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Review

Value of post-licensure data on benefits and risks of vaccination to inform vaccine policy: The example of rotavirus vaccines

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ABSTRACT

In 1999, the first rhesus-human reassortant rotavirus vaccine licensed in the United States was withdrawn within a year of its introduction after it was linked with intussusception at a rate of ~1 excess case per 10,000 vaccinated infants. While clinical trials of 60,000–70,000 infants of each of the two current live oral rotavirus vaccines, RotaTeq (RV5) and Rotarix (RV1), did not find an association with intussusception, post-licensure studies have documented a risk in several high and middle income countries, at a rate of ~1–6 excess cases per 100,000 vaccinated infants. However, considering this low risk against the large health benefits of vaccination that have been observed in many countries, including in countries with a documented vaccine-associated intussusception risk, policy makers and health organizations around the world continue to support the routine use of RV1 and RV5 in national infant immunization programs. Because the risk and benefit data from affluent settings may not be directly applicable to developing countries, further characterization of any associated intussusception risk following rotavirus vaccination as well as the health benefits of vaccination is desirable for low income settings.

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1. Introduction

Rotavirus is the leading cause of severe gastroenteritis among young children worldwide, and was estimated to account for approximately one-third of the estimated 578,000 deaths from childhood gastroenteritis and more than 2 million hospitalizations and 25 million outpatient clinic visits among children <5 years of age each year in the pre-vaccine era [1–5]. Because of this tremendous health burden, prevention of rotavirus is a priority for global health agencies. In 1999, a tetravalent rhesus reassortant rotavirus vaccine (RRV-TV, Rotashield, Wyeth) was withdrawn from the United States market within a year of its implementation because it caused intussusception, a form of bowel obstruction [6,7]. Because of this association, clinical trials of >60,000 infants each evaluated a risk of intussusception of the magnitude associated with Rotashield with both the next generation oral rotavirus vaccines–a pentavalent bovine-human reassortant vaccine (RV5, RotaTeq, Merck and Co.) and a monovalent human vaccine (RV1, Rotarix, GSK Biologicals) [8,9]. In 2009, the World Health Organization (WHO) recommended global implementation of rotavirus vaccines, noting the need for further post-licensure evaluation of risks and benefits of rotavirus vaccines [10]. As of May 2015, a total of 77 countries have implemented rotavirus vaccines in their national immunization programs. In this paper, we review the policy implications of data on intussusception risk associated with rotavirus vaccines, particularly in light of the substantial health benefits that have been documented in many countries that have implemented routine rotavirus vaccination.

2. Intussusception with the withdrawn RRV-TV vaccine

The first clear evidence of a link between RRV-TV and intussusception was identified in post-licensure surveillance through the passive US Vaccine Adverse Event Reporting System [6]. Subsequently, a national case-control study conducted in 19 US states shower that the risk was greatest (~37-fold increase) during 3 to 7 days after the first RRV-TV dose and overall translated to an excess of ~1 intussusception case in 10,000 RRV-TV recipients [6,7]. These data prompted the withdrawal of RRV-TV from the US market in 1999, less than one year after its introduction [11] and before any evidence of post-licensure benefit of RRV-TV vaccination was available. Later re-analysis of the RRV-TV case-control data prompted debate about whether the relative risk (RR) of intussusception may have been greater for first doses administered after three months

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of age [12–14]. These considerations drove the decision by policy groups to place strict age limits for administration of the first vaccine dose between 6 and 14 weeks of age next generation of rotavirus vaccines, RV5 and RV1.

3. Intussusception and current rotavirus vaccines, RV5 and RV1

3.1. Pre-licensure trials

RV5 and RV1 both underwent large clinical trials of 60,000–70,000 infants each, designed specifically to evaluate safety with respect to intussusception [8,9]. For RV5, six vaccine recipients and five placebo recipients developed confirmed intussusception within 42 days after any of the three vaccine doses (RR = 1.6 [95% CI: 0.4–6.4]). For RV1, six vaccine recipients and seven placebo recipients had intussusception within 31 days of either of the two doses (RR = 0.85 [95% CI: 0.30 to 2.42]). The encouraging safety and efficacy data led to licensure and use of both RV5 and RV1 in many countries beginning in 2006; however, post-marketing surveillance for intussusception was recommended to further evaluate this potential adverse event.

3.2. Post-licensure data

Post-marketing surveillance conducted in several countries has shown a low intussusception risk with both RV5 and RV1. An increased intussusception risk has been documented among infants within 1–7 days after receiving the first RV1 dose in Mexico and after the second RV1 dose in Brazil, translating to approximately 1 excess case per 51,000 vaccinated infants in Mexico and 1 per 68,000 vaccinated infants in Brazil [15]. Similar results for Mexico were found in a separate post-marketing study conducted by the vaccine manufacturer [16]. In Australia, an increased intussusception risk has been documented with both RV5 and RV1, estimated at about 5.6 excess cases of intussusception per 100,000 vaccinated infants [17,18]. Finally, US post-marketing studies have also identified a small increased risk of intussusception associated with both RV5 and RV1, with an estimated risk of about 1-5 excess intussusception cases per 100,000 vaccinated infants [19–23].

4. Rotavirus vaccine impact and effectiveness

4.1. Pre-licensure trials

RV5 and RV1 showed 85–98% efficacy against severe rotavirus gastroenteritis in these trials conducted in the Americas and Europe, with good protection against disease caused by rotavirus strains not included in the vaccines [8,9]. However, because the performance of vaccines in the ideal conditions of a clinical trial can differ from those in routine programmatic use, post-licensure monitoring has been ongoing in many countries that have implemented rotavirus vaccination programs.

4.2. Post-licensure data

Implementation of RV5 and RV1 has had a rapid and remarkable impact on reducing all-cause diarrhea and rotavirus diarrhea hospitalizations in many early vaccine introducing countries. In the United States, following vaccine implementation in 2006, rotavirus hospitalizations have declined 60–83% in children <5 years of age and all-cause diarrhea hospitalizations decreased by 29–50% compared with pre-vaccine years [24–29]. In addition to providing direct protection to vaccinated infants, indirect protection, likely from reduced rotavirus transmission in the community, has also been observed among children too old to have received the vaccine, as well as among adults in the United States [30–32]. One study estimated that over two seasons from 2008–2009, an estimated total of 60,000–80,000 diarrheal hospitalizations were prevented in young children resulting in a medical cost savings of $240–$280 million, and these saving have continued through subsequent rotavirus seasons [26,33]. Similar declines in rotavirus and all-cause diarrhea hospitalizations have been noted in other early vaccine introducing countries including some European countries, Australia, and Latin America [34–49].

Importantly, in addition to decreases in diarrhea hospitalizations, declines in childhood diarrhea mortality have been observed following the introduction of rotavirus vaccines in Mexico, Brazil, and Panama [45,50–54]. In Mexico, these reductions in diarrhea mortality have been sustained over 4 post-vaccine introduction years and have been observed and sustained in different geographic regions of the country [50,51].

Table 1
Risk of intussusception and benefits of rotavirus vaccination in Mexico, Brazil, Australia, and the United States.

Country	Diarrhea hospitalizations (deaths) prevented by vaccination	Intussusception cases (deaths) potentially caused by vaccination
Mexico	11,600 (663)	41 (2)
Brazil	69,600 (640)	55 (3)
Australia	7000 (0)	6 (0)
United States	53,444 (14)	35–166 (0.1–0.5)

5. Policy considerations based on risk and benefit data

The decision to continue a vaccination program in the face of a documented, modest risk of an adverse event should take into consideration the public health benefits of vaccination. As post-licensure data on the risk of intussusception associated with rotavirus vaccination has emerged, several countries have conducted analyses comparing the risks of vaccination against the observed health benefits of vaccination in their own countries. It is worth noting that data on real world benefits of RRV-TV vaccination were unavailable at the time it was withdrawn from the US market, and the availability of such data for newer vaccines has provided key information for decision making as data on intussusception risk has emerged. Based on consideration of the substantial benefits of vaccination in the face of low intussusception risk (Table 1), policy makers in the United States, Mexico, Brazil, and Australia, as well as global health authorities such as the World Health Organization (WHO), continue to strongly support routine rotavirus vaccination of infants [55].

Furthermore, it is not clear whether the short-term increased risk of intussusception in the first few weeks after vaccination translates into an overall population-level increase in intussusception incidence in the first year of life. In the United States, ecologic analyses of trends in intussusception hospitalization among infants before and after the implementation of rotavirus vaccines have not consistently demonstrated an overall increase in rates post-vaccination [56,57]. This has led some to speculate that rotavirus vaccination might "trigger" intussusception earlier among some infants among whom intussusception would have occurred anyway later in infancy. In addition, intussusception has been associated with three different attenuated live oral rotavirus vaccines, including RV1 that consists of an attenuated single human rotavirus strain of a genotype that is most prevalent globally. Thus, one might hypothesize that wild-type rotavirus infection could be a cause of intussusception. If this is the case, rotavirus vaccination may prevent cases of intussusception caused by wild-type rotavirus infection later in infancy, as was suggested by preliminary data

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from the clinical trial of RV1 conducted in Latin America [58]. However, a recent analyses exploring this hypothesis in a large database of insured US children indicates that the risk of naturally occurring intussusception was not modified by rotavirus vaccination during the period of one month to one year following vaccination [59].

6. Role of further post-licensure monitoring of rotavirus vaccine benefit and risk in low-income countries

As of May 2015, 35 low income GAVI-eligible countries (gross national income <US $1550 per capita) have implemented rotavirus vaccination with many more introductions planned in the next few years. In these settings, data on intussusception risk and vaccine effectiveness may differ from that in high- and middle-income countries; thus, further post-licensure monitoring is required.

While the pathological mechanism of rotavirus vaccination upon intussusception is not fully understood, the period of greatest risk (first week after dose 1) correlates with the peak period of intestinal vaccine virus replication. Since rates of fecal shedding of vaccine virus strains are known to be lower in low-income settings compared with high- and middle-income settings [60], the rate of vaccine-associated intussusception could be lower. This hypothesis is supported by the post-licensure evaluation that found an intussusception risk with the first dose of RV1 in Mexico but not in Brazil, where a smaller risk with the second RV1 dose was found [15]. A notable difference was that, in Mexico, RV1 was co-administered with inactivated polio vaccine (IPV), while in Brazil it was co-administered with oral polio vaccine (OPV). OPV, particularly the first vaccine dose, is known to suppress intestinal replication of rotavirus vaccines [60]. Thus, it is possible that in a greater proportion of infants in Brazil versus Mexico, replication of the first RV1 dose was suppressed by concomitantly administered OPV, and the second RV1 dose was the first effective vaccine dose. Thus, further post-licensure evaluation of the intussusception risk as well as health benefits of vaccination in developing countries is desirable to better understand the benefit-risk profile of vaccination.

An additional consideration relates to the strict upper age limits of 12–14 weeks on administration of the first rotavirus vaccine dose implemented in early introducing countries to potentially minimize the number of any excess vaccine-associated intussusception cases by giving vaccine at an age when background rates of natural intussusception are low. Such strict age limits could substantially reduce vaccination coverage, especially in developing countries where delays in vaccinations are common [61]. A scenario analysis using estimates of country-level mortality from rotavirus, vaccine efficacy by setting, and intussusception risk data showed that the potential benefits of removing these age restrictions in low and low-middle income countries outweighed the risks, resulting in 154 rotavirus deaths averted for each additional intussusception death due to vaccine [62]. Given these considerations, in 2012, WHO recommended removal of these strict age recommendations on rotavirus vaccination, although it is still recommended that the vaccine series be initiated as soon as possible after 6 weeks of age, and vaccination is not recommended for children >24 months of age [55].

Live oral vaccines against many diseases, such as polio, typhoid, and cholera, have not performed as well in developing countries than in industrialised ones. The reasons for this variability are not completely understood, but could include interference in vaccine uptake by greater levels of maternal antibody or concurrent enteric infections in developing countries, as well as reduced immune response in infants because of comorbidities or malnutrition, including micronutrient deficiency [63]. Because of these concerns, randomised efficacy trials of both RV5 and RV1 were conducted in developing countries in Africa and Asia [64–66]. These trials showed modest vaccine efficacy (50–64%) against severe rotavirus gastroenteritis. Despite this reduced efficacy, the public health benefits of vaccination in terms of number of severe rotavirus gastroenteritis episodes prevented per 100 infants was greater in developing than in industrialised countries, because of the substantially greater rate of severe rotavirus gastroenteritis in developing countries. As rotavirus vaccines are introduced into immunization programs of low income countries globally, it will be important to assess the real world impact of vaccination to gain a better understanding of vaccine effectiveness and impact in a range of settings. In this regard, data generated from regional networks will be more powerful than that from individual countries [67].

7. Summary

Post-marketing surveillance has identified a small increased risk of intussusception associated with both current rotavirus vaccines, RV1 and RV5, in high- and middle-income countries at a rate of approximately 1–6 excess cases per 100,000 vaccinated infants [68]. However, considering the large health benefits of vaccination against the low level risk of vaccine-associated intussusception, policy makers and health organizations around the world continue to support the routine use of RV1 and RV5 in national infant immunization programs. Because the risk data from affluent settings may not be directly translated in developing countries, further characterization of any associated risk following rotavirus vaccination is desirable for low income settings. A better understanding of the risks and benefits of vaccination from a diverse range of settings will promote informed decisions regarding vaccination and ensure that the immense benefits that have already been documented can continue while further minimizing the risks.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest statement

None of the authors have any relevant disclosures.

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