Rotavirus Vaccination for Prevention of Serious Acute Gastroenteritis and the Importance of Postlicensure Safety Monitoring

Michelle Clarke1,2 and H. Marshall1,2
1Women’s and Children’s Health Network and 2University of Adelaide, South Australia

(See the major article by Yen et al, on pages 41–8.)

With the ability to save millions of lives each year in both the developed and developing nations, vaccination against childhood infectious diseases is a priority area for global health. An essential aspect of the success of any vaccination program is the careful monitoring following implementation to ensure that the benefits of the program outweigh any risks to the recipients or the community. Infant rotavirus vaccination programs are an important example of the collaborative expertise required for effective and timely monitoring and reporting of any adverse events following implementation. Rotavirus vaccines have been instrumental in reducing morbidity from rotavirus infection. Prior to the introduction of rotavirus vaccine, it is estimated that >500,000 rotavirus-related child deaths occurred globally each year [1]. Studies assessing the impact of rotavirus vaccine on incidence of rotavirus hospitalizations have occurred in numerous countries, including Australia and the United States, with dramatic reductions in the incidence of rotavirus hospitalizations (up to 80% reduction) shown following implementation of the rotavirus vaccination programs and suggestions of herd immunity benefits for older, unvaccinated populations [2–6]. The development of vaccines to prevent serious infectious diseases has been a global triumph, but large-scale postlicensure studies are essential to ensure that vaccination programs deliver the anticipated benefits.

In response to the overwhelming global burden of rotavirus infections, particularly in children aged <5 years, a live, attenuated tetravalent rotavirus vaccine (RotaShield) was licensed for routine use in infants in 1998, before being withdrawn in 1999 due to concerns about an increased risk of intussusception in vaccine recipients [7]. RotaShield was estimated to cause 10–20 episodes of intussusception per 100,000 doses given to infants, and recommendations for use were subsequently withdrawn, a decision that even today remains controversial. However, with the commitment of vaccine development teams, industry partners, academic researchers, epidemiologists, and public health advocates, two second-generation rotavirus vaccines (RotaTeq [RV5] and Rotarix [RV1]) were developed, and their use has now been implemented as part of a national immunization program in at least 28 countries [8].

Monitoring following introduction of these rotavirus vaccine programs occurs in many countries, partly due to the reported association between RotaShield and intussusception and partly due to a heightened awareness of the importance of implementation of surveillance following introduction of new vaccines. Large-scale clinical trials, each involving >60,000 participants, which were conducted prior to licensing of the current rotavirus vaccines, mainly in Finland and the United States for RV5 and in Latin American countries for RV1, demonstrated no significant increase in intussusception [9–11]. In these trials, a large sample size was required to establish the safety of these vaccines because intussusception is a rare event. Although unable to entirely exclude any increased risk of intussusception, the studies were powered to detect risks of the magnitude determined following the RotaShield vaccine implementation. Because of the possibility of rare but serious adverse events following vaccination, postlicensure surveillance is essential for identifying and monitoring these events. From extensive postlicensure surveillance under way following introduction of RV5 and RV1 vaccines, suggestions of an increased risk of intussusception with the current rotavirus vaccines have come from Mexico and Australia, albeit at a much lower relative risk than identified with the earlier RotaShield vaccine. The
study in Australia, which used two active surveillance methods (hospital and pediatrician reporting) to identify cases of intussusception and linked cases with vaccination records, suggested an almost 5-fold increased relative risk of intussusception following the first dose of RV5 rotavirus vaccine but no increased risk of intussusception overall [12]. The second study, conducted in Mexico and Brazil, found an approximate 5-fold increased risk of intussusception in the first week following the first dose of RV1 in Mexico but not in Brazil [13]. With both of these studies, the confidence intervals for relative risk were considerably wide and, therefore, uncertainty remains about the true risk of intussusception following rotavirus vaccination. Addressing the question of intussusception following rotavirus vaccination is a global priority because rotavirus vaccination programs continue to be rolled out in developing countries where surveillance systems are less advanced or do not exist.

The article by Yen et al [14] in this issue of the journal is an important addition to the current knowledge and research on the safety profile of the two currently licensed rotavirus vaccines and demonstrates the commitment of researchers to ensure the public health benefits of vaccination programs. Globally, studies have demonstrated a strong reduction in the incidence of acute rotavirus gastroenteritis following introduction of the vaccine, including herd immunity benefits in older age groups not eligible to have received rotavirus vaccination directly [2–6]. However, although the benefits of routine infant vaccinations are becoming more clear, the attributable risk of intussusception is somewhat less clear. This article by Yen et al [14], which reports on trends in intussusception before and after introduction of the rotavirus vaccine program in the United States, is reassuring and adds to the developing wealth of published data. Although an ecological study design cannot directly link cause and effect, the large size of the population data reviewed (approximately 75% of the US birth cohort) provides assurances that population intussusception rates have not increased substantially. The study also provides data on intussusception hospitalizations in the age group most likely to receive a first dose of rotavirus vaccine (infants aged 8–11 weeks), in whom the risk of intussusception was the highest for the RotaShield vaccine. Whereas several prior US studies using different study designs suggested no increased association with intussusception for either RV1 or RV5 [15, 16], this article supports findings in Mexico and Australia that a low-level risk of intussusception in infants aged 8–11 weeks is associated with introduction of the program. The rate of intussusception hospitalizations significantly increased in each of the three years following rotavirus vaccine introduction when compared with the average intussusception hospitalization rate for the six-year period prior to rotavirus vaccine introduction. The study provides detailed, useful, age-specific trends in intussusception hospitalizations for a large US cohort and indicates no overall population increase in intussusception hospitalization rate. The authors are suitably cautious in their interpretations and provide thorough and well-justified discussion around the study limitations and implications for the measure of association. The potentially low increased risk of intussusception following rotavirus vaccination implementation is appropriately discussed in context with an appreciation of the current risk–benefit profile for this vaccine. The authors conclude that the benefits of the rotavirus vaccination program far outweigh the risks quantified in the US population, even if the low-level risk of intussusception identified in infants aged 8–11 weeks was a true, attributable risk [14]. The importance of using a range of different study designs to provide a comprehensive overview of vaccine safety should also be highlighted. Although ecological studies such as this may not be able to provide causal evidence, they can provide valuable information for questions such as the risk of intussusception following rotavirus vaccination, for which the outcomes are so rare that randomized controlled trials are all but impossible. Similarly, prelicensure clinical research alone is inadequate for determining risk profiles for vaccine programs.

It will be important to continue to monitor safety and efficacy of rotavirus vaccination in the field, but the authors of this article should be commended on their commitment to quantifying the risks and adding valuable data to the safety information regarding rotavirus vaccination.

Note

Potential conflicts of interest. The institution in which authors M. C. and H. M. are employed has received funding from Merck as part of their Investigator Initiated Studies Program to undertake research into the impact of rotavirus vaccine introduction in South Australia. H. M. is an investigator with the PAEDS study team in Australia and has participated in global vaccine advisory committees.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References