Enhancing Vaccine Safety Surveillance: A Capture-Recapture Analysis of Intussusception after Rotavirus Vaccination

Thomas Verstraeten,1,2 Andrew L. Baughman,3 Betsy Cadwell,3 Lynn Zanardi,4 Penina Haber,2 Robert T. Chen,2 and the Vaccine Adverse Event Reporting System Team2,5

The Vaccine Adverse Event Reporting System (VAERS) is the passive reporting system for postmarketing surveillance of vaccine safety in the United States. The proportion of cases of an adverse event after vaccination that are reported to VAERS (i.e., VAERS reporting completeness) is mostly unknown. Therefore, the risk of such an event cannot be derived from VAERS only. To study whether its reporting sensitivity and risks could be estimated, VAERS was linked to data from a case-control and a retrospective cohort study in a capture-recapture analysis of intussusception after rotavirus vaccination (RV). Cases of intussusception after RV were selected from the common time frame (December 1998 through June 1999) and the common geographic area (19 states) of the three sources. Matching occurred on birth date, gender, state, date of vaccination, and date of diagnosis. Thirty-five matches were identified among a total of 84 cases. The estimated VAERS reporting completeness was 47%. The relative risks of intussusception in the periods 3–7 and 8–14 days after RV (relative risk = 22.7 and 4.4, respectively) were comparable with those reported in the two studies. Linkage of VAERS to complimentary data sources may permit more timely postmarketing assessment of vaccine safety. Am J Epidemiol 2001;154:1006–12.

intussusception, rotavirus; vaccines

Public acceptance of immunizations has been threatened by increasing reports of adverse events that accompany increasing rates of vaccine coverage and decreasing rates of vaccine-preventable diseases (1–3). In response, vaccine safety monitoring has become more prominent in immunization programs and the subject of closer scientific and public scrutiny (4). In the United States, the Vaccine Adverse Event Reporting System (VAERS), established in 1990, is the passive surveillance system used by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration to monitor vaccine safety (5, 6). The passive nature of VAERS affects its reporting completeness, the proportion of all cases of an adverse event after vaccination that are reported (7). The magnitude of underreporting varies widely, depending upon factors such as the severity of the event, proximity in time of the event to vaccination, and preexisting awareness on the possible association of the event to the vaccine (8).

Although the reporting completeness of VAERS has been evaluated for some specific vaccine-event associations, this information cannot be generalized (4, 8). Thus, the total vaccinated population that experiences an adverse event after a specific vaccine cannot be estimated with VAERS data alone. Such a population estimate is requisite to evaluate the strength of an association between a vaccine and an adverse event.

The capture-recapture methodology was designed to estimate population sizes on the basis of the proportion of subjects (re-)captured by two or more sources. It relies on four basic assumptions. First, the population should be closed or should not change in composition between the times of capture by the various sources. Second, sufficient information should be available in each source to match subjects from different sources in a unique manner. Third, the sources should be independent, i.e., capture by one source should not affect a subject’s likelihood of being captured by another source. Finally, each subject should have an equal likelihood of capture, or certain segments of the population should not be more likely than others to be captured (9). Capture-recapture has been applied to a wide range of epidemiologic fields (10–17) since first being introduced in epidemiology by
Wittes and Sidel (10) and Wittes et al. (11). We studied how the capture-recapture methodology could be used to assess the reporting completeness of VAERS for intussusception after rotavirus vaccination (RV) and how it would allow the risk for this event to be estimated.

**MATERIALS AND METHODS**

**VAERS**

VAERS collects reports on any adverse event after receipt of any vaccine licensed in the United States. The reporting form is designed to permit a description of the adverse event, the vaccine(s) received, the timing of vaccination and the adverse event, demographic information about the recipient, concurrent medical illness or medications, and previous history of adverse events after vaccinations (5). Most reports to VAERS come from health care providers and manufacturers, who are required by law to report certain vaccine-associated adverse events. Patients and parents can also submit VAERS reports.

**RV and intussusception**

The tetravalent, rhesus-based rotavirus vaccine became the first licensed rotavirus vaccine in the United States in August 1998, and was subsequently introduced to the recommended routine childhood immunization schedule as a three-dose series at 2, 4, and 6 months of age (18). Intussusception (prolapse of a section of bowel into a more distal section, resulting in bowel obstruction) had been observed among vaccinated children in prelicensure trials of rotavirus vaccines (19). Increased rates of intussusception among vaccinated children in postlicensure trials at Northern California Kaiser Permanente, as well as the receipt of 15 reports of intussusception after RV by VAERS, led to the suspension of the RV recommendation in July 1999 (20, 21). To assess more precisely the risk of intussusception after RV administration, the CDC initiated two in-depth epidemiologic studies, a multistate case-control study and a population-based retrospective cohort study. In addition, medical records of each case reported to VAERS were reviewed by CDC investigators to confirm the reported vaccination status and diagnosis (20). Data from the two epidemiologic studies were used to assess the feasibility of utilizing the capture-recapture method to enhance vaccine safety surveillance in VAERS.

**Intussusception and RV studies**

The case-control study identified 429 cases of intussusception that occurred between December 1, 1998, and July 16, 1999, in a cohort of 463,000 children from 10 managed care organizations (MCOs) nationwide (24). This study also included children aged 1–11 months and used the same method of case ascertainment and confirmation as the case-control study. Vaccination status was obtained from individual automated vaccination records and was confirmed through medical record review. The findings of increased risk were consistent with those of the case-control study (24).

**Capture-recapture inclusion criteria and matching**

We selected all cases of intussusception after RV confirmed by charts from the computerized records of VAERS and the two studies that occurred in the common time frame (December 1, 1998, to June 30, 1999) and geographic area (the 19 states of the case-control study). We matched these on the following five variables: date of birth, state of residence, date of vaccination, date of diagnosis, and gender. To allow for recall bias in the VAERS reports, we allowed the reported vaccination and diagnosis dates to differ by up to 7 days from those found in the two studies. To further allow for coding or transcription errors on any of the five matching variables, we required only four of the five variables to match.

**Capture-recapture analysis**

We first computed Chapman estimates of the true number of cases of intussusception after RV by pairwise matching of the three sources (25). Let $n_a$ denote the number of cases captured in data source $A$, $n_b$ denote the number of cases captured in data source $B$, and $n_{ab}$ denote the number of cases captured in both sources. The Chapman estimate of the true number of cases is then calculated as

$$N = \frac{[(n_a + 1) \times (n_b + 1)]}{(n_{ab} + 1)} - 1 \quad (26).$$

We subsequently used log-linear models to estimate the true number of cases of intussusception after RV by using all three sources simultaneously. Unlike Chapman estimates, these models reveal the degree of dependence among the data sources. We constructed eight models to account for all possible two-source dependencies. From these, we selected the model with the lowest Akaike Information Criterion (AIC) score. This score is calculated by subtracting twice the number of degrees of freedom from the likelihood ratio statistic ($G^2$). The AIC score thus favors the model with the lowest likelihood ratio statistic, while penalizing for an increasing number of parameters in the model.

To evaluate the impact of the duration between vaccination and the event (onset interval) and of severity of disease on ascertainment, we fitted separate models to subsets of data, defined by different levels of onset interval duration and severity. We then recalculated the capture-recapture estimate of the total number of cases by adding the estimates for each subset. The onset interval was divided into the fol-
lowing categories, as used in the in-depth studies of intussusception after RV: 0–2, 3–7, 8–14, and more than 14 days. Severity was defined by whether or not a case had resulted in surgery.

Goodness-of-fit-based confidence intervals were calculated for all capture-recapture estimates (27). The goodness-of-fit method is based on the likelihood ratio statistic, and the resulting intervals are thus asymmetric around N. This method of calculating the confidence intervals has the advantage of providing a lower limit that is higher than the total number of all observed cases (25). Completeness of VAERS reporting was calculated as the ratio of the number of VAERS reports to the model estimate of the total number of intussusception cases.

**Risk estimation**

To evaluate the incidence rate of intussusception after RV for the previously established postvaccination risk intervals, we divided the estimated total number of cases that occurred in each interval by the total person-time for each interval. The total person-time was obtained by multiplying the total number of doses of RV, administered between December 1998, and June 1999, in the 19 states by the duration of each risk interval. The total number of first, second, and third doses administered for each state was estimated by multiplying the number of children in each state’s birth cohort by dose-specific vaccination coverage rates in the state, as found among controls in the case-control study. Because the recommendations for RV allowed children up to age 7 months to receive the first dose, we assumed that children up to 5 months older than the recommended age were being vaccinated in the early months after the release of the vaccine (18). Under this assumption, an entire birth cohort was vaccinated in the early months after the release of the vaccine. For the cohort study, however, these proportions of cases were similar for VAERS and the case-control study. Because the recommendations for RV allowed children up to age 7 months to receive the first dose, we assumed that children up to 5 months older than the recommended age were being vaccinated in the early months after the release of the vaccine (18).

None of these cases occurred in the first 2 days after RV. The majority (57 percent) occurred in the 3- to 7-day risk interval after vaccination, 16 percent occurred in the 8- to 14-day interval and 27 percent occurred after 14 days. These proportions of cases were similar for VAERS and the case-control study. For the cohort study, however, these proportions differed (43, 0, and 57 percent for the same intervals).

**RESULTS**

Overall, 107 confirmed cases of intussusception after RV were reported to VAERS, 67 were identified in the case-control study, and nine in the cohort study. When datasets were limited to the time and geographic inclusion criteria, 48 cases were retained from VAERS, 63 from the case-control study, and seven from the cohort study. Among these cases, 29 matches occurred between VAERS and the case-control study, four between VAERS and the cohort study, and two between the two studies. All of these matches occurred on all five variables, except for three matches between VAERS and the case-control study (two dates of birth differing by 10 and 46 days, respectively, and one vaccination date was missing), and one match between VAERS and the cohort study differing on gender. One case was ascertained by all sources (table 1). The total number of unique cases in the capture-recapture analysis was 84.

None of these cases occurred in the first 2 days after RV. The majority (57 percent) occurred in the 3- to 7-day risk interval after vaccination, 16 percent occurred in the 8- to 14-day interval and 27 percent occurred after 14 days. These proportions of cases were similar for VAERS and the case-control study. For the cohort study, however, these proportions differed (43, 0, and 57 percent for the same intervals).

<table>
<thead>
<tr>
<th>Capturing source</th>
<th>Case-control</th>
<th>Cohort</th>
<th>Overall</th>
<th>Risk interval (days)</th>
<th>Severity of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAERS*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
<td>3-7</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>28</td>
<td>8-14</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
<td>≥15</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>16</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>33</td>
<td>No surgery</td>
</tr>
</tbody>
</table>

* VAERS, Vaccine Adverse Event Reporting System.
† Unobserved.

Am J Epidemiol Vol. 154, No. 11, 2001
Almost half (48 percent) of the cases of intussusception after RV led to surgery. This proportion differed between all sources, at 53, 43, and 71 percent for VAERS, the case-control, and the cohort study, respectively.

**Chapman capture-recapture estimates**

The Chapman estimate of the total number of cases was 104 (95 percent confidence interval (CI): 91, 127) for the pairwise analysis using VAERS and the case-control study, 78 (95 percent CI: 57, 208) for the pairwise analysis using VAERS and the cohort study, and 170 (95 percent CI: 98, 1,228) for the pairwise analysis using the case-control and cohort studies.

**Log-linear modeling**

The model with a single dependence term between the case-control and cohort studies had the lowest AIC and was thus selected as the best-fitting model (table 2). The total number of intussusception cases after RV as estimated by this model was 102 (95 percent CI: 91, 205). The reporting completeness of VAERS derived from this estimate was 47 percent (95 percent CI: 23, 53).

The modeling results for the data restricted to the different risk intervals are summarized in table 3. The total number of cases estimated by the respective models with the lowest AIC was 55 (95 percent CI: 49, 62) for the interval 3–7 days and 40 (95 percent CI: 28, 81) for the interval more than 14 days. Because no cases occurred in the interval 8–14 days in the cohort study, we could not obtain modeled estimates for this interval. The Chapman estimate of the total number of cases for this interval, based on VAERS and the case-control study, was 15 (95 percent CI: 12, 28). The total estimate for all cases, stratified on severity, was thus 101. The VAERS reporting completeness was 54 percent among severe cases and 42 percent among nonsevere cases.

**Risk assessment**

We estimated the total number of doses administered from December 1998 through June 1999 in the 19 states to be 708,366, resulting in a follow-up time of 9,704 and 13,585 person-years in the intervals 3–7 and 8–14 days, respectively. The estimated incidence rates for these intervals were 5.7 (95 percent CI: 5.0, 6.4) cases and 1.1 (95 percent CI: 0.9, 2.1) cases per 1,000 person-years. The incidence rate ratios, when these rates were compared with the background rate, were 22.7 (95 percent CI: 14.4, 37.6) and 4.4 (95 percent CI: 2.5, 12.1) for the intervals 3–7 and 8–14 days post-RV, respectively.

**DISCUSSION**

We estimated the total number of doses administered in RV recipients, which occurred in 19 states from December 1998 through June 1999, to be 708,366, resulting in a follow-up time of 9,704 and 13,585 person-years in the intervals 3–7 and 8–14 days, respectively. The estimated incidence rates for these intervals were 5.7 (95 percent CI: 5.0, 6.4) cases and 1.1 (95 percent CI: 0.9, 2.1) cases per 1,000 person-years. The incidence rate ratios, when these rates were compared with the background rate, were 22.7 (95 percent CI: 14.4, 37.6) and 4.4 (95 percent CI: 2.5, 12.1) for the intervals 3–7 and 8–14 days post-RV, respectively.

* TABLE 2. Log-linear modeling of the total number of cases of intussusception after rotavirus vaccination, 19 US states, December 1998 through June 1999

<table>
<thead>
<tr>
<th>Interaction term(s) used in model</th>
<th>df</th>
<th>AIC*</th>
<th>Capture-recapture estimate of total cases</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3</td>
<td>-2.5</td>
<td>106</td>
<td>94, 127</td>
</tr>
<tr>
<td>VAERS–case-control</td>
<td>2</td>
<td>-0.6</td>
<td>90</td>
<td>89, 231</td>
</tr>
<tr>
<td>VAERS–cohort</td>
<td>2</td>
<td>-0.9</td>
<td>105</td>
<td>94, 130</td>
</tr>
<tr>
<td>Cohort–case-control</td>
<td>2</td>
<td>-3.6</td>
<td>102</td>
<td>91, 205</td>
</tr>
<tr>
<td>VAERS–case-control and VAERS–cohort</td>
<td>1</td>
<td>0.3</td>
<td>150</td>
<td>90, 1,521</td>
</tr>
<tr>
<td>VAERS–case-control and cohort–case-control</td>
<td>1</td>
<td>-2.0</td>
<td>103</td>
<td>84, 136</td>
</tr>
<tr>
<td>VAERS–cohort and cohort–case-control</td>
<td>1</td>
<td>-1.9</td>
<td>95</td>
<td>92, 124</td>
</tr>
<tr>
<td>All two-way interactions</td>
<td>0</td>
<td>0</td>
<td>97</td>
<td>97, 97</td>
</tr>
</tbody>
</table>

* AIC, Akaike Information Criterion; CI, confidence interval; VAERS, Vaccine Adverse Event Reporting System.
### TABLE 3. Log-linear modeling of the total number of cases of intussusception after rotavirus vaccination for different durations of onset interval, 19 US states, December 1998 through June 1999

<table>
<thead>
<tr>
<th>Interaction term(s) in model</th>
<th>df</th>
<th>3–7</th>
<th>95% CI</th>
<th>&gt;14</th>
<th>Capture-recapture estimate of total cases</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3</td>
<td>-0.4</td>
<td>56</td>
<td>50, 68</td>
<td>-3.0</td>
<td>40</td>
</tr>
<tr>
<td>VAERS–case-control</td>
<td>2</td>
<td>0.7</td>
<td>48</td>
<td>48, 89</td>
<td>-1.0</td>
<td>33</td>
</tr>
<tr>
<td>VAERS–cohort</td>
<td>2</td>
<td>1.5</td>
<td>57</td>
<td>51, 70</td>
<td>-2.2</td>
<td>44</td>
</tr>
<tr>
<td>Cohort–case-control</td>
<td>2</td>
<td>0.0</td>
<td>55</td>
<td>50, 66</td>
<td>-1.3</td>
<td>38</td>
</tr>
<tr>
<td>VAERS–case-control and VAERS–cohort</td>
<td>1</td>
<td>2.7</td>
<td>48</td>
<td>48, 151</td>
<td>-1.8</td>
<td>†</td>
</tr>
<tr>
<td>VAERS–case-control and cohort–case-control</td>
<td>1</td>
<td>-0.5</td>
<td>55</td>
<td>49, 62</td>
<td>0.7</td>
<td>43</td>
</tr>
<tr>
<td>VAERS–cohort and cohort–case-control</td>
<td>1</td>
<td>1.8</td>
<td>48</td>
<td>†</td>
<td>-0.3</td>
<td>35</td>
</tr>
<tr>
<td>All two-way interactions</td>
<td>0</td>
<td>0</td>
<td>48</td>
<td>48, 52</td>
<td>0</td>
<td>†</td>
</tr>
</tbody>
</table>

AIC, Akaike Information Criterion; CI, confidence interval; VAERS, Vaccine Adverse Event Reporting System. 
† Could not be calculated because of sparse data.

### TABLE 4. Log-linear modeling of the total number of cases of intussusception after rotavirus vaccination for different degrees of severity of disease (surgery or no surgery) 19 US states, December 1998 through June 1999

<table>
<thead>
<tr>
<th>Interaction term(s) in model</th>
<th>df</th>
<th>Surgery</th>
<th>95% CI</th>
<th>No surgery</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3</td>
<td>-0.9</td>
<td>50</td>
<td>43, 65</td>
<td>-3.7</td>
</tr>
<tr>
<td>VAERS–case-control</td>
<td>2</td>
<td>1.1</td>
<td>43</td>
<td>40, 102</td>
<td>-2.6</td>
</tr>
<tr>
<td>VAERS–cohort</td>
<td>2</td>
<td>-0.9</td>
<td>52</td>
<td>44, 73</td>
<td>-3.8</td>
</tr>
<tr>
<td>Cohort–case-control</td>
<td>2</td>
<td>-1.9</td>
<td>48</td>
<td>42, 61</td>
<td>-1.9</td>
</tr>
<tr>
<td>VAERS–case-control and VAERS–cohort</td>
<td>1</td>
<td>-0.4</td>
<td>†</td>
<td>-2.0</td>
<td>64</td>
</tr>
<tr>
<td>VAERS–case-control and cohort–case-control</td>
<td>1</td>
<td>-0.7</td>
<td>49</td>
<td>40, 68</td>
<td>-0.9</td>
</tr>
<tr>
<td>VAERS–cohort and cohort–case-control</td>
<td>1</td>
<td>-1.5</td>
<td>43</td>
<td>42, 66</td>
<td>-2.0</td>
</tr>
<tr>
<td>All two-way interactions</td>
<td>0</td>
<td>0</td>
<td>†</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

AIC, Akaike Information Criterion; CI, confidence interval; VAERS, Vaccine Adverse Event Reporting System. 
† Could not be calculated because of sparse data.
VAERS cases included in our analyses, all of which occurred before July, only seven were reported to VAERS before the publication.

We estimated the relative risk of intussusception after RV to be 22.7 and 4.4 for the intervals 3–7 and 8–14 days after vaccination, respectively. The estimates from the case-control and cohort studies were 14.4 and 13.5 for the 3–7 days interval and 5.3 and 2.5 for the 8–14 days interval, respectively (22, 24). Although our estimate for the first interval is larger than that of either study, the order of magnitude is comparable.

Our study was limited mostly by the last two of the four basic assumptions underlying capture-recapture (closed population, unique matching, independence of sources, and equal likelihood of capture). The population was closed because all sources captured subjects simultaneously. Matching was possible and unique, given the information available for the three sources. We estimated the likelihood of two distinct cases coincidentally matching by at least four of the matching variables (false-positive matching), given the total number of captured cases, to be only 0.04. Because of potential coding or reporting errors, we allowed one of the five matching variables to differ among matching cases. Had we not provided this possibility, four of the 35 matches would not have occurred. We confirmed all of these to be true matches, however, by identifying coding errors in the nonmatching variable for three matches (after comparison to the paper records) and by identifying an additional matching variable (date of receipt of another RV dose) for the fourth. In this fourth case, the nonmatching date differed by only one digit (05/06/98 vs. 05/16/98).

By using three sources, we only had to assume three-source independence, while using the log-linear models to test and possibly adjust for two-source interaction. We expected dependence to occur between the case-control and cohort studies, since cases of intussusception were ascertained in both studies through review of hospital discharge records. We expected cases ascertained by either source to be likely to also be ascertained by the other source (positive dependence). The denominator in the Chapman equation would then be artificially high and the capture-recapture estimate artificially low. The estimate of 170 derived from one digit (05/06/98 vs. 05/16/98).

Positive dependence could also have originated between VAERS and the case-control study if case identification by the case-control study led to an increased likelihood of being reported to VAERS. If this were true, the proportion of VAERS reports coming from the 19 states in the case-control study would have increased after the start of the study in July 1999. This proportion decreased, however, from 82 percent before July to 69 percent afterward. This suggests that the increase in VAERS reporting was caused by a general increased awareness, rather than just increased reporting among collaborating investigators of the case-control study. Similarly, dependence between VAERS and the cohort study could have originated if MCOs were more or less likely to report to VAERS. We could not explore this further because no information on MCO membership is collected in the VAERS reports.

Finally, we checked the equal likelihood of capture by stratifying our analyses by two variables known to affect ascertainment in VAERS: duration of the onset interval and severity of disease. Like Rosenthal and Chen (8), we found a slight decrease in the completeness of reporting with increasing interval between vaccination and the adverse event. We also observed a higher ascertainment rate by VAERS for severe cases compared with nonsevere cases. Stratifying the analyses on these variables hardly affected the total estimated number of cases, however. Unavailable variables that would have been of additional interest include the level of parental education and the type of health care provider or insurance.

The applicability of capture-recapture to epidemiology is still under debate. Cormack (28) went as far as to state that many capture-recapture studies lack the necessary information to give any reliable population size estimate. Although we followed the recommendations of Hook and Regal (29), made in reply to Cormack’s statement, we agree with the latter that our capture-recapture estimates should be interpreted with great caution, especially given the sparseness of some of the data. Our results, although not so different, are certainly not comparable in strength with the estimates obtained in the two epidemiologic studies used as sources for our analysis.

Some additional limitations of our study should be mentioned besides those inherent to the capture-recapture methodology. We based our estimated number of doses of RV on the vaccine coverage levels among controls in the case-control study. Because this study focused on areas of high coverage within the 19 states, we may have overestimated the number of doses and underestimated the relative risks of intussusception after RV. On the other hand, our estimate of 708,366 doses is lower than the total number of doses distributed by the manufacturer minus the number returned (1,156,813 for these 19 states) (P. Paradiso, Wyeth Lederle Vaccines, personal communication, 2000). In the unlikely event that all unreturned vaccines had been administered, the estimate of the relative risk of intussusception after RV would be 13.9 and 2.7 for the intervals 3–7 and 8–14 days, respectively.

We compared the incidence of intussusception in vaccinated children with the recent background estimate of intussusception in unvaccinated children. We judged this estimate to be the most accurate estimate available because it relied upon cases confirmed by charts. The estimated background rate is only half of an earlier estimate derived from hospital discharge records in New York, however (21). Using the earlier estimate as the background rate, we would have found our risk estimates to be exactly half of the ones reported.

Allegations of adverse events being caused by vaccination will occur more frequently in our world of increasing numbers of new vaccines, increasing vaccine coverage rates, and decreasing tolerance of adverse events. How applicable will our approach be for a different vaccine and a different
adverse event? For our analysis of intussusception after RV, we were fortunate to have two additional sources of exposed cases available. Clearly, studies such as the case-control and cohort studies of intussusception after RV cannot be carried out to investigate every new concern of an association between an adverse event and a vaccine. In the context of increased automatization of medical records, however, complimentary sources for linkage to VAERS may be available, such as hospital discharge or clinic record databases. For denominator data in the incidence calculations, manufacturers’ distribution data can be used to estimate the number of vaccines administered. A capture-recapture analysis may then be considered to evaluate the need of more costly case-control or cohort studies. In some regions of the world, automated databases are unlikely to be available, and the cost and effort of case-control or cohort studies may be prohibitive. Construction of ad hoc case registries through a sampled case-finding exercise to allow capture-recapture analyses may be considered as an alternative.

ACKNOWLEDGMENTS

The authors thank Dr. Mary McCauley for her assistance in preparing the final text.

REFERENCES