–99) ^{a,b}
	IIS + provider, restricted	45	3 (7)	35	14 (40)	92 (63–99) ^{a,c}
Controls: IIS (matched)						
8–11 mo	IIS	109	3 (3)	1009	194 (19)	94 (78–99)
12–23 mo	IIS	116	17 (15)	988	517 (52)	88 (80–93)
≥ 24 mo	IIS	58	3 (5)	523	139 (27)	87 (56–96)
	IIS, restricted	40	3 (8)	372	138 (37)	86 (50–96)
VE for 3 vs 0 doses among children aged ≥ 8 mo, according to case hospital setting						
Controls: rotavirus-negative						
Inpatient/short-stay cases	IIS + provider	140	20 (14)	280	163 (58)	92 (86–96) ^a
ED cases	IIS + provider	41	8 (20)	280	163 (58)	81 (53–92) ^a
Controls: IIS (matched)						
Inpatient/short-stay cases	IIS	221	17 (8)	1953	672 (34)	90 (84–94)
ED cases	IIS	62	6 (10)	567	138 (31)	84 (58–94)

Restricted indicates that analysis was restricted to those children whose IIS record (or provider record, for those with provider records) indicated that the child had received 3 doses of RV, DTaP, IPV, or PCV through 8 months of age, stated that the child was delayed on immunizations, or that the parents had refused immunizations. Eight children were in the last 2 categories combined. Results with only an IIS as the source of immunization data are from seasons 1 through 3 combined. Results with combined IIS and provider as the sources of immunization data are from seasons 2 and 3 combined.

^a Results using IIS plus provider records are from Georgia and Minnesota combined. The model included site, season, and birth quarter.

^b Exact logistic regression.

^c Exact logistic regression; median age of vaccinated rotavirus-negative controls: 27.8 months (interquartile range: 27.1–29.6).

tive case-subject. The effectiveness of 3 vs 0 RV doses among children aged 8 months or older was 89% (95% CI: 83%–93%), which is the same point estimate as with rotavirus-negative controls (Table 2). In Minnesota, the point estimate increased from 88% to 94% when limited to the children who met vaccine restriction; the point estimate was virtually unchanged in Georgia.

The 3-dose RV effectiveness among subsets of children was examined (Table 3). Using rotavirus-negative controls and the maximum RV doses, the VE estimate for 3 vs 0 RV doses among children aged 24 months or older was similar (91% [95% CI: 62%–99%]) to that obtained among children aged 8 through 11 months (93% [95% CI: 75%–99%]), which suggests no waning of protection (Table 3). The VE for 3 vs 0 RV doses among children aged 8 months or older against the outcome of hospitalization/short-stay manage-

ment for rotavirus disease was 92% (95% CI: 86%–96%) (Table 3). On the basis of a smaller number of cases, VE against rotavirus disease managed with ED care was 81% (95% CI: 53%–92%). Similar VE results for age and care-setting subsets were obtained with the IIS controls (Table 3).

VE for 2 and 1 RV Dose

Using rotavirus-negative controls, the VE for 2 RV doses compared with 0 doses among children aged 8 months or older was 90% (95% CI: 75%–96%) and 98% (95% CI: 79%–100%), which is similar to the VE estimates for 3 doses (Table 4). Among children aged 6 weeks through 5 months at rotavirus evaluation, the VE for 1 vs 0 RV dose was 66% (95% CI: 16%–86%) (Table 4). When using the maximum doses from the combined IIS/provider record and the vaccine restriction, few case-subjects and rotavirus-negative con-

trols aged 8 months or older had received 1 RV dose only, and the resulting VE estimate CIs included 0. Similar results were obtained for partial-series VE by using the IIS controls (Table 4).

During season 3 in Minnesota, G9P8 was the most common strain (60%) identified in 20 samples tested; in Georgia, G3P8 was the most common strain (57% of 23 samples) (Supplemental Table 7).

DISCUSSION

Using rotavirus case-subjects identified by provider testing at hospitals in 3 states, we obtained high VE estimates for 2 and 3 doses of RV5. Overall, our 3-dose VE results are consistent with the 1 other published RV5 VE evaluation with rotavirus testing (from a single hospital in Houston, TX) with a VE of 83% to 86% using predominantly ED rotavirus cases.^{8,9} Most of our case-subjects were managed as inpatients,

TABLE 4 VE for 2 and 1 RV Dose Versus 0 Doses

	Source of Immunization Data	Minnesota + Georgia + Connecticut				VE (95% CI)
		Cases		Controls		
		<i>n</i>	<i>n</i> (%) Vaccinated	<i>n</i>	<i>n</i> (%) Vaccinated	
VE for 2 vs 0 doses, age ≥ 8 mo						
Controls: rotavirus-negative	IIS + provider	160	7 (4)	153	36 (24)	90 (75 to 96) ^a
	IIS + provider, restricted	117	1 (1)	114	20 (18)	98 (79 to 100) ^{a,b}
Controls: IIS (matched)	IIS	268	8 (3)	1962	292 (15)	91 (79 to 96)
	IIS, restricted	165	0 (0)	1116	117 (10)	100 (NA)
VE for 1 vs 0 doses, age 6 wk through 5 mo						
Controls: rotavirus-negative	IIS	69	11 (16)	248	97 (39)	71 (40 to 87) ^c
	IIS, restricted	44	9 (20)	176	82 (47)	66 (16 to 86) ^d
Controls: IIS (matched)	IIS	69	11 (16)	633	184 (29)	62 (20 to 82)
	IIS, restricted	44	9 (20)	376	144 (38)	66 (11 to 87)
VE for 1 vs 0 doses, age ≥ 8 mo ^e						
Controls: rotavirus-negative	IIS + provider	163	10 (6)	137	20 (15)	69 (27 to 87) ^a
	IIS + provider, restricted	125	9 (7)	106	12 (11)	47 (−41 to 80) ^a

Restricted indicates that analysis was restricted to those children whose IIS record (or provider record, for those with provider records) indicated that the child had received 3 doses of RV, DTaP, IPV, or PCV through 8 months of age, stated that the child was delayed on immunizations, or that the parents had refused immunizations. Eight children were in the last 2 categories combined. Results with only an IIS as the source of immunization data are from seasons 1 through 3 combined. Results with combined IIS and provider as the sources of immunization data are from seasons 2 and 3 combined.

^a Results using IIS plus provider records are from Georgia and Minnesota combined. The model included site, season, and birth quarter.

^b Median age vaccinated rotavirus-negative controls: 13.8 months (interquartile range: 10.6–18.1).

^c Median age: rotavirus cases, 3.8 months; rotavirus-negative controls, 3.6 months. The model included site, season, and birth quarter.

^d Median age: rotavirus cases, 3.8 months; rotavirus-negative controls, 3.5 months. The model included site, season, and birth quarter.

^e VE for 1 vs 0 RV doses using IIS controls is not presented for age of 8 months or older because of concerns with missing additional RV doses in this group in the absence of provider records.

so our overall VE estimates are weighted to severe cases. Unique aspects of our evaluation include (1) examination of VE for 2 RV5 doses among children aged 8 months or older and for any potential waning of effectiveness of 3 RV5 doses during the first 3 years of life, (2) use of immunization data from the IISs and comparison with VE results in 2 states in which provider records were also obtained, and (3) use of controls selected from the IISs and comparison with VE results obtained by using rotavirus-negative controls. The similarity of our VE estimates when using the different immunization sources suggest that, with some caveats (as described below), IISs can be valuable tools in the United States for measuring the effectiveness of vaccines given in early childhood.

With our large sample size, we were able to evaluate important aspects of RV5 protection. Our 2-dose VE results of ≥90% among children aged 8 months or older that included immunization data from providers suggest

that 2 RV5 doses might be sufficient to protect against severe rotavirus disease in US children. Boom et al⁸ obtained a 2-dose VE over 1 season of 82% (95% CI: 15%–96%) using rotavirus-negative controls, which included younger children between second and third doses. Additional data on partial-dose VE among older US children would be valuable, but such data are difficult to obtain given high 3-dose RV5 coverage among children who start the series. That 3-dose VE remained high in the second and third years of life is also an important finding, given that, in the prevaccine era, more than half of the rotavirus hospitalizations among US children younger than 5 years occurred after the age of 1 year.^{1,10} Our VE result of 66% for 1 RV5 dose among young infants was similar to that reported by Boom et al⁸ (69% [95% CI: 13%]89%]) and suggests that 1 dose provides moderately good protection at least until the second dose is given.

As expected, some IIS records had fewer RV doses than found in provider records, particularly in Minnesota. With an effective vaccine, it is not surprising for undercounting of doses to occur more frequently among controls than case-subjects, because case-subjects would be more likely to be unvaccinated and have no chance of being undercounted for RV doses. In Minnesota, where proportionately more rotavirus-negative children were undercounted for RV doses in the IISs compared with case-subjects, this would result in an underestimate of the true VE for a full series by reducing the controls counted as fully vaccinated and increasing those counted as unvaccinated. This bias becomes more important when evaluating the VE of a partial series. By falsely inflating the number of controls who are counted as partially vaccinated but in truth are fully vaccinated, the resulting partial-series VE can be falsely high. We reduced the proportion of Minnesota rotavirus-negative children under-

counted for RV doses by the IISs (and for IIS controls in all sites) by restricting the comparison to only those children whose IIS record included 3 doses of an infant vaccine series through 8 months of age, which makes it more likely that the record used accurately covered early infancy. The VE estimates for 3 RV5 doses were similar with and without this restriction. In the other direction, it is also possible that the IIS record overcounts the number of RV doses in some children, but such errors should not bias VE results unless they occur more commonly in 1 group. Some of our provider records did show fewer RV doses than those found in the IISs. Although it is possible that these are IIS errors, it might be more likely that we missed additional providers for these children.

Overall, we obtained similar VE results when we used IISs as the source of controls as when we used rotavirus-negative children. The IIS controls can be considered community controls and, unlike other methods of obtaining community controls, these controls and their immunization records were readily obtained. We are aware of only 1 other published VE study that included a control group from a public IIS (from Houston), which also evaluated RV5. In that evaluation,³ VE for 3 vs 0 RV doses using IIS controls was similar to results obtained with 2 other control groups: rotavirus-negative children and those with acute respiratory infection.^{8,9} In our evaluation (as well as the one in Houston), because IIS controls were not interviewed and queried for seeking care at any hospital for rotavirus disease, it is possible that some of them did seek such care. However, as long as the case-subjects

we included highly represent the rotavirus vaccination status of all case-subjects evaluated at hospitals, our VE results should be valid. In addition, unintentionally including case-subjects among our controls would make the vaccination status of our control group more like that of the case group and, hence, lower the VE. Therefore, obtaining a high VE is reassuring that the vaccine is effective. We also used rotavirus-negative children as a control group,^{10,11} which helps control for health-seeking behavior for gastroenteritis.

Some aspects might have biased our VE estimates. First, case-subjects and rotavirus-negative controls were those on whom a rotavirus test was ordered by the clinician. Using these children for case-subjects could bias the VE if RV status was used by clinicians to determine who to test for rotavirus (eg, test only unvaccinated children). However, it is not likely that this occurred during the first few years after RV introduction and vaccine status is usually not known to the hospital staff at illness presentation. In addition, both case-subjects and rotavirus-negative controls would suffer this same potential bias. Second, case-subjects who were not found in the IISs were excluded, and such case-subjects might have different RV status from those found. However, $\leq 6\%$ of case-subjects in Minnesota and Georgia and 11% in Connecticut were excluded, and both control groups also excluded children not found in the IISs. Last, we did not obtain provider records on children with 3 RV doses in IISs, so we cannot estimate the accuracy of these records. However, it is likely that IIS errors of commission are less frequent

than errors of omission,¹² and there is no a priori reason to believe that commission errors would have occurred more commonly in children who became controls compared with those who became case-subjects.

CONCLUSIONS

Three doses of RV5 provide sustained protection against rotavirus disease in US children. Two RV5 doses also seem to provide good protection. IISs can be powerful tools for assessing VE for childhood vaccines and should be explored further for this important benefit.

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