

# Rotavirus vaccines: a major impact on public health six years post-licensure

Vacinas contra Rotavírus: o grande impacto na saúde pública seis anos após seu licenciamento

Vacunas anti-Rotavirus: el gran impacto en la salud pública seis años después de licenciadas

Recent estimates have shown a yet staggering worldwide burden of rotavirus disease. Indeed, as reported in a recent publication in the prestigious journal *The Lancet Infectious Diseases*, rotavirus remains a major "killer" during childhood, taking annually the lives of approximately 450,000 children aged less than five years; this translates into 1,200 deaths per day and 5% of all deaths in children in this age group. The worst scenario is seen in five countries which account for over 50% of all deaths due to rotavirus: Democratic Republic of the Congo, Ethiopia, India, Nigeria and Pakistan. In 2006 two effective oral rotavirus vaccines were licensed: a pentavalent (G1, G2, G3, G3 and P[8] genotypes) bovine-human reassortant vaccine (RotaTeq™; Merck and Co.) and a single-strain vaccine composed of an attenuated human G1P[8] strain (Rotarix™; GlaxoSmithKline Biologicals). Both vaccines were evaluated in a variety of settings worldwide through the largest trials ever conducted to assess safety and efficacy since the poliovirus vaccine efficacy studies in the 1950s. Overall the large pre-licensure clinical trials with RotaTeq™ and Rotarix™ involved 60,000-70,000 infants each and were designed to assess vaccine efficacy and safety with particular emphasis to intussusception which is a form of bowel obstruction in infants. In these studies both vaccines have proven highly efficacious (>80% protective efficacy) against severe rotavirus acute gastroenteritis (RVGE) during the first two years of life. As expected, a trend for lower efficacy was seen in resource-limited countries of Africa and Asia, although the overall impact of vaccination was considered significant owing to the high rates of severe RVGE in these settings. With regards to safety, the large phase III studies with RotaTeq™ and Rotarix™ have not revealed any increased risk of IS following administration of vaccine doses. Recent data from phase III trials in Africa and Asia have shown that both vaccines are efficacious even in resource-poor settings, leading WHO to recommend that, as from 2009, rotavirus vaccination should be incorporated into all countries' national immunisation programs worldwide. This recommendation was stressed mainly for those countries where mortality rates among children less than five years of age are equal or more than 10%. Importantly, implementing worldwide introduction of rotavirus vaccines is currently regarded by WHO as a crucial step toward the achievement of the United Nation's Millennium Development Goal 4 of reducing by two-thirds the mortality rate in children aged less than five years. To date RotaTeq™ and Rotarix™ have been licensed in over 120 countries in the Americas, Europe, Australia, Africa and Asia, of which about 35 have introduced rotavirus vaccines into their national programs. It is worth mentioning that Latin America played a key role in pre-licensure vaccine trials, and pioneered the introduction of rotavirus vaccination into the majority of its national programs. As a result, lessons learned including operational, financial and political issues can be useful for the current ongoing efforts to introduce rotavirus vaccine in several countries all over the world.

In the current scenario of progressive and swift introduction of rotavirus vaccines into the national immunization programs of several countries around the globe, the need for assessing the "real-world" performance of these vaccines gains high priority. Several post-licensure, controlled studies conducted to date have in general provided reassuring evidence for rotavirus vaccine effectiveness, that is, efficacy under "real conditions". The effectiveness of RotaTeq™ against severe RVGE was assessed in at least six studies including the USA (four studies), France and Nicaragua. The vaccine effectiveness was lower (46%) in Nicaragua as compared to rates of greater than 70% in USA and France. In addition, the effectiveness of Rotarix™ under programmatic use was assessed in five studies conducted in El Salvador, Mexico and Brazil (three studies). Overall, effectiveness rates against rotavirus gastroenteritis hospitalizations and emergency department visits were in the range of 76% to 94%. Effectiveness of Rotarix™ was also measured during outbreaks of AGE in Australia with rates being as high as 85%.

To date, several observational studies have explored the effect of both vaccines on GE-related hospitalizations in a variety of low-middle, middle, and high-income countries. Studies conducted in upper-middle income countries (Panama, Mexico and Brazil) that have implemented Rotarix™ into their national immunization programs have shown a substantial decline (17%-40%) in admissions for all-cause GE hospitalizations among children less than five years of age. Furthermore, a significant reduction (42%) in admissions for RV-associated GE was seen during an active surveillance carried out in one sentinel hospital in São Paulo. A significant decrease in admissions for RV-related GE was also reported in El Salvador (a lower-middle income country), where a 79% reduction was reported among children aged less than two years, when comparing 2009 to the pre-vaccine year 2006. The impact caused by rotavirus vaccination on hospitalizations for community-acquired GE was also assessed in (high-income) countries (USA, France and Austria) where RotaTeq™ had been introduced for nationwide routine use. Significant reduction rates of 69%-81%, 35%-66% and 65%-83% were achieved in studies conducted in USA (10 studies across the country), France and Austria, respectively. A pronounced decline in the number GE-related hospitalizations was also reported for Australia (68%-93%), Spain (45%) and Belgium

(20%-83%), following inclusion of both vaccines in national immunization programs. The impact of RV vaccination on childhood GE-related mortality was assessed in a few studies in Latin American countries, all of which having adopted universal use Rotarix™. GE-related mortality in less than 1 year-old children decreased significantly in Mexico, Brazil (two studies across the country), and Panama, at rates of 41%, 22%-39%, and 45%, respectively.

Recent studies using case-series and case-control methodology revealed a small, albeit significant increased risk of intussusception (IS) within seven days after the first vaccine dose in Mexican and Australian infants. Nevertheless, such a potential risk appears substantially lower than that reported previously for the human-rhesus tetravalent vaccine RotaShield™ (Wyeth) which was withdrawn from the US market due to a significantly increased risk (>30-fold) of IS during 3-7 days after the first vaccine dose. In light of these findings it has been suggested that the substantive benefits of rotavirus vaccination would far outweigh any potential risk of IS.

In parallel with continuous development of new rotavirus vaccines, including early experiments with inactivated viruses or viral subunits, currently licensed vaccines still pose a number of challenges for the near future. In this context several issues remain to be addressed in studies that should focus on:

- (a) Possible alternative vaccine schedule including a neonatal dose
- (b) Altering breastfeeding practices
- (c) Assessing herd immunity and herd protection
- (d) Assessing the potential effect of vaccination on rotavirus strains
- (e) Introducing an interval in relation to polio vaccination
- (f) Using zinc or probiotic supplementation
- (g) Further evaluating any potential risk of IS following progressive implementation of rotavirus vaccination
- (h) Exploring the still controversial issue of apparent waning immunity in the second year of life.

Although robust, currently available scientific evidence point to the significant health benefits of rotavirus vaccination in reducing the burden of severe rotavirus disease, it seems crucial to broadening advocacy initiatives for rotavirus vaccination. This would include mainly raising awareness on the tremendous benefits of rotavirus vaccination among decision makers, potential donors, scientific community, medical societies, opinion leaders and official advisory bodies.

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