Intussusception Risk and Disease Prevention Associated With Rotavirus Vaccines in Australia’s National Immunization Program

John B. Carlin,1,2 Kristine K. Macartney,5,6,7 Katherine J. Lee,1,2 Helen E. Quinn,5,6 Jim Buttery,1,3,4 Ruth Lopert,8 Julie Bines,1,2 and Peter B. McIntyre5,6,7

1Murdoch Children’s Research Institute, Royal Children’s Hospital, 2Department of Paediatrics, University of Melbourne, 3Infectious Diseases Department, Monash Children’s Hospital, and 4Department of Paediatrics, Monash University, Melbourne; 5National Centre for Immunisation Research & Surveillance, 6Discipline of Paediatrics and Child Health, University of Sydney, and 7Department of Microbiology and Infectious Diseases, The Children’s Hospital at Westmead, Sydney; and 8Therapeutic Goods Administration, Canberra, Australia

(See the Editorial Commentary by Parashar and Orenstein on pages 1435–7.)

Background. Estimates of the risk of intussusception (IS) associated with currently licensed rotavirus vaccines (RV1 [Rotarix; GSK] and RV5 [RotaTeq; Merck]) diverge. Contemporaneous introduction of both vaccines in Australia enabled a population-based assessment of risk.

Methods. Confirmed cases of IS in infants aged 1 to <12 months were identified from national hospitalization databases, supplemented by active hospital-based surveillance, from July 2007 through June 2010. Vaccination histories were verified by the Australian Childhood Immunisation Register, which was also used to identify age-matched controls. Self-controlled case series and case-control methods were used to assess the risk of IS associated with both vaccines in prespecified periods after vaccination. The estimated burden of vaccine-attributable IS was compared with estimated reductions in gastroenteritis hospitalizations.

Results. Based on 306 confirmed cases of IS, the relative incidence of IS in the 1–7-day period after the first vaccine dose, was 6.8 (95% confidence interval, 2.4–19.0; P < .001) for RV1, and 9.9 (95% confidence interval, 3.7–26.4; P < .001) for RV5. There was a smaller increased risk 1–7 days after the second dose of each vaccine. The case-control analysis gave similar results. We estimate an excess of 14 IS cases and >6500 fewer gastroenteritis hospitalizations in young children annually in Australia after vaccine introduction.

Conclusions. We found a similarly increased risk of IS after both vaccines, but the balance of benefits and risks at population level was highly favorable, a finding likely to extend to other settings despite varying incidence of IS and potentially higher morbidity and mortality from both gastroenteritis and IS.

Keywords. rotavirus vaccine; intussusception; vaccine surveillance; vaccine adverse events; vaccination risk-benefit.

Worldwide, rotavirus is the leading cause of acute gastroenteritis, responsible in recent estimates for 200,000 deaths and 10 million episodes of severe diarrhea annually among children <5 years old [1, 2]. Efforts to reduce the global burden of rotavirus disease suffered a setback in 1999 when the first licensed vaccine, a rhesus-human reassortant (RRV-TV; RotaShield; Wyeth-Lederle) was withdrawn from use when found to be associated with an attributable risk of intussusception (IS) of about 1 in 10,000 recipients after the first dose in infants 2 months of age or older [3, 4]. Intussusception is the invagination of bowel into an adjacent segment, causing intestinal obstruction that unless promptly reduced progresses to bleeding and/or intestinal perforation [5]. Since 2005, 2 new oral rotavirus vaccines, a pentavalent human-bovine reassortant (RV5; RotaTeq; Merck) and a monovalent human rotavirus vaccine (RV1; Rotarix; GSK), have been
widely licensed. Neither vaccine was associated with IS in large-scale prelicensure clinical trials [6, 7]. In 2009, the World Health Organization recommended routine rotavirus vaccine for all infants worldwide [8].

At least 40 countries have introduced rotavirus vaccines into their national immunization programs, and the health impact of rotavirus vaccines is now emerging in a range of settings. A decline in diarrhea mortality after the introduction of rotavirus vaccines has been reported in Mexico and Brazil [9, 10]. Reductions in diarrhea-related hospitalizations have been observed in Australia, the United States, Mexico, Belgium, Brazil, and El Salvador [11–18]. In Australia, hospitalization rates for rotavirus-attributable gastroenteritis have dropped by >70% since vaccine introduction in 2007 [19].

In light of the experience with RRV-TV, the World Health Organization recommends that countries implementing rotavirus vaccination should conduct postmarketing surveillance to identify rare or unexpected adverse events, including IS. A complicating factor is that the reported (prerotavirus vaccination) incidence of IS varies widely across regions and by ethnicity [5] and it has generally been based on nonconfirmed ICD-coded hospitalization data, for example, in Panama and the United States, estimated incidence rates are similar (30 and 38 cases per 100,000 children <1 year old, respectively), whereas in Australia incidence is 81 cases per 100,000 and in Vietnam it is substantially higher (304 cases per 100,000). The incidence of IS increases sharply through the first 6–8 months of life, coinciding with the period of routine immunization.

Since introduction of rotavirus vaccines into routine use, postlicensure studies of the association between IS and RV5 [20–23], RV1 [24, 25], and both vaccines [26] have been published from the United States, Latin America, and Australia, respectively. Evidence of an association between IS and RV1 was found in Mexico [24, 25], Brazil [24], and Australia [26]. For RV5, evidence of an association was reported in Australia [26] and indirectly in 1 of 3 studies from the United States [21–23].

Rotavirus vaccination was introduced to the Australian national immunization program in July 2007 and is delivered by jurisdictional (state or territory) health authorities, some of whom introduced RV5 (3-dose schedule at 2, 4, and 6 months of age) and others RV1 (2-dose schedule at 2 and 4 months of age) [27]. This resulted in both vaccines being used contemporaneously in demographically similar populations. After the preliminary report of an association between both vaccines and IS based on active surveillance in 4 sentinel hospitals [26], the Australian regulatory agency, the Therapeutic Goods Administration (TGA), commissioned a national study to assess the risk of IS after rotavirus vaccination. The aim of this study was to evaluate the association between IS and receipt of either RV1 or RV5 vaccine in the previous 21 days nationally during a 3-year period. We also compared the vaccine-attributable risk of IS with the estimated reduction in gastroenteritis hospitalizations after vaccine introduction.

**METHODS**

**Case Ascertainment**

We identified cases of IS in children between 1 and 12 months of age from the introduction of rotavirus vaccines on 1 July 2007 to the end of June 2010. The 6 jurisdictions included in the study account for >95% of the Australian population (22 million; annual birth cohort approximately 290,000): New South Wales, Victoria, Western Australia, South Australia, Queensland, and the Northern Territory. RV1 was used in New South Wales and the Northern Territory; RV5 was used in Victoria, South Australia, and Queensland. In Western Australia, RV1 was used from July 2007 to April 2009, when it was replaced by RV5.

Hospitaialized IS case patients were identified retrospectively by searching hospital discharge databases for infants who had the International Classification of Diseases (ICD) (International Classification of Diseases, 10th Revision, Australian Modification) discharge code for IS (K56.1) recorded in any diagnostic field. Only IS cases confirmed to have the highest level of diagnostic certainty, level 1 of the Brighton Collaboration classification [28], were analyzed. Case notes were reviewed by physicians or nurses using a standardized data extraction form. Reviewers were not explicitly blinded to vaccination status, but it was not generally recorded in clinical case notes. A small number of additional cases were identified by the Paediatric Active Enhanced Disease Surveillance (PAEDS) system, which performed active surveillance in 4 large tertiary pediatric hospitals [29]. Further detail on ascertainment of cases is provided in the Supplementary Material. Vaccination history for each case patient was obtained from the Australian Childhood Immunisation Register (ACIR), which has near-complete capture (>98%) of national immunization program–funded vaccines provided to children aged <7 years [30].

**Control Selection**

For each confirmed IS case, 10 matched control subjects were randomly selected from the ACIR database, after matching on date of birth (within ±1 day), sex, and state or territory of residence.

**Ethical Approval**

The study was conducted on behalf of the TGA, in conjunction with state and territory government health departments, as a public health investigation, with authorization for compilation of routinely collected data provided by these statutory bodies. The use of deidentified data from the ACIR for selection of controls for the case-control study was approved by the Australian Government Department of Health and Ageing.

**Statistical Analysis**

The analysis assessed risk associated with 2 exposure periods following each dose of vaccine, chosen on the basis of
previously published literature: 1–7 and 8–21 days after vaccination. Unexposed time was defined as time before vaccination or >21 days after a dose of vaccine, within the 1–12-month age window. The analysis included only case patients (and controls, for the case-control analysis) for whom vaccination records were available on the ACIR. We excluded case patients (and controls) whose ACIR record indicated receipt of a second (or third) dose of rotavirus vaccine but had missing data for the earlier dose(s). Inclusion was otherwise independent of vaccination history, with minor exceptions in the case-control analysis as detailed in the Supplementary Material. Analysis was performed using Stata 11.2 software (StataCorp; 2009).

**Self-Controlled Case Series Analysis**

The self-controlled case series (SCCS) method compares the frequency with which the outcome occurred in periods of time after vaccination (“exposure”) relative to its occurrence in unexposed time, in case patients only [31]. Results (obtained from a conditional Poisson regression model) are reported as relative incidence (RI), with 95% confidence intervals (CIs), for each exposure period compared with time outside this window. We treated IS as a nonrecurring event and analyzed first occurrences only. Because the incidence of IS is strongly age related, we adjusted for the effect of age using indicators for month of age categories in the regression model [31]. Alternative approaches to the method of age adjustment, which varied the age categorization and smoothed the age effect, were explored in sensitivity analyses (see Supplementary Material). All cases of IS were included in a single model; this allowed all case patients to contribute information on the age effect, whereas those children who received each vaccine contributed information on the potential vaccine-related risk for that vaccine. In further

![Figure 1](cid:2013:57(15 November))

Summary of intussusception cases, and their clinical review, in children 1 to <12 months of age (Brighton level 1 primary cases only). The combined data set includes all 282 cases from the state-based admissions data plus another 38 captured by Paediatric Active Enhanced Disease Surveillance (PAEDS; numbers in parentheses). In the 8 case patients with incomplete records, the Australian Childhood Immunisation Register (ACIR) record documented receipt of a second (or third) dose of rotavirus vaccine but was missing data for the earlier dose(s). NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; SCCS, self-controlled case series; VIC, Victoria; WA, Western Australia.
sensitivity analyses we excluded case patients who received a dose of vaccine later than the recommended age limit for administration [32] and allowed for a “healthy vaccinee effect” by allowing for a different (lower) RI of IS during the 2-week period before each vaccine dose [31].

**Matched Case-Control Analysis**

Case-control analysis was performed by assigning controls the same “event date” as their matched IS case and comparing the frequency with which the event date fell within the postvaccination exposure windows between case patients and controls. We used conditional logistic regression to estimate odds ratios (ORs) for each vaccine dose and exposure window. Because of the rarity of the outcome, the OR in this model is equivalent to the RI parameter estimated by the SCCS method, and both may be interpreted as measures of relative risk. Analysis was performed separately for each vaccine type, restricting to jurisdictions which administered that vaccine within their official immunization program; we excluded the few case patients who received the nonstandard vaccine for their jurisdiction of residence. A range of sensitivity analyses was conducted, using an approach similar to that used for the SCCS method (Supplementary Material).

**Risk-Benefit Analysis: Excess IS Compared With Rotavirus Disease Averted**

A simple risk-benefit analysis was conducted to compare the estimated number of vaccine-attributable cases of IS (risk) with the estimated number of rotavirus hospitalizations averted by vaccination in Australia (benefit). Risks and benefits were calculated using national estimates of vaccine coverage along with the estimated baseline incidence of IS and the RI of IS after vaccination, on the risk side, and incidence of hospitalization for rotavirus diarrhea and vaccine efficacy, on the benefit side [24]. (See Supplementary Material for further details.)

**RESULTS**

Ascertainment of cases is summarized in Figure 1. Most cases included in the analysis were identified through hospitalization databases. A total of 393 putative cases from the 2 systems was reduced to 306 after exclusions detailed in Figure 1. Table 1 displays numbers of case patients and controls with “event date” within 1–7 or 8–21 days of vaccination. Further details on cases and their timing is provided in the Supplementary Material.

**SCCS Analysis**

Table 2 displays results from the SCCS analysis for each vaccine dose. For both vaccines, the estimates of RI for the 1–7-day period after dose 1 indicate very strong evidence ($P < .001$) of elevated risk, with the lower limits of the 95% CIs both higher than a doubling in risk. Elevated risk extended to the 8–21-day postvaccination period for both vaccines but at a lower and less statistically significant level. For both risk periods, the point estimate of the RI associated with RV5 was somewhat higher than for RV1, but as the 95% CIs substantially overlapped, the risk associated with each vaccine could not be distinguished. There was weaker evidence of an increased risk of IS after dose 2 of both vaccines, particularly in the 1–7–day period after vaccination, but no suggestion of increased risk after dose 3 of RV5. A range of sensitivity analyses is reported in the Supplementary Material (Supplementary Tables 3–10). None of these produced substantially different conclusions, although there was some variation in RI estimates, especially for dose 1; in particular, when case patients who received RV1 outside the

<table>
<thead>
<tr>
<th>Vaccine Doses</th>
<th>Case Patients</th>
<th>Controls</th>
</tr>
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<tbody>
<tr>
<td>RV1 jurisdictions</td>
<td>17</td>
<td>241</td>
</tr>
<tr>
<td>RV5 jurisdictions</td>
<td>29</td>
<td>375</td>
</tr>
</tbody>
</table>

* The event date was defined as the date of admission for case patients with intussusception and the date of the matched case patient’s admission for each control infant.

* Numbers in parentheses represent the number of case patients who received the standard vaccine for their jurisdiction of residence and were included in the case-control analysis, if different from the total number of case patients.

* Percentages of those who received that vaccine.

* These case patients were not included in the case-control study, so there are no corresponding controls.
recommended age range were excluded, the association between RV1 and IS was diminished, (eg, RI for 1–7 days after dose 1, 4.11 [95% CI, 1.09–8]).

B. Based on cases in Queensland, South Australia, Victoria, and WA; 159 case patients and 1501 matched controls. Data for WA were restricted to infants born after 1 April 2009, when RV1 was replaced by RV5 in the state immunization program.

**Table 2. Self-Controlled Case Series Analysis Based on 306 Cases of Intussusception in Children Aged 1 to `<12 Months`**

<table>
<thead>
<tr>
<th>Vaccine and Dose</th>
<th>Relative Incidence (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV1 vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1, 1–7 d</td>
<td>6.76 (2.40–19.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dose 1, 8–21 d</td>
<td>3.45 (1.33–8.94)</td>
<td>.01</td>
</tr>
<tr>
<td>Dose 2, 1–7</td>
<td>2.84 (1.10–7.34)</td>
<td>.03</td>
</tr>
<tr>
<td>Dose 2, 8–21 d</td>
<td>2.11 (.97–4.62)</td>
<td>.06</td>
</tr>
<tr>
<td>RV5 vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1, 1–7 d</td>
<td>9.89 (3.70–26.42)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dose 1, 8–21 d</td>
<td>6.32 (2.78–14.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dose 2, 1–7</td>
<td>2.81 (1.16–6.80)</td>
<td>.02</td>
</tr>
<tr>
<td>Dose 2, 8–21 d</td>
<td>1.77 (.81–3.88)</td>
<td>.16</td>
</tr>
<tr>
<td>Dose 3, 1–7</td>
<td>0.75 (.18–3.11)</td>
<td>.69</td>
</tr>
<tr>
<td>Dose 3, 8–21 d</td>
<td>0.56 (.17–1.82)</td>
<td>.33</td>
</tr>
</tbody>
</table>

**Abbreviation:** CI, confidence interval.

* Cases occurring between 1 July 2007 and 30 June 2010.

**Matched Case-Control Analysis**

Table 3 shows estimated ORs for IS in the risk periods 1–7 and 8–21 days after each vaccine dose from the matched case-control analysis. These analyses found a generally similar pattern of results to the SCCS analysis, with an increased risk of IS in the 1–7- and 8–21-day periods after dose 1 for both vaccines and some suggestion of an increased risk 1–7 days after dose 2. Most estimates of the relative risk of IS after dose 1 were higher in the case-control than in the SCCS analysis. The results from the sensitivity analysis excluding case patients and controls who received RV1 outside the recommended age range showed effects similar to those of the corresponding SCCS analysis (Supplementary Tables 11 and 12).

**Risk-Benefit Assessment**

The vaccine attributable risk for IS, based on the estimated RI in the 1–21 days after dose 1 and the 1–7 days after dose 2 derived from the SCCS analysis, was estimated to be 4.3 (95% CI, 0.8–23.3) cases per 100 000 infants vaccinated for RV1 and 7.0 (95% CI, 1.5–33.1) cases per 100 000 for RV5. Given the substantial overlap in the CIs, we considered attributable risk to be the same for both vaccines and used a mid-range estimate of 5.6 additional cases of IS per 100 000 vaccinated infants. This resulted in an estimated excess of 14.3 cases annually at the national level (11.7 after dose 1 and 2.6 after dose 2), assuming 85% vaccination coverage from 3 months of age. On the other hand, rotavirus vaccination was conservatively estimated to prevent 2180 cases per 100 000 infants, or 6500 cases overall, of acute gastroenteritis hospitalizations per year among children <5 years of age (Table 4).

**DISCUSSION**

Our results provide evidence that both currently licensed rotavirus vaccines are associated with a similar increase in the incidence of IS in the 21 days after the first vaccine dose, estimated at 6- to 10- fold in the first 7 days and 3- to 6-fold in the 8–21 days after vaccination. For RV1, these findings are similar to those from a smaller

**Table 3. Case-Control Analysis of Association Between Intussusception Incidence and RV1 or RV5 Vaccination**

<table>
<thead>
<tr>
<th>Vaccine and Dose</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>RV1 vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1, 1–7 d</td>
<td>15.61 (3.36–72.57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dose 1, 8–21 d</td>
<td>6.48 (1.74–24.16)</td>
<td>.005</td>
</tr>
<tr>
<td>Dose 2, 1–7</td>
<td>2.44 (1.80–7.47)</td>
<td>.12</td>
</tr>
<tr>
<td>Dose 2, 8–21 d</td>
<td>1.35 (.50–3.63)</td>
<td>.56</td>
</tr>
<tr>
<td>RV5 vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1, 1–7 d</td>
<td>11.74 (3.18–43.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dose 1, 8–21 d</td>
<td>4.65 (1.80–12.00)</td>
<td>.001</td>
</tr>
<tr>
<td>Dose 2, 1–7</td>
<td>2.53 (1.89–7.20)</td>
<td>.08</td>
</tr>
<tr>
<td>Dose 2, 8–21 d</td>
<td>1.38 (.53–3.62)</td>
<td>.51</td>
</tr>
<tr>
<td>Dose 3, 1–7</td>
<td>1.06 (.23–4.84)</td>
<td>.94</td>
</tr>
<tr>
<td>Dose 3, 8–21 d</td>
<td>0.80 (.18–3.64)</td>
<td>.77</td>
</tr>
</tbody>
</table>

a Based on cases in New South Wales, the Northern Territory, and Western Australia (WA); total of 132 case patients and 1319 matched controls. Data for WA were restricted to infants born before 1 April 2009, when RV1 was replaced by RV5 in the state immunization program.

b Based on cases in Queensland, South Australia, Victoria, and WA; 159 case patients and 1501 matched controls. Data for WA were restricted to infants born after 1 April 2009.
Australian study, which included some of the same cases but used different methods [26], and to those from Mexico [24, 25]. Two postmarketing studies in the United States found no evidence of an association between IS and RV5 [21, 22], but a more recent ecological study reported a small secular increase in IS rates among infants aged 8–11 weeks after the introduction of rotavirus vaccination (principally with RV5), consistent with our findings [23]. Ours is the first epidemiological study to examine a sizeable number of cases potentially associated with RV5 vaccination and also the first study to find evidence of an increased risk of IS after the second dose of both vaccines, although a 2-fold relative risk was reported after the second dose of RV1 in Brazil [24, 33]. A unique aspect of our study was the ability to compare IS risk after administration of RV1 and RV5 within very similar populations over the same period of time.

Our study was based on population-based capture of clinically verified IS cases during a 3-year period. High vaccine coverage (84% for a full vaccine course [34]), the capacity to confirm dates of administration and vaccine type for each vaccination using the ACIR, and access to data on IS presentations from population-based hospitalization databases, supplemented by active surveillance at the largest pediatric hospitals, ensured extensive capture of large numbers of vaccinated case patients. Cases excluded because verification was not possible were unlikely to have caused bias, because vaccination exposure does not vary substantially by geographic location in Australia [35]. Although we cannot completely rule out variations in the ascertainment of cases by ICD coding, evidence of high sensitivity in detecting IS was provided by active surveillance that identified very few additional cases at sentinel sites. In addition, the case-note review confirmed approximately 60% of ICD-coded cases as Brighton level 1 in the New South Wales series, suggesting that the coding may overascertain but is unlikely to miss many confirmed cases [36]. The available data enabled us only to examine the relative risk of IS associated with specified postvaccination time windows, so it remains unclear whether our findings reflect an increase in the cumulative incidence of IS during the first year of life or earlier occurrence (triggering) of IS in infants among whom it would have occurred later in infancy in the absence of rotavirus vaccination.

Results similar to those of the SCCS analysis were seen in the matched case-control analysis, although estimates of relative risk were higher and CIs were wider. Greater precision might be expected in the SCCS, provided that our assumption of a common pattern of age dependence of IS incidence across Australia holds. A range of sensitivity analyses did not change the overall pattern of results, although there was variation in the estimate of relative risk after dose 1 for both vaccines. Dose 1 is given at about age 2 months, when the incidence of IS increases sharply, so SCCS estimates of vaccine-related risk are somewhat sensitive to the method used for modeling the age-dependent background incidence of IS. Weaker associations between RV1 and IS risk were observed when case patients who were vaccinated at an age beyond recommended upper age limits (predominantly during the first year of the program) were excluded. Although these case patients were few, the findings suggest that adherence to upper age limits for vaccine administration may, in some settings, reduce the likelihood of vaccination-related IS. In low- and middle-income countries, however, prescribing strict age limits may not be warranted, because of differences in IS incidence and morbidity relative to rotavirus gastroenteritis [37].

The attributable risk of IS associated with rotavirus vaccination identified in our study was conservatively estimated at 14 excess cases per year within the annual birth cohort of approximately 300,000. In countries such as Australia, with good access to specialist hospital care, IS is usually diagnosed within 24 hours of symptom onset, and prompt treatment by enema is associated with a good outcome. Deaths from IS are rare and there were none in this study (data not shown). In contrast, in low-income countries, IS may be treated surgically and the case fatality rate associated with delayed diagnosis may be as high as 25% [37]. However, these regions also tend to have a high rotavirus disease burden, and rotavirus vaccination is likely to have a major beneficial impact. Studies to assess the postmarketing risk of IS alongside vaccine benefits in these settings would be helpful.

In conclusion, our analysis indicates that the 2 currently licensed rotavirus vaccines (RV1 and RV5) give rise to a small but measurable increase in the incidence of IS in young infants. The ability to detect a rare vaccine-related adverse event associated with the implementation of a new vaccine, and to accurately evaluate the risk-benefit, is testimony to the value of robust and sensitive vaccine adverse event surveillance and investigation systems. Despite a small increased risk of IS associated with both RV1 and RV5 in Australia, the benefits of rotavirus vaccination in preventing rotavirus gastroenteritis clearly outweigh the risks. Although countries planning to introduce rotavirus vaccines will need to consider their rotavirus disease burden in relation to the incidence of IS and the ability to diagnosis and treat it, it seems likely that the benefits of these vaccines will outweigh the risks in other settings.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

**Acknowledgments.** This work was made possible by the extensive cooperation of numerous individuals working in or on behalf of the health
In 2006, the World Health Organization (WHO) published a position paper on rotavirus vaccines. The paper highlighted the importance of rotavirus vaccines in controlling rotavirus disease and reducing its related mortality.


