The Rotavirus Experience in Mexico: Discovery to Control

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The recent introduction of a rotavirus vaccine program in Mexico to control rotavirus disease, a common killer of children worldwide, has dramatically reduced the number of Mexican children dying and being hospitalized because of diarrhea. The successful introduction of a rotavirus vaccine program was preceded by several decades of focused research efforts to document the burden of disease and to generate the knowledge base to develop and deploy a vaccine. The postlicensure experience from Mexico demonstrates that evaluating the impact and safety of the vaccination program is vitally necessary for sustaining it. All in all, the immensely successful Mexico experience with control of rotavirus disease, if copied, could yield tremendously favorable results for children and parents worldwide.

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In 2000, leaders of more than 190 nations put forth the Millennium Development Goals (MDGs)—one of these goals, the fourth MDG or MDG4, called for a two-thirds reduction in deaths among children <5 years of age between 1990 and 2015 [1]. One of the basic pillars for attaining MDG4 is the introduction of new vaccines. Mexico, which had a mortality in this age group of 20–22 per 1000 live births between 2003 and 2005, heeded this call by introducing a vaccine in 2006 to control rotavirus infection, one of the most common killers of children worldwide [2]. Consequently, the number of Mexican children dying because of diarrhea has decreased substantially, and vaccine introduction has paved the way for accelerating MDG4 in Mexico and abroad [3]. These gains were not easy and were a culmination of >2 decades of intense research efforts in Mexico to document the burden of rotavirus disease and generate the knowledge base to develop and deploy a vaccine. The Mexican experience with control of rotavirus disease, if copied, could spread success for control of diarrheal disease worldwide.

During the previous 4 decades, diarrheal disease persisted as one of the top killers of children <5 years of age in Mexico [4]. Even before the causes of diarrhea in Mexico were elucidated in the 1970s, the government made substantial investments toward improving health and infrastructure, including improving water supply and sanitation. These efforts were accelerated after large outbreaks of cholera in Latin America in the early 1990s and led to substantial progress in preventing deaths from childhood diarrhea [4]. Interestingly, these broad public health measures were particularly effective in reducing diarrhea-related deaths during the summer months when bacterial pathogens predominate, whereas deaths during the winter months when rotavirus circulates in Mexico were less affected. Consequently, the traditional summer peaks in childhood diarrhea–related deaths in Mexican children were replaced by winter peaks by the late 1990s [5].
In 1973, Ruth Bishop and colleagues, using electron microscopy, discovered the 70-nm wheel-shaped (rota) virus-like particles in the intestinal mucosa of infants with acute gastroenteritis, which were eventually named rotavirus [6]. Soon after its discovery, rotavirus was identified as the causative microbe in a large proportion of children with severe diarrhea in a series of studies from across the world, including Mexico [7]. Most importantly, studies from various locations across Mexico repeatedly observed that most of the burden of rotavirus diarrhea occurred during the winter months of November–May, similar to the pattern observed in the United States and neighboring Central American countries [8–10].

Perhaps one of the most important studies in the rotavirus literature that comprehensively improved our understanding of rotavirus epidemiology and solidified the case for a live, attenuated vaccine for controlling severe rotavirus disease was a longitudinal study among 200 Mexican infants who were followed up from birth through 2 years of age in the early 1990s [11, 12]. Four crucial findings from this study embody basic principles of rotavirus vaccination. First, children with rotavirus infection, both symptomatic and asymptomatic, were protected against subsequent rotavirus infection and disease, indicating that a vaccine mimicking natural infection could be successful. Second, protection increased progressively with each repeated rotavirus infection; the first infection primarily generated a strain-specific response, but subsequent infections led to a broadening of the immune response, underscoring the need for multiple doses. Third, protection was greater against severe rotavirus disease than against mild disease or infection, demonstrating that the main goal of rotavirus vaccine programs would be to prevent severe rotavirus disease, including mortality. Finally, because most rotavirus infections occurred during between 6 and 12 months of life, immunizing children early in life would be crucial.

These principles were successfully validated by trials of a highly effective rhesus-reassortant vaccine (RotaShield) that was introduced in the United States in 1998, and poised for wide-scale rollout globally [13]. However, the vaccine suffered a low-level risk of intussusception, a form of bowel blockage, occurring at a rate of 1 per 10 000 vaccinees. These events led the manufacturer to withdraw the vaccine from the US market in 1999.

Despite the RotaShield experience, scientists, donors, and manufacturers continued forward with collaboration to develop and test safer rotavirus vaccines [2]. Two candidate vaccines emerged from this collaborative process (Rotarix and RotaTeq). Mexico played a crucial role in the testing, deployment, and postlicensure evaluation for Rotarix, which was tested in over 60 000 infants mostly from middle-income settings in Latin America, of which approximately 13 000 (21%) were from Mexico [14]. RotaTeq meanwhile was tested mostly in US and European infants [15]. For both vaccines, a risk of intussusception similar to that found with RotaShield was excluded. Disease burden and economic studies found rotavirus vaccines to be highly cost-effective in Mexico across a wide-range of price-per-dose scenarios [9, 16]. These vaccines were made available in the Mexican private market in 2005, and subsequently the Ministry of Health began immunizing all children—beginning first with high-risk populations in 2006 and then all Mexican infants in 2007—with Rotarix at 2 and 4 months of age [3].

By the end of 2007, just before the annual rotavirus epidemic began, nearly three-quarters of Mexican infants had received Rotarix [3]. Since then, the single winter peak in diarrhea-related deaths, which had persisted since the early 1990s, has been substantially blunted for 4 continuous years (Figure 1). In 2008, diarrhea mortality declined by 41% among infants in Mexico, the age cohort with the highest vaccination coverage, and by 46% among all children <5 years of age during 2009 and 2010 [3, 17]. An unanticipated finding after vaccination was that the decline was substantially greater than expected on the basis of vaccine coverage alone, suggesting indirect protection due to a reduction in transmission of rotavirus from the vaccinated population. The prominent reductions during the winter months, when rotavirus accounts for most of the diarrhea hospitalizations, and the sustained reduction over 3 years with progressive declines among older vaccinated age cohorts support the contention that the reduction would have been unlikely without vaccination. Similarly, nationwide declines in childhood diarrhea hospitalizations have also been documented [18].

Rotavirus vaccines provide good heterotypic protection against a broad range of circulating rotavirus strains [19]. However, because rotavirus strains vary from year to year and might differ from strains included in the vaccine, emergence of novel strains is possible and warrants close attention during the postlicensure era. In 2009, the detection of a novel G9P[4] strain, one fully heterotypic to the vaccine strain, in a large proportion of children with diarrhea in Mexico prompted concerns of vaccine failure [20]. However, a case-control evaluation allowed the Ministry to determine that most children with G9P[4]-associated diarrhea were unvaccinated, indicating that failure to vaccinate was the reason for predominance of this strain in Mexico [20]. Similar studies in other settings also highlight the need for careful epidemiologic assessments to determine the role of vaccine in altering strain ecology [21–25].

The large-scale rollout of rotavirus vaccine in Mexico also provided an opportunity to monitor the safety of the vaccine with regard to intussusception. In 2 large, nationwide studies, investigators found a low-level risk of intussusception after Rotarix, at a rate of approximately 1–4 excess cases per 100 000 vaccinees, compared with a background rate of about 38–88 intussusception cases per 100 000 infants [26, 27]. The
availability of local data on the benefits of vaccination in reducing diarrhea mortality and hospitalizations in Mexican children helped put this level of risk in context—the new vaccine program would cause some 40 intussusception hospitalizations and 2 deaths, while averting some 700 diarrhea-related deaths and 11,600 hospitalizations per year in Mexico under current rates of vaccine coverage [26]. An appraisal of these findings by in-country decision makers and international policy-makers favored vaccine benefits and sustained vaccine use for controlling severe rotavirus diarrhea.

How might the lessons from Mexico help accelerate the MDGs globally? Mexico certainly has been a linchpin in the evolution of the control of severe and fatal rotavirus disease in children, from elaborating disease epidemiology and defining principles of vaccine-induced protection to ultimately demonstrating actual reductions in diarrhea-related deaths and hospitalizations after the introduction of vaccine. During the same period, vaccination programs have also been launched against influenza and pneumococcal disease, and overall mortality in children <5 years of age has declined by 22% from 21.6 per 1000 live births in 2004 to 16.8 in 2010. These are impressive achievements that should be replicated elsewhere, yet approximately 90% of the world’s children still do not have access to rotavirus vaccines, and broadening the use of rotavirus and other childhood vaccines is one important part of the effort to reach the MDGs [22]. Moreover, the efficacy of rotavirus vaccines is lower in low-income than in high-income settings [28, 29], possibly owing to factors that decrease the effective titer of the vaccine virus reaching the intestine (eg, transplacental maternal antibodies, breast milk) or those that impair the infant’s immune response (eg, micronutrient malnutrition, coinfection, interfering gut flora, human immunodeficiency virus infection) [30]. Expanding commitment to identify ways to close the divergence in efficacy between poor and wealthy populations is also vital. Nonetheless, overall child mortality and the proportion attributed to diarrhea is much higher in Asia and Africa than in Mexico, and even with lower efficacy, vaccination would have a substantial health impact in high-mortality settings.

The rotavirus experience from Mexico demonstrates how long-term investments in research can improve child health and eventually population productivity, and could be copied for other childhood diseases. It also offers some key insights relevant for scientists and policy-makers worldwide and has identified issues warranting close monitoring as rotavirus vaccines are more broadly introduced. First, although studies have confirmed that rotavirus causes some 40% of diarrhea-related hospitalizations worldwide, because of testing challenges, the fraction of the 1.3 million diarrhea-related deaths worldwide caused by rotavirus remains largely unknown [31, 32]. The 46% reduction in diarrhea-related deaths among children <5 years of age in Mexico after the introduction of a rotavirus vaccine provides the strongest evidence of the fraction of childhood diarrhea-related deaths that is attributable to rotavirus. Second, mortality reduction in Mexico offers robust support that these vaccines confer protection against fatal disease and may promote health equity. Third, as countries consider introducing RV vaccines, it is important to establish a good surveillance system for rotavirus disease in order to monitor the impact of the vaccine and any potential resurgence of nonvaccine strains that may occur. Without longitudinal surveillance, it will not be possible to differentiate between temporal changes in rotavirus serotypes and serotype replacement due to rotavirus vaccines. To date, there has been no documented evidence of serotype replacement after the introduction of these vaccines in countries that have conducted careful epidemiologic studies [22]. Fourth, the finding of
indirect protection could tilt the cost-benefit ratio in favor of vaccines in countries where vaccine coverage and efficacy may be suboptimal. Finally, as the experience from Mexico demonstrates, evaluating the impact and safety of the vaccination program and documenting disease reductions is crucial for sustaining vaccine use. Embracing this synergistic approach to monitor the safety and impact of rotavirus vaccines as they are rolled out across Africa and Asia will secure the promise of rotavirus vaccines as a strong driving force behind efforts to meet MDG4 and reduce deaths among children <5 years of age.

Notes

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