Measles-Mumps-Rubella and Other Measles-Containing Vaccines Do Not Increase the Risk for Inflammatory Bowel Disease

A Case-Control Study From the Vaccine Safety Datalink Project

Robert L. Davis, MD, MPH; Piotr Kramarz, MD; Kari Bohlke, ScD; Patti Benson, MPH; Robert S. Thompson, MD; John Mullooly, PhD; Steve Black, MD; Henry Shinefield, MD; Edwin Lewis, MPH; Joel Ward, MD; S. Michael Marcy, MD; Eileen Eriksen, MPH; Frank Destefano, MD, MPH; Robert Chen, MD; for the Vaccine Safety Datalink Team

Context: A link between measles virus–containing vaccines and inflammatory bowel disease (IBD) has been suggested by recent studies.

Objectives: To address whether receipt or timing of measles-containing vaccine (MCV) increases risk for IBD.

Design: A case-control study.

Setting: Four large health maintenance organizations (HMOs) that are part of the Centers for Disease Control and Prevention’s Vaccine Safety Datalink project.

Patients or Other Participants: A total of 155 persons with codes from International Classification of Diseases, Ninth Revision specific for IBD, born between 1958 and 1989 and enrolled from birth to the onset of disease, were identified. Up to 5 controls were matched by sex, HMO, and birth year.

Intervention: None.

Main Outcome Measures: Risk for IBD, Crohn’s disease, and ulcerative colitis.

Results: Past vaccination was not associated with an increased risk for Crohn’s disease (odds ratio [OR] for measles-mumps-rubella vaccine [MMR], 0.4; 95% confidence interval [CI], 0.08-2.0), ulcerative colitis (OR, 0.8; 95% CI, 0.18-3.56), or IBD (OR, 0.59; 95% CI, 0.21-1.68). Risk for IBD was not increased among children vaccinated who were younger than 12 months (OR for MMR, 0.61; 95% CI, 0.15-2.45) or aged 12 to 18 months (OR, 0.86; 95% CI, 0.28-2.59) relative to unvaccinated children. Children vaccinated with MMR who were older than 18 months were at significantly decreased risk for IBD (OR, 0.16; 95% CI, 0.04-0.68). Neither past vaccination nor age at vaccination with other MCV was associated with increased risk for Crohn’s disease, ulcerative colitis, or IBD. Risk for Crohn’s disease, ulcerative colitis, or IBD was not elevated in the time immediately following vaccination with either vaccine.

Conclusions: Vaccination with MMR or other MCV, or the timing of vaccination early in life, did not increase the risk for IBD.
SUBJECTS AND METHODS

STUDY SITES
This study was carried out in the 4 HMOs of the VSD: (1) Group Health Cooperative, Seattle, Wash; (2) Kaiser Permanente of Northern California, Oakland; (3) Kaiser Permanente Northwest, Portland, Ore; and (4) Southern California Kaiser Permanente, Los Angeles. The VSD project was started in 1991, and the computerized medical databases at each HMO include information on vaccinations and hospitalizations. Information on outpatient visit encounters and emergency department visits are available for 3 of the HMOs.

CASE AND CONTROL ASCERTAINMENT
We selected potential cases for medical record review by identifying persons with International Classification of Diseases, Ninth Revision (ICD-9) codes specific for Crohn’s disease, ulcerative colitis, and idiopathic proctocolitis (ICD-9 codes 535 and 536) in the computerized databases. At 3 sites, we drew our study sample from the population of HMO members born between 1938 (when membership files were first available) and 1989. At 1 site, case and control selection was limited to people born after 1979 since automated membership data were not available prior to that year. At all 4 HMOs, cases were ascertained from hospital databases covering hospital admissions. Outpatient visits, emergency department visits, and urgent care clinic visits were ascertained from 3 HMOs; the earliest dates of case ascertainment from these respective databases were determined by the year the respective databases (eg, outpatient visits) were created. Because outpatient, emergency department, and urgent care clinic databases were not available at 1 HMO, only hospitalized cases were ascertained at this site.

To be included in our sample, cases and controls had to be enrolled from age 6 months up to the index date (the first date of disease diagnosis or symptoms for cases) or reference date for controls. For both cases and controls, we allowed up to 6 months of continuous disenrollment at any time during life to account for transient lapses in insurance coverage. For each case, we matched up to 5 controls according to sex, HMO, and birth year. The reference date of each control was established as the date that the disease was diagnosed for their matched case.

EXPOSURE ASSESSMENT
To accurately capture information on exposure to first MMR or other MCV, we limited our selection of study subjects, as described in the previous section, to patients enrolled for the entire period between 6 months of age and disease onset (for cases) or reference date (for controls). The entire medical record for cases and controls was abstracted to collect information on vaccination history with all types of MCVs. Information on vaccines administered in all health care settings was collected. A second MMR vaccination is recommended either at age 4 to 6 years or 10 to 12 years, but these vaccinations were not analyzed in the current study.

MEDICAL RECORD ABSTRACTION
Trained medical record abstractors at each HMO reviewed medical records using a standardized instrument. Cases were classified according to type of disease (Crohn’s, ulcerative colitis/proctitis, or IBD unspecified) and by certainty of diagnosis. We defined cases of “definite IBD” as persons diagnosed with IBD by a gastroenterologist at one of the HMOs who had at least 1 sign or symptom compatible with IBD (such as bloody stool and/or bloody diarrhea or severe and/or recurrent abdominal pain) recorded and a diagnostic test result (such as biopsy with pathology specimen, colonoscopy, or sigmoidoscopy) consistent with IBD. Cases were defined as having “probable IBD” if the diagnosis of IBD was made by either an HMO non-gastroenterologist physician or a gastroenterologist outside the HMO, there was at least 1 sign or symptom compatible with IBD, and there was a diagnostic test result consistent with IBD. Potential subjects with possible or questionable IBD who did not meet these criteria were excluded from further study.

STATISTICAL ANALYSES
We used conditional logistic regression to estimate the strength of association between vaccination and disease, while accounting for the matching and enrollment criteria. In all analyses we further adjusted for race, where race was categorized as white (reference category, including Hispanics and non-Hispanics), African American, and other/unknown.

We excluded cases categorized as “possible” or “questionable” from all analyses. Separate analyses were performed on datasets that were limited to definite and probable cases combined or of definite cases only. Because the results from these analyses did not differ appreciably, we present only the results on the larger dataset of definite and probable cases combined.

Finally, we performed analyses with 2 different onset dates. For the analysis of whether receipt of vaccination was associated with an increased risk for IBD, Crohn’s disease, or ulcerative colitis, we used the onset date the first date a diagnosis was made by a physician. The analysis of whether vaccination was associated with the acute onset of symptoms consistent with IBD, Crohn’s disease, or ulcerative colitis was dependent on using the onset date of first symptoms rather than the date of first diagnosis (which might lag symptom onset by months). Therefore, for this part of the analysis, we used the patient’s first reported symptoms as the onset date. This lowered our case number by a small amount because not all cases with a known date of first diagnosis had a specified date of symptom onset in the medical record.

2% of all children in the US population younger than age 7 years. Our study focused on a series of questions: Was the age of first vaccination with MMR or other MCV, or receipt of vaccination itself, associated with an increased risk for Crohn’s disease or ulcerative colitis later in life? Was receipt of MMR or other MCV associated with the acute onset of disease shortly following vaccination?
Table 1. General Descriptives of Cases and Controls*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 142)</th>
<th>Controls (n = 432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>75 (53)</td>
<td>...</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>67 (47)</td>
<td>...</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>74 (52)</td>
<td>224 (52)</td>
</tr>
<tr>
<td>M</td>
<td>68 (48)</td>
<td>208 (48)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>95 (67)</td>
<td>256 (59)</td>
</tr>
<tr>
<td>African American</td>
<td>12 (8)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (7)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (17)</td>
<td>132 (31)</td>
</tr>
<tr>
<td>Age at diagnosis, y†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>7 (5)</td>
<td>24 (6)</td>
</tr>
<tr>
<td>6-10</td>
<td>29 (20)</td>
<td>81 (19)</td>
</tr>
<tr>
<td>11-14</td>
<td>40 (28)</td>
<td>120 (28)</td>
</tr>
<tr>
<td>15-19</td>
<td>43 (30)</td>
<td>144 (33)</td>
</tr>
<tr>
<td>20-24</td>
<td>15 (11)</td>
<td>46 (11)</td>
</tr>
<tr>
<td>25+</td>
<td>8 (6)</td>
<td>20 (5)</td>
</tr>
</tbody>
</table>

* All values given as numbers (percentages). Percentages do not always equal 100 due to rounding. Ellipses indicate not applicable.
† For controls, age at the date the disease was diagnosed for their matched case.

 RESULTS

DESCRIPTIVE

There was a total of 155 cases of IBD. Of these 155 cases, 152 were either definite or probable cases, while 3 were listed as possible or questionable. After excluding the latter 3 cases, along with 7 that lacked a clearly discernible diagnosis and symptom onset date, 2 cases of IBD unspecified, and 1 case with a late age of vaccination (>10 years), there was a total of 142 cases for the analysis of timing of vaccination and diagnosis of IBD.

Of these 142 cases, there were 75 cases of Crohn’s disease and 67 cases of ulcerative colitis (Table 1). There was a slight excess of cases classified as white or African American compared with controls. Overall, 52% of both cases and controls, respectively, were female, and 58% of cases were diagnosed between age 11 and 19 years, with few cases being diagnosed either after age 25 years or before age 5 years.

Among all cases (n=142), 94 (66%) had been vaccinated with MMR, 38 (27%) with other MCV, and 10 (7%) had never been vaccinated with either. Among the controls (n=432), 300 (69%) had been vaccinated with MMR, 109 (25%) with other MCV, and 23 (5%) had never been vaccinated with either. There were 13 cases that did not have a clearly demarcated first date of symptoms, leaving a total of 129 cases for the separate analysis of vaccination and acute symptom onset.

VACCINATION AND RISK FOR IBD

There were no differences in the lag between vaccination with MMR or other MCV and the case index date (mean and median time between vaccination and onset of symptoms of 143.4 and 136.3 months, respectively) or the control reference date (mean and median time between vaccination and reference date of 143.0 and 136.7 months, respectively). As given in Table 2, cases of Crohn’s disease, ulcerative colitis, or of all IBD combined were no more likely than controls to have ever been vaccinated.

AGE AT VACCINATION AND RISK FOR IBD

Vaccination with MMR or other MCV was most common for both cases and controls who were 12 to 18 months old (Table 3). Cases of Crohn’s disease, ulcerative colitis, or all IBD combined were no more likely than controls to have been vaccinated while younger than 12 months with either MMR or other MCV (Table 3). Similarly, cases of IBD, Crohn’s disease, or ulcerative colitis were no more likely than controls to have been vaccinated at age 12 to 18 months or after age 18 months. Cases of all IBD combined were less likely to have ever been vaccinated with MMR after age 18 months than controls. This decrease was present but not statistically significant when cases were restricted to Crohn’s disease or ulcerative colitis and analyzed separately. A significant decrease was not found for vaccination with other MCV after age 18 months.

VACCINATION AND ACUTE ONSET OF SYMPTOMS

The analysis of vaccination and the acute onset of symptoms of IBD revealed no cases of Crohn’s disease or ulcerative colitis who were vaccinated in the 2- or 4-month time period just prior to the first symptoms. One case of Crohn’s disease (1.5% of cases with defined onset of symptoms) was vaccinated with MMR within the 6-month time window prior to first symptoms, compared with 2 of the controls (1.0%) (odds ratio [OR], 1.86; 95% confidence interval [CI], 0.09-39.4 for Crohn’s disease in the 6 months following vaccination). In the year prior to onset of symptoms, there was 1 case (the same that was exposed within 6 months) of Crohn’s disease who was vaccinated with MMR (1.5%) and 3 controls (1.4%) (OR, 0.72; 95% CI, 0.06-8.29 for Crohn’s disease in the 12 months following vaccination). Overall, there were no statistically significant elevations in risk for developing symptoms of
Crohn's disease, ulcerative colitis, or all IBD together in the 2, 4, 6, or 12 months following vaccination with either MMR or other MCV.

**COMMENT**

In this population-based study of IBD at 4 large HMOs, we found no evidence that vaccination with MMR or other MCV, or that the age of vaccination early in life, was associated with an increased risk for development of IBD. In addition, we did not find evidence that MMR or other MCV acutely triggers the onset of either ulcerative colitis/proctitis or Crohn's disease.

This study was performed to address concerns raised by others regarding whether MMR is associated with an increased risk for either IBD or nonspecific colitis. Because MMR coverage in the US pediatric population is currently greater than 90% and vaccination with MMR is generally required for school attendance, a link with a serious chronic condition such as IBD would understandably raise widespread concern and would lead to questions about the safety of the currently recommended vaccination schedule for children. In the first study to suggest a possible association, a cohort of children aged 10 to 24 months were enrolled in a 1964 United Kingdom Medical Research Council vaccine trial of the Schwarz strain (derived from the Enders-Edmonston B strain) and followed through 1994. Children in this cohort were compared with a group of presumably nonvaccinated children in the National Child Development Study, a longitudinal study of children born in a single week in 1958. Among vaccinated children, the rate of reported Crohn's disease was 3-fold higher (relative risk [RR], 3.01; 95% CI, 1.45-6.23), and ulcerative colitis 2.5-fold higher (RR, 2.33; 95% CI, 1.15-5.38), than in the National Child Development Study comparison group.

These findings by Thompson et al were questioned most seriously because the method of disease ascertainment differed considerably between the 2 cohorts. The ascertainment of disease among the vaccinated children relied on questions specifically focused on gastrointestinal disease, while the unvaccinated group was asked about long-standing illnesses or disabilities. In addition, follow-up among the vaccinated group was approximately half that of the unvaccinated cohort, raising the possibility for biased response rates related to disease status. As a result, it was not clear whether the observed relationship between measles vaccine and IBD was due to the vaccine itself or to study design limitations.

The study by Wakefield et al did not look specifically at IBD but focused on a group of 12 children with a complex of nonspecific colitis, ileolymphoid hyperplasia, and pervasive developmental disability, in which most but not all reported that symptoms began following vaccination with an MCV. Of these 12 children, 6 had gastrointestinal symptoms, and 11 had abnormal histological findings in ileum and colon biopsy specimens (most commonly of nonspecific colitis and lymphoid hyperplasia). This study was questioned owing to lack of specification of the source population, making it impossible to determine whether vaccination was more common among these cases than among a comparable set of children without disease. Because MMR is given to approximately 600000 children yearly in the United Kingdom, some cases of disease will likely follow vaccine temporally, although not necessarily as a result of cause and effect. Others questioned whether the gastrointestinal findings were unusual or represented nonspecific findings common in the age group studied.

Several other studies have subsequently addressed the risk for IBD following MCV. A case-control study by Feeney et al from the United Kingdom looked at 140 patients with IBD born after 1968, matched to 280 controls by age, sex, and location. No increased risk was found for either Crohn's disease (OR, 1.08; 95% CI, 0.6-1.9) or ulcerative colitis (OR, 0.84; 95% CI, 0.4-1.6) among children receiving measles vaccine compared with unvaccinated children. Other data by Morris et al on a national longitudinal study of children born in the United Kingdom found no increased risk for Crohn's disease or ulcerative colitis by age 25 to 26 years associated with measles vaccination. Only sparse details were reported, but there were no significantly increased risks (Crohn's disease: RR, 1.21; 95% CI, 0.5-2.9; ulcerative colitis: RR, 1.31; 95% CI, 0.47-3.7; and IBD: RR, 1.25; 95% CI, 0.64-2.43).

Multiple ecological analyses have also shown no apparent increase in IBD following the introduction of, or increased use of, MMR. In one study, Miller and Waight used computerized hospital discharge statistics from 1992 through 1996 to look for evidence of an increase in Crohn's disease subsequent to a 1994 national measles-

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**Table 3. Age at Vaccination and Risk for Inflammatory Bowel Disease**

<table>
<thead>
<tr>
<th>Age Vaccinated, mo</th>
<th>Crohn's Disease</th>
<th>UC</th>
<th>All IBD Cases, No.</th>
<th>Controls, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR, &lt;12</td>
<td>0.38 (0.05-2.86)</td>
<td>0.96 (0.12-7.57)</td>
<td>0.61 (0.15-2.45)</td>
<td>6</td>
</tr>
<tr>
<td>MCV, &lt;12</td>
<td>0.43 (0.05-3.54)</td>
<td>1.75 (0.20-15.3)</td>
<td>0.78 (0.18-3.37)</td>
<td>5</td>
</tr>
<tr>
<td>MMR, 12-18</td>
<td>0.54 (0.10-3.07)</td>
<td>1.14 (0.23-5.59)</td>
<td>0.86 (0.28-2.59)</td>
<td>84</td>
</tr>
<tr>
<td>MCV, 12-18</td>
<td>1.16 (0.24-5.53)</td>
<td>1.25 (0.23-6.72)</td>
<td>1.07 (0.35-3.26)</td>
<td>22</td>
</tr>
<tr>
<td>MMR, &gt;18</td>
<td>0.18 (0.03-1.21)</td>
<td>0 (0)</td>
<td>0.16 (0.04-0.88)</td>
<td>4</td>
</tr>
<tr>
<td>MCV, &gt;18</td>
<td>1.56 (0.25-9.92)</td>
<td>0.71 (0.09-5.38)</td>
<td>0.88 (0.24-3.28)</td>
<td>11</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>10</td>
</tr>
</tbody>
</table>

*All estimates shown are from conditional logistic regression, matched on health maintenance organization, sex, and birth year, and adjusted for race. Values are given as odds ratios (95% confidence intervals), except where indicated. UC indicates ulcerative colitis; IBD, inflammatory bowel disease; MMR, measles-mumps-rubella vaccine; and MCV, measles-containing vaccine.*


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rubella vaccination campaign aimed at school-aged children. Although the follow-up time was limited to only the first 16 months following vaccination, there was no apparent increase in the rate of hospital admissions for Crohn's disease and hence no suggestion that MMR triggered the onset of symptoms as suggested in the study by Wakefield et al. 2

In a second study, Pelody et al12 used Finnish data and contrasted the rate of Crohn's disease with the proportion of the population receiving measles vaccine. Although there was an increase over time in the proportion of the population receiving 1 or more doses of measles virus vaccine, the rate of Crohn's disease remained stable among 2 age groups of children and adolescents aged 0 to 14 years and adolescents and young adults aged 15 to 24 years. Finally, a study by Hermann-Taylor et al13 contrasted the annual incidence of Crohn's disease at 3 United Kingdom centers (south Wales, Derby, and northeast Scotland) with the introduction of measles vaccine and MMR. In this study there was a marked rise in the rate of Crohn's disease over the study period, but the increased rate of disease predated introduction of the measles vaccine by approximately 20 years.

A number of studies have attempted to find evidence of persistent measles virus genome in pathology specimens obtained from patients with IBD. These investigations were prompted by a report of measles virus nucleocapsid protein found in 13 of 15 patients with Crohn's disease.14 Most subsequent studies by Afzal et al15 on 19 patients with IBD, by Chadwick et al16 on 20 cases, and by Lizuka et al17 on 21 cases have failed to replicate these findings, arguing that measles virus genome is not present in the gut mucosa of patients with Crohn's disease or ulcerative colitis. However, a recent study by Kawashima et al18 detected measles genomic RNA in peripheral mononuclear cells in 1 of 8 cases of Crohn's disease and 1 of 3 with ulcerative colitis but no measles RNA in 8 subjects with subacute sclerosing panencephalitis, systemic lupus erythematosus, or HIV (human immunodeficiency virus) infection. This latter study did not examine intestinal pathology specimens.

There are some unique aspects to our study that deserve mention. First, previous studies of the relationship between measles vaccine and IBD have been conducted on populations outside of the United States. This is the first study of MMR and other MCVs and IBD used historically and presently in the United States. Second, that we did not find a relationship between MMR vaccine and IBD argues against the suggestion that concurrent exposure to measles and mumps antigens increases the risk for IBD19 and against the need to deliver these vaccinations as individual antigens.20 Third, this study uses information from a population-based group of HMO members and was therefore likely free from the biases that might occur in a study that relied on self-referred patients or patients studied specifically because symptoms might have occurred following vaccination. Finally, our study included only patients enrolled from (or shortly after) birth up to the time of disease or the similar age for controls, and we reviewed each patient's medical record to ascertain vaccination status. Consequently, the completeness and quality of information on the timing and type of vaccine received is likely to be good. Because we were able to ascertain the timing of the first symptoms and date of first diagnosis of disease from the outpatient medical records at each HMO, we were able to calculate an unbiased relationship between receipt of vaccination and disease onset.

There are some limitations to our study. We included only patients with a physician diagnosis (usually a gastroenterologist) of IBD, and we have the inherent limitations of diagnostic accuracy in a retrospective study. We have little information on children or adults who had nonspecific colitis that did not eventually lead to a diagnosis of IBD. Nevertheless, our study provides evidence against the hypothesis that MMR or other MCV leads to IBD. Another limitation to our study concerned power. We were able to effectively rule out associations larger than 2-fold between ever being vaccinated with MMR and developing IBD and associations larger than 3-fold between vaccination with other MCV and IBD. However, we had a limited sample size from which to look at the independent associations between vaccination and either Crohn's disease or ulcerative colitis (Table 2) or at the relationship between timing of vaccination early in life and subsequent risk for Crohn's disease or ulcerative colitis (Table 3).

There has been recent interest in the role of early exposure to measles virus and subsequent risk for development of IBD. A few studies have suggested that intrauterine or early-in-life exposure to infectious agents or measles virus may lead to an increased risk for IBD,21,22 although we collected information on intrauterine and early-in-life measles exposure, we did not identify any mothers of case or control subjects who were noted to have first trimester measles infection. In addition, only 1 case of IBD and 2 controls had had measles infection. These small numbers precluded analysis of the relationship between measles infection and subsequent development of IBD; however, if such a risk does exist, the magnitude must be too small to identify accurately with a study of our size.

Finally, it is important to recognize that the apparent protective effect against IBD of primary vaccination with MMR after 18 months of age was not an a priori hypothesis of ours, and a similar finding was not seen among children vaccinated after age 18 months with other MCV. If subsequent studies are conducted on the relationship between IBD and primary vaccination, attention should be paid to the risk among children vaccinated after age 18 months with MMR.

In conclusion, our study of IBD using a population-based sample of cases from 4 large HMOs did not find evidence of an elevated risk for disease following vaccination with MMR or other MCV.

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From the Departments of Pediatrics (Dr Davis), University of Washington School of Medicine, and Epidemiology (Dr Davis), University of Washington School of Public Health, Seattle, and the Center for Health Studies (Drs Davis, Bohlke, and Thompson and Ms Benson), Group Health, Seattle, Washington.

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National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Ga; the Vaccine Safety and Development Branch (Drs Kramarz, Destefano, and Chen), National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Ga; the Division of Research (Drs Black and Shinefield and Mr Lewis), Kaiser Permanente of Northern California, Oakland; the UCLA Center for Vaccine Research (Dr Ward and Ms Eriksen), Harbor-UCLA Medical Center, Torrance; and the Kaiser-UCLA Vaccine Research Group (Dr Marcy), Southern California Kaiser Permanente, Panorama City.

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Corresponding author and reprints: Robert L. Davis, MD, MPH, Immunization Studies Program, Center for Health Studies Group Health Cooperative, 1730 Minor Ave, Suite 1600, Seattle, WA 98101-1448.