Unexpected Benefits of Rotavirus Vaccination in the United States

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The large-scale introduction of a new vaccine can uncover many secrets and surprises about the epidemiology of disease that might not be discovered in any other way. Examination of the outcome of a vaccine introduction can validate prior assumptions concerning the burden of disease and the economic consequences of the vaccination program, as well as determine herd effects of the program arising from either a reduction in the environmental load of the infectious agent or a decrease in the group of susceptibles that might blunt transmission of the agent. In this issue of the Journal, Lopman et al document the impact of the introduction of rotavirus vaccines in the United States and find some surprises that could not have been fully anticipated or predicted in advance [1].

In 2006, the United States introduced a new rotavirus vaccine that was immediately recommended for the routine immunization of all children [2]. Uptake was slow at first but by 2008, about 60% of American infants were being immunized. Small local surveys of diarrheal illnesses in children <2 years who had been immunized indicated a substantial reduction in hospitalizations and emergency room visits [3–8], outcomes predicted by the large clinical trials that determined the vaccine’s efficacy to be 85% or more against severe disease [9, 10]. However, this was not the whole story. Lopman et al at the Centers for Disease Control and Prevention have analyzed a large database covering approximately 20% of all US hospital admissions and looked at the numbers of discharges coded for diarrhea due to rotavirus or for any unspecified cause among children from 0 to 24 years of age. They compared baseline rates of these hospital discharge records in the prevaccination years, 2000–2006, versus the postvaccination year 2008, as well as the trend over the 2-year period when the vaccine was being introduced. From this analysis, they have made several remarkable observations on the indirect effects of the vaccine that could not have been anticipated before the vaccine was introduced.

The first surprise was the herd effect of the vaccination program. In 2008 when vaccine coverage had reached 57% of infants (ie, <1 year) and 17% of children 1–2 years of age, they found a 78% reduction in hospital discharges coded specifically for rotavirus. This mismatch—the greater reduction in diarrheal hospitalizations than that which could be explained given lower rates of vaccine coverage—had been noted previously in smaller local surveys but confirmation in this large national database was striking. Overall, the number of all hospitalizations for diarrhea in children 0–4 years decreased between 2008 and the prevaccine years 2000–2006—a decrease of 69% for cases specifically coded as rotavirus and 36% for those coded as “cause-unspecified.” Clearly, the herd effect seen in the smaller studies was confirmed in this larger database. While 2008 might have been a low-incidence year for diarrhea in general and rotavirus in particular, this seems unlikely since the greatest decline in both measures was during those winter months when seasonal rotavirus peaks, suggesting that rotavirus was the cause.

A second surprising finding relates to the age of rotavirus infection and disease. Rotavirus has always been considered a universal infection of early childhood. Hospitalizations reach a peak in the first 3 years of life and most children have been infected and should be immune by the age of 5 years. Consequently, we have never considered rotavirus to be a problem in older children and young adults, who have a relatively low incidence of diarrhea, although rotavirus is occasionally detected among patients in these age groups. Moving to the next age strata of children
5–14 years, Lopman found a remarkable 71% reduction in hospitalizations coded as rotavirus and a 30% reduction in diarrhea of unspecified causes among these older children who were not vaccinated and should have been immune due to early childhood infections. Although this observation might have been confounded by low rates of diarrhea in this age group, the winter seasonality of this marked reduction (maximum in March) exactly matched the timing of the reduction in the younger age group that had been vaccinated. Consequently, while older children do have a relatively low incidence of severe diarrhea leading to hospitalizations, the role of rotavirus as a cause of these episodes appears to be much greater than ever anticipated.

Furthermore, the intervention that led to this marked reduction of diarrhea and rotavirus diarrhea in this older age group was the immunization of younger children. This linkage, like that observed for influenza vaccination of children that protects infection of adults, suggests that young children may be the source of infections in these older children and adults. Therefore, vaccination not only reduces the rate of infection in the younger children who are vaccinated, but it protects older children as well, another remarkable and unanticipated indirect effect of the vaccination program. A smaller and less pronounced impact was observed in the older age group from 15 to 24 years where again, hospitalizations declined throughout the rotavirus season, most significantly in March and April. Finally, even in adults 25–64 and the elderly (≥65 years), a small but significant deficit of rotavirus discharges occurred in the peak rotavirus month of March, consistent in time with the peak deficit of cases in the target age group of children <5 years. Outbreaks of rotavirus have been reported in nursing homes and rotavirus is a common infection in mothers and caretakers of children with rotavirus, so this small but significant deficit in winter diarrheal cases in adults could well represent this additional indirect effect of vaccination [11, 12]. These findings might be supported even further if the authors had provided a gender breakdown of the cases because we might expect a larger decline in mothers and female caregivers of small children than in men. Future studies of the etiology of diarrhea in older children and adults would do well to include surveillance for rotavirus as a key agent of concern.

Before rotavirus vaccines were introduced into the routine immunization schedule, cost-effectiveness studies examined the value of the vaccine program exclusively for children <5 years of age [13]. The current analysis suggests that those previous studies underestimated the burden of disease and its economic consequences in 2 different ways. First, much of the prior estimates of the burden of disease came from hospital surveillance of children <5 years who were admitted for diarrhea and had a fecal specimen tested for rotavirus. While different studies reported rates of detection that ranged in the United States from 30% to 50%, the delayed timing and incomplete collection of fecal specimens likely led to an underestimate of cases. Of note, Pang et al noted that when they carefully collected and tested fecal specimens from children enrolled in their vaccine studies, the prevalence of rotavirus was about one-third greater when they used a more sensitive polymerase chain reaction assay than the commercial immunoassay [14]. The current analysis, a “probe study” where the impact of the disease is directly measured as the reduction in a specific disease following a targeted intervention, suggests that the true percentage of rotavirus as the etiologic agent of gastroenteritis among children <5 years who are hospitalized must be somewhat greater than that predicted from sentinel hospital surveillance. Second, no prior estimates have been made to assess the impact of the vaccination program to protect against the spread of disease to older children. This study indicates that as much as 15% of the true burden of rotavirus disease and 20% of the economic cost accrues to children and young adults ages 5–24 years, outside of the target range of children whose health appears to be improved by vaccinating the infants.

Whereas this study clearly documents the indirect effect of the rotavirus vaccine program in the United States, it is unclear whether we can expect similar indirect effects when the vaccine is introduced into low-income settings. Several striking features distinguish the epidemiology of rotavirus in

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**Table 1. Unanticipated Findings About Rotavirus Epidemiology From the US Study**

| 1. | The reduction in hospitalizations following the introduction of rotavirus vaccine is greater than that which can be attributed to the vaccine. There is clearly strong evidence of herd effect. |
| 2. | Rotavirus detection rates determined from routine sentinel hospital surveillance may underestimate the true burden of rotavirus among those hospitalized. |
| 3. | Infants are the source of transmission of rotavirus to older children: Reduction of rotavirus in infants through immunization has directly reduced the incidence among older children and adults. |
| 4. | While both rotavirus and diarrhea are most common in children <5 years, rates of rotavirus detection among children with diarrhea aged 5–14 years appear to be similar to those of children <5 years, even though the incidence of diarrhea in this older age group is less. |
| 5. | Prior estimates of the burden and expense of rotavirus disease did not include estimates of the disease among older children. An added benefit of the vaccine is to reduce by 15% the burden of disease, and by 20% the economic estimates attributable to rotavirus in individuals ages 5–24 years. |
industrialized countries versus developing countries, which might alter the indirect effects observed here [15]. In developing countries, rotavirus occurs year round, most severe disease (up to 80%) occurs in the first year of life, mixed infections with multiple serotypes are common, and a large diversity of serotypes are in circulation at any one time. By contrast, in the United States, the disease is limited to the cooler seasons, only 40% of hospitalizations occur in the first year of life, mixed infections are uncommon, and a small number of serotypes are in circulation at any one time. New rotavirus vaccines that have been extremely effective (>90%) in the United States and other industrialized countries have performed less well (<50%) in low-income settings [16–18]. The lower efficacy of these vaccines has been attributed to higher levels of immunity among mothers in low-income settings (World Bank per capita <$900), which is passed to their infants transplacentally through cord blood or orally through breast milk [19, 20]. These mechanisms could effectively reduce the titer of vaccine viruses that reach the infant gut and decrease the infant’s response to the vaccine, and each of them has been documented, although the true cause of this lower efficacy is still under investigation. Consequently, these differences between children in high- and low-income countries in the epidemiology of rotavirus disease and the efficacy of existing oral vaccine make it hard to predict whether the indirect effects seen in this study in the United States might also apply in a low-income setting. This study provides a strong impetus to look intensively to determine whether the indirect effects seen here are at play once vaccines are introduced in those developing nations, where 600,000 children die each year from rotavirus infection. Demonstration of such enhancement could raise the value of the vaccine even in settings where the vaccine has demonstrated a lower efficacy. Several low-income countries are now embarking on national programs to introduce rotavirus vaccine. Future evaluation of their impact should address these indirect effects. These could make a big difference in our ability to prevent deaths and severe disease from rotavirus in the developing world.

References