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REVIEW

Rotarix in Japan: Expectations and Concerns

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ABSTRACT

A live-attenuated, orally-administered, monovalent, human rotavirus vaccine, Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), was licensed and launched in 2011 as the first rotavirus vaccine in Japan. The rotavirus causes a substantial disease burden with an estimated 790,000 outpatient visits, 27,000-78,000 hospitalizations, and approximately 10 deaths each year in Japan. Since a recent clinical trial showed that Rotarix was as efficacious in Japan as in other industrialized countries, it is expected that the annual number of rotavirus hospitalizations will be reduced to between 1000-3000, and that outpatient visits will be reduced to 200,000. The universal rotavirus immunization program with Rotarix was calculated to be at the threshold of being cost-effective, even from the healthcare perspective, and it was highly cost-effective from the societal perspective, assuming that Rotarix is co-administered with other childhood vaccines. While Rotarix contains only a single G1P[8] human rotavirus, the postlicensure studies in Brazil showed that Rotarix provided a 75%-85% protective efficacy against severe dehydrating diarrhea or hospitalizations due to fully-heterotypic G2P[4] strains. While postlicensure studies detected a small and finite risk of intussusception associated with the administration of Rotarix, the authors conclude that Rotarix is safe to administer to infants between 6-12 weeks of age for the first dose and by 24 weeks of age for the second dose. However, the authors strongly discourage the delayed administration of the first dose between 13-20 weeks of age, which is allowed without any warning. Given the high incidence of naturally-occurring intussusception in Japan (185 cases per 100,000 children/year among children less than 1 year of age), this should prevent pediatricians and parents from having ill-perceptions of Rotarix being associated with an increased number of temporally-associated

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intussusception, and fully appreciate the benefit of the rotavirus vaccine.

Keywords: diarrhea; heterotypic immunity; immunization; intussusception; Japan; Rotarix; rotavirus

INTRODUCTION

Acute diarrhea is the leading cause of childhood morbidity and mortality worldwide, accounting for approximately 15% of deaths occurring in children less than 5 years of age.[1] Rotavirus has been recognized as the single most important etiological agent of severe diarrhea[2] causing an estimated 453,000 deaths annually.[3] Thus, after reviewing the recent efficacy data generated by studies on Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) in African countries, the Strategic Advisory Group of Experts of the World Health Organization (WHO) in 2009 recommended incorporation of rotavirus vaccines into the national immunization programs of all countries, with an emphasis in those regions where mortality rates in children less than 5 years of age are ≥10%.[4-6] Two major rotavirus vaccines that were prequalified by the WHO are the monovalent, human rotavirus-based vaccine, Rotarix,[7] and the pentavalent, bovine-human re-assortant vaccine, RotaTeq® (Merck & Co, Inc., NJ, USA).[8] These rotavirus vaccines are licensed in more than 120 countries, but it was not until 2011 that the Ministry of Health, Labor, and Welfare in Japan approved the rotavirus vaccine (Rotarix) for use in infants to prevent rotavirus gastroenteritis. In this review the authors briefly describe two important issues to understand the rotavirus vaccine: the nature of protective immunity after natural rotavirus infection and the burden of rotavirus diarrhea in Japan. The authors then concisely summarize the product profile of Rotarix that is most relevant in practice. Finally, the authors address two key issues for practitioners and parents: the efficacy of Rotarix against fully heterotypic strains and the safety of Rotarix with respect to intussusception.

ROTAVIRUS AND ITS SEROTYPES

Rotavirus, taxonomically a species *(Rotavirus A)* within genus *Rotavirus*, family *Reoviridae*, is a nonenveloped RNA virus with icosahedral symmetry.[9] The outer surface of the virion consists of viral spikes (made up of the VP4 trimers) and the outercapsid proteins (made up of the VP7 trimers).[9] Both VP4 and VP7 independently serve as a neutralization antigen, and define the protease-sensitive protein (P) type and the glycoprotein (G) type, respectively.[2,9] While serotype should, by definition, be determined by serologic assays, molecular assays have replaced serologic assays in the determination of G and P types of a rotavirus in clinical specimens; hence, referred to as the genotype.[9] While there is an exact match between G serotype and G genotype, different numbering systems were adopted to designate P serotype and P genotype, with P genotype being designated within squared brackets. Thus, the P serotype of RIX4414, the vaccine strain in Rotarix, is P1A, whereas its P genotype is P[8]. There are 27 G genotypes and 35 P genotypes described to date,[10] but the G and P type combinations detected in human rotaviruses are mostly limited to G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8].[11,12] However, previously rare G12 strains appear to have emerged across the globe[13-15] and G8 strains, with either P[6] or P[4], account for a significant proportion of human rotavirus strains in Africa.[16,17] Such genetic diversity appears to be generated by frequent reassortment of the genome segments and interspecies transmission of rotaviruses between humans and animals.[18-21]

PROTECTIVE IMMUNITY AFTER NATURAL INFECTION AND THE GUIDING PRINCIPLE OF ROTAVIRUS VACCINES

Complete protection against moderate-to-severe rotavirus-associated diarrhea, but not against mild diarrhea or infection itself, is obtained after asymptomatic infection in the neonatal period[22] or after two infections with rotavirus, regardless of whether the infections are symptomatic or asymptomatic.[23] In a cohort study in Mexico,[23] the adjusted efficacy in protecting against subsequent rotavirus infection was 38% after one infection, 60% after two infections, and 66% after three infections. In contrast, the efficacy against rotavirus-associated diarrhea of any severity was 77% after one infection, 83% after two infections, and 92% after three infections. Against moderate-to-severe rotavirus-associated diarrhea, protection is greater with 87% after one infection and 100% after two or three infections. In the same study, repeated infections with the same G type were less likely to occur, suggesting the presence of homotypic immunity. It is generally believed that, while infection with one serotype provides serotype-specific (homotypic) protection, repeated infections tend to provide broader protection that exerts over different serotypes; ie, heterotypic protection.[24] Thus, it is clear from the natural history of rotavirus infection that the aim of the rotavirus vaccine should be to prevent severe, dehydrating diarrhea and deaths due to rotavirus infection in the first 3 years of life when rotavirus-associated diarrhea is most severe, rather than to prevent mild diarrhea or infection.[25] However, this guiding principle was challenged by a recent study in India that showed a much lower protection effect of natural rotavirus infection against subsequent diseases in a setting with high viral load and diversity.[26]

THE BURDEN OF ROTAVIRUS DIARRHEA IN JAPAN

Given that the aim of the rotavirus vaccine is to reduce the burden of rotavirus-associated diarrhea in the society, the key information is the annual number of cases of rotavirus-associated diarrhea and the associated cost. The cost needs to be viewed from both the healthcare and the societal perspectives. With regard to the annual number of cases of rotavirus-associated diarrhea, the most important is the number of rotavirus hospitalization at a national level and whether the estimated reduction of the disease burden will be cost-effective. The major difference between the cost calculated from the healthcare perspective and that calculated from the societal perspective is that the latter includes the productivity loss of care-givers of sick children. This productivity loss accounts for the vast majority of the indirect cost associated with rotavirus-associated diarrhea.[27,28]

The birth cohort in Japan is approximately 1 million and the information required is the number of children who will be hospitalized due to rotavirus-associated diarrhea when the cohort is followed for 5 years. Only a few studies are available in Japan, and it was estimated that there were 790,000 outpatient visits,[29] 27,000-78,000 hospitalizations,[30-32] and approximately 10 deaths due to rotavirus gastroenteritis in the entire country. The variability in the estimate of the annual number of rotavirus hospitalizations was due to the variability in the incidence of rotavirus hospitalizations in different locations and dates in Japan: 4.9 per 1000 children/year in the Mie prefecture between 2003-2007,[30] 5.3 per 1000 children/year in the Kyoto prefecture between 2008-2010,[31] and 13 per 1000 children/year in the Akita prefecture between 2001-2002.[32] These variable incidences, however, were not dissimilar from those reported from other industrialized

countries; for example, in seven European countries that included Belgium, France, Germany, Italy, Spain, Sweden, and the UK (the REVEAL study), the incidence ranged from a minimum of 2.9 per 1000 children/year in the UK to a maximum of 9.9 per 1000 children/year in Belgium, with a median of 6.5 per 1000 children/year in Spain.[33,34]

If the rotavirus vaccine is as efficacious in Japan as in other industrialized countries, it is expected that the annual number of rotavirus hospitalizations could be reduced to between 1000-3000, and that the number of the outpatient visits could be reduced to 200,000. To determine whether this reduction will be cost-effective, one needs to calculate the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained. In Japan, a prevention measure is said to be cost-effective if its ICER per QALY gained is JPY 6 million. From a healthcare perspective, the universal rotavirus immunization program with Rotarix was calculated to be almost at the threshold of being cost-effective, assuming the vaccine cost of JPY 20,000 per course. From the societal perspective, it was highly cost-effective with an ICER of JPY 900,000 per QALY gained.[28] A caveat to this analysis is that the authors assumed co-administration of Rotarix with other childhood vaccines. However, co-administration is unpopular under the current situation in Japan (see later). If given independently from other vaccines, the productivity loss arising from the rotavirus immunization would become substantial, and the rotavirus vaccination would be less cost-effective, with an ICER of JPY 8.8 million per QALY gained.[28]

PRODUCT PROFILE OF ROTARIX

Indications

Rotarix is indicated for the prevention of rotavirus gastroenteritis. Its protective efficacy is suggested against rotavirus strains carrying G1P[8], G2P[4], G3P[8], G4P[8], or G9P[8].[35]

Product Specifications of Rotarix

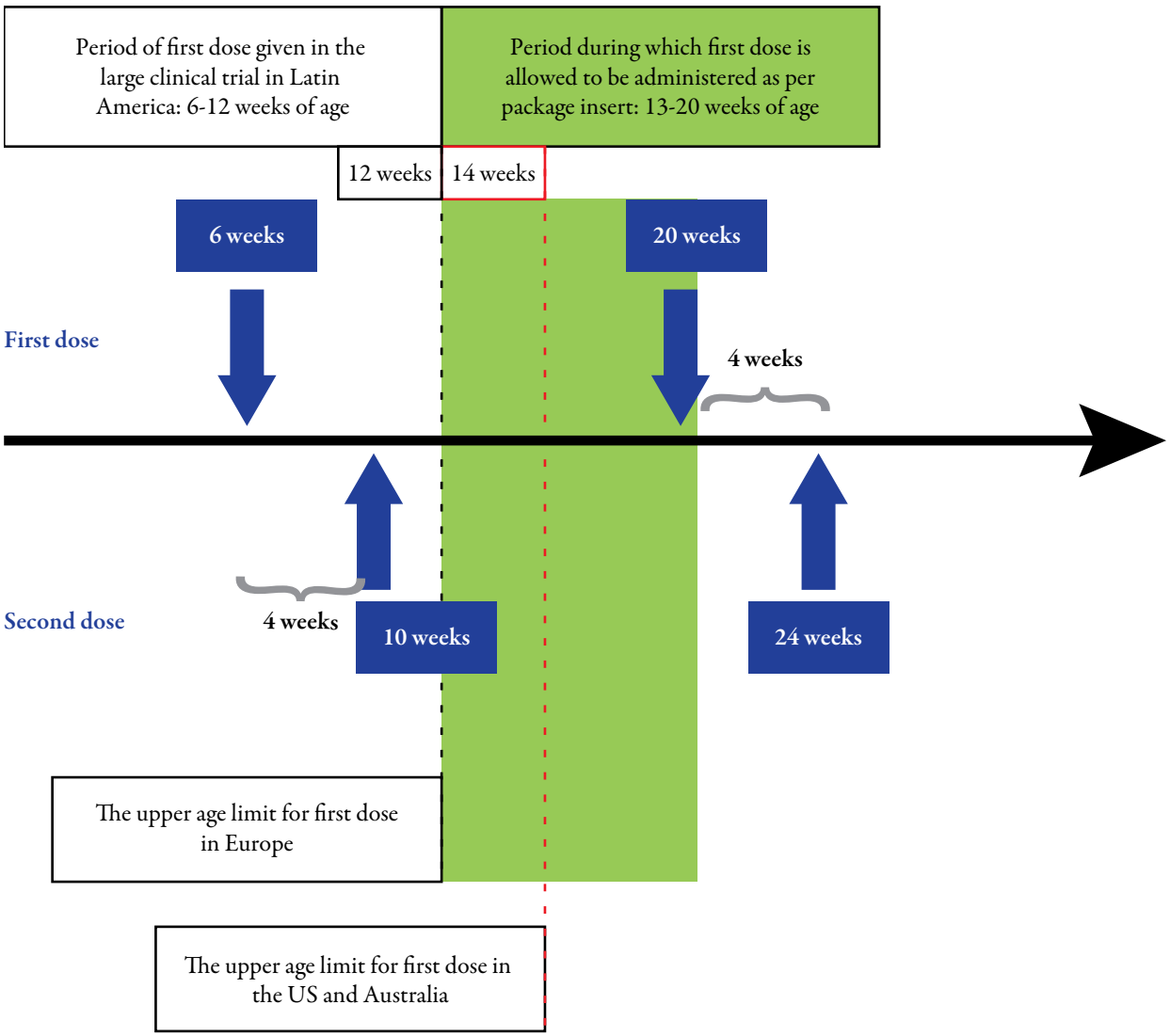
Rotarix contains a live-attenuated G1P[8] human rotavirus strain, RIX4414, that contains at least 1 million median cell culture infective dose ($CCID_{50}$) in 1.5 mL of calcium carbonate buffer. While a ready-to-use liquid formulation is a welcome addition, a 50% increase in volume from the formulation that requires reconstitution (1 mL) may present technical inconvenience to the oral administration of the liquid into the mouth of small infants of as early as 6 weeks of age. This larger volume of the liquid formulation relates to the content of sucrose (excipient) in the liquid formulation, which is higher than that used in the lyophilized vaccine that is reconstituted with 1 mL of calcium bicarbonate buffer.[36]

The Standard Schedule and the Upper Limits of Age for Administration

Rotarix is to be administered orally in a two-dose schedule. According to the package insert,[35] the first dose should be administered to infants beginning at 6 weeks of age and the second dose should be completed by 24 weeks of age, with an interval of at least 4 weeks between the first and the second dose (Figure 1). The company's official promotion pamphlet clearly illustrates that the period for the first dose is between 6-20 weeks, and that the period for the second dose is between 10-24 weeks.[37]

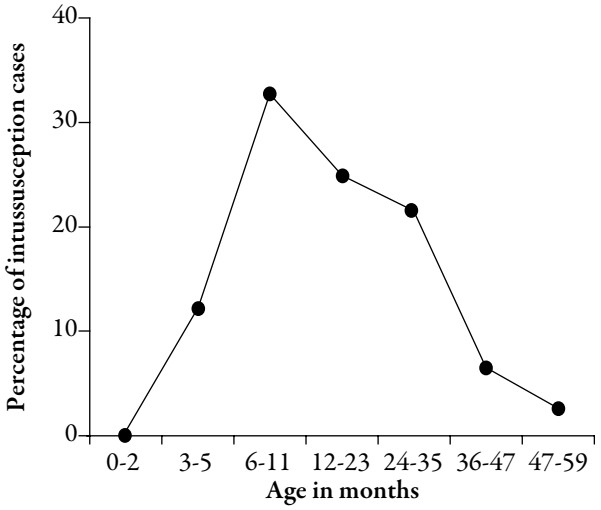
Globally, the upper-limit of age for the first dose is an important issue that may significantly affect the uptake rate of the vaccine and the increase in the temporally associated cases of intussusception. Naturally-occurring intussusception is rare in the first 3 months of age

Figure 1. The age period during which the first and the second dose of Rotarix are to be administered according to the package insert distributed in Japan. The first dose may start at 6 weeks of age but before 20 weeks of age, and the second dose may start at 10 weeks of age and end before 24 weeks of age. In Europe, the upper limit of the first dose is 12 weeks, while in the US and Australia it is 14 weeks. As the first dose of Rotarix is allowed to be given to infants between 13-20 weeks of age in Japan (the area highlighted in green), a concern arises that there will be an increased number of Rotarix recipients who develop intussusception by chance alone in the first week after the first dose.



but it increases rapidly thereafter[38,39] (Figure 2[40]). The WHO recommends that the first dose should be administered at age 6-15 weeks.[41] In Australia, the first dose of Rotarix is scheduled to be given to infants between 6-14 weeks of age (Figure 1).[42] In the US, the Advisory Committee on Immunization Practices (ACIP) revised its recommendation in 2009 to extend the maximum age for the first dose to be 14 weeks and 6 days,[43] but it clearly stated that vaccination should not be initiated for infants after 15 weeks and 0 days (Figure 1). In Europe, the European Medicines Agency[44] states that both doses should preferably be administered before 16 weeks of age, meaning that the first dose is to be given to infants at

Figure 2. Age distribution of patients with naturally-occurring intussusception in a sentinel hospital in northern Japan. Note that there was no case of intussusception during the first 3 months of life (0-2 months of age). *Adapted from the figure published in Nakagomi T, Takahashi Y, Arisawa K, Nakagomi O. A high incidence of intussusception in Japan as studied in a sentinel hospital over a 25-year period (1978-2002). Epidemiol Infect. 2006;134:57-61.*[40]



6 weeks and no later than 12 weeks of age (a minimum interval of 4 weeks between the doses being taken into account; Figure 1). The expert group of the European Society for Paediatric Diseases and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPID/ESPGHAN) also recommended that the first dose of rotavirus vaccine should be given between 6-12 weeks of age, and did not recommend catch-up vaccination with the first dose in infants older than 3 months of age.[45]

Failed Administration (Regurgitation)

The Rotarix package insert states that a single replacement dose may be given at the same vaccination visit in the event that the infant spits out or regurgitates most of the vaccine dose.[35] The ACIP does not recommend re-dosing after regurgitation of any amount on the basis of the absence of data on the benefits or risks with re-dosing.[43] From a practical perspective, who should pay the cost of re-dosing may also be an issue.

Concomitant Vaccine Administration

In countries where Rotarix is given as part of the routine immunization schedule, such as in the US, Rotarix is administered together with other childhood vaccines, including diphtheria-tetanus-acellular pertussis (DTaP), inactivated poliovirus, hepatitis B, *Haemophilus influenzae* type B conjugate vaccine, and heptavalent pneumococcal conjugate vaccine.[43] Thus, Rotarix may be conveniently administered at the time of the first and the second visits of DTaP immunization which, in the US, are scheduled to be given to infants at 2 and 4 months of age. Unfortunately, in Japan, the DTaP immunization does not start until the infant is 3 months of age. However, Rotarix can also be administered at 2 months of age together with *Haemophilus influenzae* type b conjugate vaccine or heptavalent pneumococcal conjugate vaccine. It may appear strange, however, to find in the package insert that such concomitant administration is allowed only when the immunization practitioner judges it necessary.[35]

With regard to the oral polio vaccine, the expert group of ESPID/ESPGHAN discouraged co-administration with Rotarix in its guidelines[45] due to the insufficient clinical efficacy and safety data available to support it. However, there are data available that failed to detect any difference in efficacies[46] or rotavirus Ig (immunoglobulin) A seroconversion rates[47,48] between those who were co-administered Rotarix with oral polio vaccine and those who were not. Another issue specific to Japan may be the arrangement of the scheduled BCG (Bacillus Calmette-Guérin

tuberculosis vaccine) immunization, which is administered between 3-6 months of age.

Contraindications

Contraindications include uncorrected congenital malformation of the gastrointestinal tract, such as Meckel's diverticulum, because such malformation would predispose the infant to intussusception.[35] The Centers for Disease Control and Prevention (CDC) in the US has recently updated the contraindications for rotavirus vaccines (Rotarix and RotaTeq) to include a history of intussusception.[49] It has been reported that patients with severe combined immunodeficiency never eliminate the vaccine strains.[50] Therefore, current contraindications are: (a) infants with a history of severe allergic reaction after a previous dose; (b) infants diagnosed with severe combined immunodeficiency; and (c) infants with a history of intussusception.

THE RESULTS OF CLINICAL TRIAL OF ROTARIX IN JAPAN

Prior to filing an application for licensure in Japan, a phase 3, randomized (vaccine: placebo = 2:1 ratio), double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy, reactogenicity, safety, and immunogenicity of Rotarix in Japanese infants when it was administered as two doses at 2 and 3 months of age.[51] More specifically, 765 infants aged 6-14 weeks were enrolled, of whom 750 were estimated to be administered the first dose (either the vaccine or the placebo) before 12 weeks of age. Efficacy against any severe rotavirus gastroenteritis leading to medical intervention, caused by circulating wild-type rotavirus, from 2 weeks after the second dose until 2 years of age was 79.3% (95% CI: 60.5-89.8%) and 91.6% (95% CI: 62.4-99.1%), respectively. Seroconversion at the time of 1 month after the second dose was 85% (95% CI: 68.9-95%) in the Rotarix group, whereas only one in 20 infants (5%) in the placebo group seroconverted (due to wild-type rotavirus infection).

TWO KEY ISSUES RELATING TO THE ROTARIX INTRODUCTION IN JAPAN

Lastly, the authors will conclude this review by addressing the two important issues. These issues fall on the specific area of rotavirus research where the authors believe that they have expert views; whether Rotarix is effective in preventing severe diarrhea caused by fully heterotypic G2P[4] rotavirus strains and whether Rotarix is safe with respect to intussusception.

The first issue is about a persisting concern derived from the fact that Rotarix is a vaccine containing only a single human G1P[8] strain, RIX4414. The guiding principle for the development of a single-strain human rotavirus vaccine was that the induction of protective immunity does not entirely depend on neutralizing antibodies specific to either G or P serotype, but more on factors that mediate heterotypic immunity.[52-55] In a large clinical trial in Latin America, and later in Europe, Rotarix was shown to be effective in preventing severe rotavirus diarrhea caused by partially heterotypic G3P[8], G4P[8], and G9P[8] strains, as well as fully-homotypic G1P[8] strains.[56,57] Since fully-heterotypic G2P[4] strains were infrequent during these clinical trials, protective efficacy appeared less convincing, with wide 95% CIs. Soon after the introduction of Rotarix into the universal immunization schedule in Brazil, Gurgel et al.[58] and Nakagomi et al.[59] noticed a high predominance of G2P[4] strains,

although there was also a simultaneous marked decrease in the detection rate of rotavirus.[59] While these studies suggested a shift in the predominantly circulating strains to G2P[4] in highly vaccinated regions, it remained unclear whether such phenomena resulted from Rotarix use or were a simple reflection of natural variation.[60-62] Thus, the key issue here is whether Rotarix would be effective in preventing severe rotavirus diarrhea caused by fully-heterotypic G2P[4] strains. Three case-control studies to quantitatively measure the effectiveness of Rotarix against G2P[4] strains were carried out in different locations in Brazil.[63-65] In the areas of Brazil where these studies were conducted the proportion of G2P[4] genotypes were high (82%-100%), and the effectiveness of Rotarix against severe acute diarrhea or hospitalization due to G2P[4] strains were 79% (95% CI: 74-82) in Aracaju,[63] 85% (95% CI: 54-95) in Recife,[64] and 75% (95% CI: 57-86) in Belém.[65] These data provide strong evidence for the protective efficacy of Rotarix even against rotaviruses fully heterotypic to the vaccine strain. This has important implications because Rotarix would also be expected to provide a reasonable level of protection against fully heterotypic strains other than G2P[4]; these include G12P[6], prevalent in Nepal,[14] and G8P[6], prevalent in Malawi.[16] However, a recent study that analyzed an outbreak of gastroenteritis hospitalizations caused by G2P[4] rotavirus in an impoverished region in Australia failed to provide evidence of effectiveness against G2P[4] rotavirus strains.[66] Thus, the issue of protection against fully-heterotypic G2P[4] strains still warrants closer attention, especially in poorer regions.

The second issue concerns the safety of Rotarix with respect to intussusception. This safety was established in a large-scale clinical trial involving more than 63,000 infants from 11 countries in Latin America and Finland. This trial revealed no statistically significant increases in the risk of Rotarix causing intussusception when it was administered to infants aged between 6-12 weeks in 10 Latin American countries (Figure 1), between 6-13 weeks in Chile, and 6-14 weeks in Finland.[7] The study was powered to detect as small a risk as approximately six cases per 10,000 vaccine recipients; it was, thus, concluded that Rotarix was not considered to cause intussuseption as frequently as Rotashield® (Wyeth-Lederle Vaccines, Radnor, PA, USA) did. However, two postlicensure studies conducted in Mexico and Brazil detected a small, yet statistically significant, relative risk of 5.3 (95% CI: 3.9-9.3), translating into an excess risk of intussuseption of one in 51,000 vaccinees in Mexico in the first week after the first dose; a relative risk of 2.6 (95% CI: 1.3-5.2), in Brazil, translating into an excess risk of one in 68,000 vaccinees in the first week after the second dose.[67] These risks were smaller than those that prelicensure clinical trials were powered to detect. Another study conducted in Australia, where either Rotarix or RotaTeq were introduced into the universal immunization program depending on the Australian state, detected a relative risk of 3.5 (95% CI: 0.7-10.1) in the first week after the first dose of Rotarix, and a relative risk of 5.3 (95% CI: 1.1-15.4) in the first week after the first dose of RotaTeq.[68] The implications from these studies are clear; firstly, the hypothesis that intussusception is unique to the Rotashield vaccine and that other rotavirus vaccines are inherently free from the risk of intussusception has clearly been questioned. Secondly, since RIX4414 was originally derived from a virulent human rotavirus, natural infection with wild-type rotavirus can also cause intussusceptions; a hypothesis that the authors have previously maintained.[69,70]

Reviewing these emerging data and recognizing a very small, yet finite, level of risk associated with the Rotarix vaccination, the authors conclude that Rotarix is safe to administer to infants at the globally-recommended age period, such as between 6-12 weeks of age, when naturally occurring intussusception is rare (Figures 1 and 2). On the other hand, the authors see no reason to be bold enough to recommend the Rotarix immunization beyond 13-15 weeks of age, as is allowed according to the package insert of Rotarix in Japan[35] and promotional pamphlets.[37] The benefits that will be gained by expanding the immunization period for the first dose to 20 weeks of age very unlikely outweighs the risk of an increased number of intussusception cases, whose causal relationship with Rotarix will never be ruled out at the individual case level. If one were to suppose that the attributable risk is 5%, there would be no way to tell which one of 20 patients (5%) with intussusception that occurred in the first week after the first dose was due to the vaccine. A greater number of such temporally associated cases of intussusception would be expected in Japan than in countries such as Australia and the US. This is due to the greater incidence of intussusception in the first year of life in Japan (185 per 100,000 people/year [95% CI: 133-250])[40] than in the US (30-50 per 100,000 people/year)[71] or Australia (71 per 100,000 people/year [95% CI: 52-97]).[72]

CONCLUSION

A live-attenuated, orally-administered, monovalent rotavirus vaccine, Rotarix, has been launched on the Japanese market. Rotarix has, thus far, shown a remarkable track record in the reduction of morbidity and mortality primarily in Latin American countries, purging itself of the skepticism regarding its effectiveness against serologically unrelated G2P[4] strains. While recent postlicensure surveillance detected a small, yet finite, risk of Rotarix causing intussusception, the authors conclude that Rotarix is safe to administer to infants between 6-12 weeks of age for the first dose and by 24 weeks of age for the second dose. However, the authors strongly discourage the delayed administration of the first dose between 13-20 weeks of age, which is allowed without any warning. Given the high incidence of naturally occurring intussusception in Japan, this should prevent pediatricians and parents from having ill-perceptions of Rotarix being associated with an increased number of temporally associated intussusception, and fully appreciate the benefit of the rotavirus vaccine.

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