Time to Begin a New Chapter and Expand Rotavirus Immunization

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Rotavirus immunization has been limited to young infants owing to intussusception events noted with a prior rotavirus vaccine, RotaShield. Dramatic declines occurred in rotavirus-related disease beginning in 2008 after implementation of rotavirus vaccination in young infants. These declines occurred in vaccinated children and unvaccinated children and adults (through indirect protection). Despite these declines, reasons for concern exist about the durability of these declines. These reasons include an incomplete immune response that is not lifelong and rotavirus immunization completion rates that have plateaued at <70% of eligible children. Current rotavirus infant vaccination strategies and indirect protection of unvaccinated children will result in a large population of immunologically susceptible persons who will be at risk of rotavirus disease. Expansion of US rotavirus vaccination outside the current Advisory Committee on Immunization Practices recommended immunization age limits would provide important benefits that outweigh risk related to intussusception.

Keywords. age; immunization; intussusception; rotavirus; vaccines.

We stand at the end of the current chapter of US rotavirus vaccination, hesitant to begin the next chapter. Tremendous successes have been achieved since 2006 when the first new rotavirus vaccine was licensed in the United States. The burden of rotavirus disease in the US has declined dramatically in both vaccinated and unvaccinated persons owing to herd protection. Although a small increased risk of intussusception has been identified in the few weeks immediately after rotavirus vaccination, the documented benefit of these vaccines clearly outweighs this risk. Despite these successes, we are beginning to face new challenges, as illustrated by my family’s personal experience with rotavirus.

We were leaving Atlanta on a 600-mile drive to Florida, anticipating a week of rest and relaxation at the beach. It was our children’s February 2013 school break. The car was packed, and 3 of our 4 children were already seated and buckled. Our 7-year-old daughter, who had previously complained that she did not feel well, proceeded to vomit outside our front door. My wife and I grabbed a bucket, and helped our daughter into the minivan. Although we hadn’t left the driveway, it was too late to turn back.

Our 7-year-old daughter, born in 2005, had been 9 months old when the pentavalent rotavirus vaccine was licensed, too old to receive the vaccine. As a first child, she had relatively minimal exposure to other children during her early years. Beginning in 2008, the rate of rotavirus declined dramatically in US children and has remained markedly reduced, although with biennial increases [1, 2]. Thus, I did not know whether our daughter had previously been infected with rotavirus. Our 3 younger children, however, had been fully immunized. Immunization is very effective in preventing severe outcomes such as hospitalization but, as with wild-type rotavirus infection [3], does not protect nearly as well against mild infections [4–6]. Pediatric rotavirus vaccination protects not only vaccinated children but also indirectly protects unvaccinated children and adults by decreasing rotavirus circulation in the community [1, 7–9].

Over the next several days, our daughter was mildly ill with abdominal pain, occasional vomiting, and diarrhea. Although she showed glimmers of improvement, 3 days later she awoke with bilious vomiting and periumbilical abdominal pain. On arrival at the closest pediatric hospital, the physician noted significant...
dehydration, administered ondansetron, attempted oral hydration, and thought that intravenous rehydration and basic laboratory tests were needed. He stated that she probably had gastroenteritis and lectured us about norovirus and the impact of the rotavirus vaccines. I bit my tongue and avoided clarifying that not only was 2013 a bad year for norovirus, it was also a relatively bad year for rotavirus [2, 10]. Our daughter’s laboratory results were notable for bicarbonate level of 10 mmol/L and an anion gap of 33. On hospital admission, bacterial stool culture and rotavirus antigen tests were ordered. As anyone who studies gastroenteritis knows, the best way to stop diarrhea is to send stool studies. After receiving hydration overnight, our daughter recovered, and we left the hospital to resume our family vacation.

Within 5 minutes of returning from the hospital, our 5-year-old son vomited while attempting to reach the bathroom. That night both the 5-year-old and the 2-year-old had vomiting and diarrhea, and both missed the toilet. I wondered whether I should save a large, foul, watery stool that the 2-year-old left in his portable potty. Was it norovirus, rotavirus, or something else? As I cleaned up, I wondered whether sheer exposure to billions of virions might overcome my preexisting immunity. Waivering in uncertainty, I found a plastic container, poured the entire stool into it and then placed it in the refrigerator on the only open shelf, next to the produce. Although I persuaded myself that it was important scientifically, she just shook her head in disbelief and horror and asked how we were going to transport it the 600 miles back to Atlanta.

Then on day 8, the last day of our Florida vacation, I felt a sudden chill and my stomach felt queasy. I went to bed early knowing that I was probably next. Then the diarrhea began. Clearly I didn’t have cholera, because I hadn’t traveled, but listening to rice-water stool hit the toilet again and again, I wasn’t so sure.

When the dust finally settled, 6 of 6 family members had become ill within 2 weeks. Stool specimens that I had saved from myself and 2 other family members all included rotavirus of genotype G12P[8]. The degree of illness varied from 2 larger- and looser-than-usual bowel movements in a single day in the fully immunized 10-month-old (which would not meet criteria for gastroenteritis in many studies) [4–6], to severe dehydration requiring hospitalization in the unvaccinated 7-year-old. Fortunately, as I write, everyone has recovered with no lasting effects. Importantly, the experience changed my mind regarding the need to expand rotavirus vaccination outside the current Advisory Committee on Immunization Practices (ACIP) recommendations in the United States.

BACKGROUND

In the prevaccine era, initial rotavirus infection occurred in nearly all children by 5 years of age. Because of this finding and the lack of data in older populations, many considered rotavirus disease to be exclusively a disease of young children. Five or more rotavirus infections can occur by 2 years of age, usually due to different genotypes [3]. Although the incidence of severe rotavirus disease peaked in the prevaccine era at 6–24 months of age [11], children and adolescents 5–18 years of age, adults, and the elderly all can experience symptomatic disease [7, 12–15]. According to estimates based on data coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), in the prevaccine era rotavirus accounted for 586 000 ambulatory visits, 100 000 emergency department visits, and 24 000 hospitalizations per year in the United States in persons ≥5 years of age [14, 16]. Among adults, rotavirus was estimated to account for 3%–5% of all gastroenteritis-related hospital discharges, at a cost of $152 million per year [14]. Epidemiological risk factors for rotavirus infections include direct contact with young children (eg, parents), residing in a community that has been sheltered from exposure to children (eg, retirement communities), and in the immunocompromised (eg, persons with human immunodeficiency virus infection) [7, 12, 13, 15].

Understanding the Food and Drug Administration licensure and ACIP recommendations for the current licensed US rotavirus vaccines (RotaTeq [RV5; Merck] and Rotarix [RV1; GlaxoSmithKline]) requires recognizing that these vaccines were studied and licensed after observation of an increased number of cases of intussusception in 1999, within 1 year after licensure of RotaShield, a prior rotavirus vaccine. This increased risk of intussusception with RotaShield affected about 1 in every 10 000 children and was primarily observed after the first dose of vaccine [17]. Determining the reasons for the association between RotaShield and intussusception and evaluating for similar risks with RV1 and RV5 was of paramount importance.

One of the debates in the aftermath of the RotaShield was whether there was an age-related risk of intussusception with RotaShield (eg, whether late administration of the first dose of RotaShield was responsible for some of the increased risk of intussusception). The limited data were analyzed using multiple different study designs and statistical approaches, with widely discrepant conclusions [18–21]. Ultimately the limited number of intussusception events that occurred related to RotaShield was insufficient to completely rule in or rule out an age-related risk of intussusception. Nonetheless, the debate greatly affected the conduct of RV5 and RV1 licensure studies and subsequent ACIP recommendations.

Large prelicensure studies (>60 000 infants in each study) were necessary to provide sufficient power to identify a risk on the order of magnitude of that observed with RotaShield [4–6]. Vaccine efficacy in the prevention of severe rotavirus-related disease and rotavirus-related hospitalization was ≥85% [4–6]. The vaccines were well tolerated in these studies, with intussusception occurring in similar numbers of vaccine and placebo recipients [4–6]. Importantly, these studies also did not
identify an increased risk of intussusception in large numbers of children who were followed up through 1–2 years of age [22]. Although initial 2006 ACIP recommendations mirrored the RV5 licensure studies, with the US licensure of RV1 in 2008 the ACIP expanded the range for administration of both vaccines to harmonize the administration schedule (first dose by 6 weeks through 14 weeks 6 days; maximum age for the last dose, 8 months 0 days) [23]. The ACIP did not recommend a catch-up immunization schedule [23].

In 2008 a marked decline in rotavirus-related disease was observed among both vaccinated and unvaccinated children [1,8] and adults [7–9]. This protection of unvaccinated persons occurred owing to indirect protection or herd protection. The herd is not immune but is rather protected from exposure to rotavirus and subsequent disease by the immunization of young children. A slight increase in the risk of intussusception (0.5–6.9 cases per 100 000 vaccinated infants) has now been observed in the days to 3 weeks after the first dose of rotavirus vaccine [2,24,25]. Importantly, no net increase in the number of intussusception-related hospital discharges [26] or sustained population-level change in the rates of rotavirus-related intussusception hospitalizations has been observed to date [27].

Limitations of the Current Vaccination Strategy

Although we have achieved dramatic successes with the current US infant rotavirus vaccination strategy, significant limitations and issues with the current approach may threaten these successes. These reasons are listed below:

- More than 30% of US children are unvaccinated or under-vaccinated for rotavirus as documented in the last National Immunization Survey [28]. The rate of progress in improving complete rotavirus vaccination rates has now plateaued after initial rapid increases (44% in 2009, 59% in 2010, 67% in 2011, and 69% in 2012). This leaves >30% of US children in the current birth cohorts incompletely protected against rotavirus disease. Immunization rates among older children are much lower [28], and many older children who were unvaccinated or undervaccinated have temporarily benefited from indirect or herd protection (eg, my daughter).
- Prior barriers to rotavirus vaccine usage (eg, lack of insurance coverage and reimbursement, cost of vaccine, concerns about safety and adding another vaccine to the immunization schedule) [29] had declined significantly by the beginning of 2011 [30]. Residual challenges exist in adequately improving vaccination rates in smaller metropolitan, urban, or rural areas [31] and among family medicine physicians [29–31]. Improving communication with healthcare providers and patients about the risk-benefit analysis of rotavirus vaccination is important, but now, >8 years after implementation of rotavirus vaccination, reliance on this strategy is unlikely to substantially affect vaccination rates. It should be noted that the best predictor for initiation of rotavirus vaccination is the receipt of diphtheria, tetanus, and pertussis vaccine (relative risk, 7.91; 95% confidence interval, 7.69–8.13) and that the number of RV5 doses administered highly correlates with the number of doses of diphtheria, tetanus, and pertussis received [31]. Thus, it seems that provider and patient education alone will not alone be sufficient to improve vaccination rates.
- Although vaccine efficacy against severe rotavirus-related disease and hospitalizations is ≥85%, efficacy against any rotavirus infection is consistently lower [4–6]. Postlicensure vaccine effectiveness rates for complete rotavirus vaccination range from 70% to 91% against rotavirus emergency department visits and hospitalizations but are lower for persons who are incompletely immunized [2,32,33]. Thus, rotavirus will continue to cause emergency department visits and hospitalizations, not only in unvaccinated or incompletely vaccinated children but also occasionally in completely vaccinated children.
- Rotavirus can cause severe disease in older children and adults. In the prevaccine era when rotavirus infections occurred in nearly all children by 5 years of age, 28% of rotavirus-related hospitalizations occurred among persons >5 years of age [14]. Although unvaccinated children and adults benefit from indirect protection from rotavirus infection [7–9], indirect protection is not the same as herd immunity, and protection may vary by year [7,34]. For example, although my daughter (and family) was indirectly protected for many years against rotavirus infection, in 2013 this indirect protection failed.
- Unlike other viruses (eg, measles and polio), rotavirus will not be eliminated owing to the presence of both animal and human rotavirus reservoirs. Circulation of previously uncommon genotypes (eg, G12 and G9P[4]) suggests the possibility of viral reassortment or escape from vaccine-induced population-based immunity [1,7]. Fortunately, current evidence suggests that rotavirus vaccine effectiveness against these genotypes is preserved [32]. It is important, however, to note that rotavirus has not disappeared and that peaks of disease are still observed every other year [2,10]. Ongoing active surveillance for rotavirus in children of all ages through multicenter collaborations (eg, the New Vaccine Surveillance Network [1,11,32]) is needed to identify changes in the epidemiology and genotypes of rotavirus over time.

Without increasing rotavirus immunization, our current strategy will result in a large population of susceptible individuals in whom disease will occur over time (see my family’s example). Rotavirus disease is likely to continue to follow prior predictions, in which the age at hospitalization will continue to increase and peaks of rotavirus-related disease will occur at intervals of ≥2 years [35].

Data for Expansion of Rotavirus Vaccination in Infants

Although a small US study is planned to evaluate the safety and immunogenicity of immunizing infants earlier against rotavirus
(NCT01960725), no prospective studies of older children are listed at clinicaltrials.gov for either RV5 or RV1 [36]. Retrospective data regarding infants who receive vaccine outside the currently recommended window are limited. One study published in 2013 suggested that 8% of children received their first rotavirus vaccine dose after age 14 weeks 6 days, and another 2% received their last dose of rotavirus vaccine after age 8 months 0 days (ie, outside current ACIP recommendations) [31]. In data from Mexico and Brazil, late administration of rotavirus vaccine was not associated with an increased risk of intussusception [37].

Analysis of the risks and benefits of rotavirus vaccination using the risks identified in the data from Mexico and Brazil clearly demonstrated that the benefits or rotavirus vaccination far outweigh any intussusception-related risk [38], even using the highest risk estimates [2]. A recent modeling study demonstrated that removing the age restriction on rotavirus immunization would potentially avert >47 000 rotavirus-related deaths worldwide while potentially causing 294 intussusception-related deaths [39]. After reviewing these and other data, the World Health Organization recommended expanding the age of rotavirus vaccine administration to coincide with administration of the first 2–3 doses of diphtheria, tetanus, and pertussis vaccine [40].

**Suggestions for the New Chapter**

It is not tenable to perform the massive studies that would be needed to rule out a risk of intussusception on the order of magnitude observed with RotaShield (much less RV5 or RV1) by immunizing outside ACIP recommendations. Smaller studies can and should be performed to assess the safety, immunogenicity, and number of doses needed to vaccinate older toddlers and children who are unvaccinated or incompletely vaccinated. Unfortunately, to the best of my knowledge, no such studies are registered [36] and thus such data would no be available to inform decision making for years. In the meanwhile thousands of US children will continue to suffer severe and potentially life-threatening rotavirus gastroenteritis. A short-term solution awaiting additional data would be to immunize children with catch-up doses of rotavirus vaccine beginning at 1 year of age when rates of naturally occurring intussusception have declined to or below the rates observed at 3 months of age [41, 42]. In the prevaccine era, such a strategy might have been too late, because disease peaked between 6 and 24 months of age [11]. In the postvaccine era, the median age of rotavirus disease has increased [1] potentially allowing a window for catch-up vaccination. The safety of this approach could be assessed using postlicensure mechanisms such as Vaccine Safety Datalink, Vaccine Adverse Event Reporting System, hospital discharge databases, and ICD9-coded data that can provide sufficient power to detect very small differences in risk. It will be important not to focus analysis only on the days to weeks immediately after immunization but also to assess the impact on the overall risk of intussusception through 1 year after immunization. Such an approach would be similar to current World Health Organization recommendations regarding rotavirus vaccination. Implementing such a catch-up immunization plan would decrease the number of immunologically susceptible children and would be expected to prevent disease in this vaccinated cohort. It also might also indirectly protect, at least temporarily, other unvaccinated children and adults. Ongoing surveillance is needed to ascertain rotavirus disease in all populations and to determine whether additional expansions of rotavirus vaccination might be needed.

**Conclusions**

Although dramatic declines have occurred in rotavirus-related disease in both vaccinated and unvaccinated persons, reasons exist for ongoing concern. Human immunity after wild-type infection is incomplete, and asymptomatic infections occur. The rotavirus immunization rate (<70% completed the vaccination series in 2012) has plateaued and lags far behind the immunization rates achieved for most pediatric vaccines [28]. Although the indirect protection of unvaccinated children and adults provides substantial short- to intermediate-term benefit [7, 8], it contributes to an immunologically susceptible population [34]. We can and should begin a new chapter in US rotavirus vaccination, expanding rotavirus vaccination outside the current ACIP-recommended age limits and implementing a catch-up vaccination plan to extend the benefits of such vaccination.

**Notes**

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**References**


