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Intussusception and Rotavirus Vaccination—Balancing Risk Against Benefit

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An association between intussusception, a form of bowel obstruction, and live oral rotavirus vaccines was first identified with Rotashield, a rhesus-human reassortant rotavirus vaccine that was recommended for routine immunization of US infants in 1998 [1]. During the first year after vaccine introduction, a cluster of intussusception cases temporally linked to Rotashield vaccination was reported to the US Vaccine Adverse Event Reporting System (VAERS), a national passive reporting system [2]. This prompted a national case-control study, which confirmed the association between Rotashield and intussusception [3], with the greatest risk (an approximately 37-fold increase) occurring 3–7 days after the first vaccine dose. A smaller increase was seen in the second week after dose 1 and during the first week after dose 2. The excess risk of approximately 1 intussusception case in 10 000 Rotashield recipients led to withdrawal of the vaccine from the US market in 1999 [4].

Because of the legacy of Rotashield, the 2 other live oral rotavirus vaccines in advanced stages of clinical testing at the time—a pentavalent bovine-human reassortant vaccine (RV5, RotaTeq, Merck.) and a monovalent human vaccine (RV1, Rotarix, GSK Biologicals)—each underwent large clinical trials of approximately 60 000–70 000 infants specifically to assess the risk of intussusception [5, 6]. No elevated risk was found 42 and 30 days after vaccination after any of the 3 doses of RV5 and either of the 2 doses of RV1, respectively, in these trials. This facilitated licensure of both products and a recommendation for universal use in the United States and around the world. The World Health Organization (WHO) recommends both RV5 and RV1 for global use and encourages postlicensure monitoring to further assess the intussusception risk during routine programmatic use [7].

In this issue, Carlin et al present an elegant analysis of postlicensure intussusception data from Australia that has several notable strengths [8]. First, given that different states in Australia exclusively implemented either RV5 or RV1 with a relatively equitable national

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distribution of the 2 vaccines, this evaluation was able to evaluate risk with both vaccines during contemporaneous use in demographically similar populations. Second, robust and nationally representative evidence could be generated because of a relatively comprehensive capture of intussusception cases through examination of hospital discharge databases (with review of case records to restrict analysis to cases that met the highest Brighton Collaboration level 1 diagnostic certainty) and because of the availability of immunization data through a national registry with a near-complete (>98%) capture of vaccines provided through the National Immunization Program. Third, both the case-series and case-control methods were used to assess intussusception, and the consistency of estimates from both approaches provides additional reassurance about the validity of the findings. Fourth, the authors present side-by-side data on both the excess number of intussusception cases that might be caused by vaccination against the expected reduction in rotavirus hospitalizations, so that the risks could be interpreted in the context of benefits. Last, a range of sensitivity analyses were conducted around various assumptions and parameters that informed the analysis, with none influencing the overall conclusions substantially.

The results show that in Australia both rotavirus vaccines are associated with an increased risk of intussusception in the first 3 weeks after the first vaccine dose and the first week after the second dose, with the greatest risk in the first week after dose 1. An increased intussusception risk in the first week after dose 1 of RV1 was also documented in a previous smaller study from Australia and in 2 separate evaluations in Mexico [9–11]. In addition, recent passive reporting data from the VAERS showed a clustering of intussusception cases in the first week after RV1 doses that would be consistent with a possible vaccine risk [12], and early data from active monitoring of the US Vaccine Safety Datalink (VSD) cohort supports this association. For RV5, active monitoring in the VSD did not show an increased risk of intussusception after >800 000 RV5 doses, including >300 000 first doses, had been administered; however, the VSD data were able to exclude only a risk greater than about 1 case per 65 000 doses [13]. A recent analysis from the Mini-Sentinel program after >1.2 million RV5 doses, including 507 000 first doses, had been administered found an increased intussusception risk in the first 3 of weeks of dose 1 of RV5, again primarily within with first week, translating to an excess risk of 1–1.5 excess intussusception cases per 100 000 vaccinated infants [14]. In addition, while passively reported VAERS data have some limitations, the persistent pattern of clustering of intussusception reports to VAERS in the 3–6-day period following dose 1 of RV5 supports the possibility of an increased risk, also in the range of about 1 case of intussusception in 100 000 first doses [12]. Collectively, these global data support the results of this evaluation in Australia that both rotavirus vaccines are likely associated with a small risk of intussusception.

The policy decision to continue a vaccination program in the face of a documented risk has to take into consideration the public health benefits of vaccination. The data from Australia, as well as data from 3 US and other international studies, were recently reviewed by the US Advisory Committee on Immunization Practices on 20 June 2013. For RV5, the estimates for attributable risk for intussusception ranged from 1 in 67 000 vaccinated infants to 1 in 199 000 infants in the US studies. For RV1, only 1 US estimate was available for attributable risk, about 1 per 19 000 vaccinated infants [15]. The data from Carlin et al show higher risks for both RV1 and RV5 than those reported from other studies, but confidence intervals

overlap. Regardless, rotavirus vaccines still cause a relatively few excess cases of intussusception, and this risk needs to be weighed against the benefits of hospitalizations and emergency department visits prevented through rotavirus vaccination. For example, as illustrated by Carlin et al, given the level of risk seen in their study, rotavirus vaccination of all Australian infants with 85% coverage would annually cause an excess of 14 intussusceptions, while preventing 6 500 hospitalizations for acute gastroenteritis in children <5 years of age. Based on similar considerations of large benefits of vaccination in the face of low intussusception risk, policy makers in the United States and in other countries with documented risk, such as Mexico and Brazil, as well as global health authorities such as the WHO, continue to strongly support routine rotavirus vaccination of infants.

It is not known 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. Carlin et al speculate that rotavirus vaccination might “trigger” intussusception earlier among some infants among whom intussusception would have occurred anyway later in infancy. In addition, given that intussusception has been associated with 3 different attenuated live oral rotavirus vaccines, including RV1, which contains a rotavirus strain isolated from a child with diarrhea, 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 from the clinical trial of RV1 conducted in Latin America [16]. Examination of data on trends in population-level intussusception before and after vaccination and epidemiologic studies are needed to further assess the overall impact of rotavirus vaccination on intussusception incidence [17, 18].

As of April 2013, 14 low-income countries eligible for funding support from the GAVI Alliance have implemented rotavirus vaccination [19], with many more introductions planned in the next few years. The implications in these less affluent settings of postlicensure data on the intussusception risk from Australia and other high- and middle-income countries are not clear. While the mechanism of intussusception with rotavirus vaccination is not fully understood, the period of greatest risk (ie, the first week after dose 1) correlates with the peak period of intestinal vaccine virus replication. Rates of fecal shedding of vaccine virus strains are known to be lower in low-income settings, compared with high- and middle-income settings [20]; thus, the rate of vaccine-associated intussusception could be lower. This hypothesis is supported by a postlicensure evaluation that found an intussusception risk with the first dose of RV1 in Mexico but not in Brazil [10], where a smaller risk with the second RV1 dose was found. A notable difference was that in Mexico RV1 was coadministered with inactivated polio vaccine, but in Brazil it was coadministered with oral polio vaccine (OPV). OPV, particularly the first vaccine dose, is known to suppress intestinal replication of rotavirus vaccines [20]. 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 effectively the first dose associated with replication and immune response. Hence, it would be desirable to generate postlicensure data for both rotavirus vaccines on both intussusception risk, as well as health benefits of vaccination, from a range of low-income countries to better understand the benefit-risk profile in these settings.

In closing, the article by Carlin et al highlights the usefulness of robust postlicensure surveillance to detect infrequent vaccine-associated adverse events that may be impractical or cost-prohibitive to evaluate in clinical trials. It also illustrates the value of evaluating risk data in the context of benefit to reach optimal policy decisions. As rotavirus vaccines are rolled out worldwide, evaluations of both vaccine benefits and risks should continue in a range of socioeconomic and demographically diverse settings to guide appropriate vaccine policy decisions.

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