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Impact of Rotavirus Vaccines in Sub-Saharan African Countries

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In 2009, the World Health Organization (WHO) recommended use of rotavirus vaccine in all countries globally, particularly those with high mortality due to diarrhea.[1] Following this recommendation, South Africa, a middle-income country, because the first country in WHO's African Region to introduce rotavirus vaccine into its national immunization program in 2009. Also, following the WHO global recommendation, support for rotavirus vaccine procurement became available through Gavi for low-income countries and rotavirus vaccine introductions increased rapidly in the African region with the first Gavi supported introductions occurring in 2012. By the end of 2017, 32 (68%) of 47 countries in the African Region had introduced rotavirus vaccine into their national immunization programs, including 27 countries that received support from the Gavi Alliance [2]

Two live, attenuated, oral rotavirus vaccines, pre-qualified by WHO, are currently being widely used globally. Rotarix (GlaxoSmithKline) is a 2-dose, monovalent rotavirus vaccine based on an attenuated G1P[8] human rotavirus strain and RotaTeq (Merck) is a 3-dose, bovine human reassortant pentavalent vaccine incorporating genotypes G1, G2, G3, G4, and P[8].[3, 4] These vaccines were highly efficacious against severe rotavirus disease (85% −98%) in clinical trials conducted in the Americas and Europe.[3, 4] Additional clinical trials performed in developing countries in Africa and Asia found more modest efficacy (51%−64%).[5–7] However, given the considerable disease burden in developing countries, many of which are in sub-Saharan Africa, the burden of disease prevented is expected to be substantial even with moderately efficacious vaccines. In 2016, almost 135,000 rotavirus hospitalizations and 21,000 rotavirus deaths in children <5 years of age were estimated to have been prevented in the 29 African countries that introduced rotavirus vaccine into their national immunization programs by the end of 2014.[8] If all countries in Africa introduced rotavirus vaccine into their national immunization programs at vaccine coverage levels similar to other routine infant immunizations, an estimated 273,000 rotavirus hospitalizations and 47,000 rotavirus deaths could be prevented annually.[8]

Several early introducing African countries including South Africa, Ghana, Rwanda, Malawi, Botswana, Tanzania, Zambia, and Zimbabwe, have previously evaluated the impact, vaccine effectiveness, and/or cost effectiveness of their routine rotavirus vaccination

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programs. These programs found comparable effectiveness to that which was seen in the clinical trials and substantial impact on severe rotavirus disease burden.[9–20] Under conditions of routine use, rotavirus vaccine was 52–78% effective against rotavirus hospitalization during the first year of life.[9, 11, 12, 14, 17, 18] Declines of 35%−80% in the proportion of diarrhea hospitalizations due to rotavirus among children <5 years of age were observed following rotavirus vaccine introduction.[11, 13, 15, 19, 20] All-cause diarrhea hospitalizations among children <5 years of age decreased 17%−57% with larger declines observed among children <1 year of age and during the rotavirus season.[10, 13, 16, 20] Similarly, in-hospital mortality due to diarrhea in infants declined 27%−46%.[16, 20] In a cost-effectiveness analysis of the rotavirus vaccination program conducted after vaccine introduction in Malawi, rotavirus gastroenteritis was found to cause significant economic burden and the rotavirus vaccination program was highly cost-effective with a societal cost per DALY averted of $10 and a cost per rotavirus case averted of $1.[21]

The objective of this Special Issue of *Vaccine* is to provide additional rotavirus vaccine effectiveness and impact data from a broader range of African countries, to describe the longer term impact and potential indirect benefits of rotavirus vaccination programs, to describe trends in circulating genotypes in the pre- and post-vaccine introduction eras, and to evaluate the cost-effectiveness of a rotavirus vaccination program in a post-introduction setting.

Rotavirus Vaccine Effectiveness

Evaluations of vaccine effectiveness conducted in Burkina Faso, Malawi, and Tanzania reaffirm the moderate efficacy of rotavirus vaccines against moderate-to-severe diarrhea in these countries, with a trend toward diminished effectiveness after the first year of life. Burkina Faso introduced pentavalent rotavirus vaccine in October 2013 with 3 doses given at 2, 3, and 4 months of age. In vaccine-eligible children ≥6 months of age in Burkina Faso, a full series of vaccine was 35% (95% confidence interval (CI): −15%, 63%) effective against rotavirus hospitalizations.[22] When restricting the analysis to children 6–11 months of age, a full course of vaccine was 58% (95% CI: 10%, 81%) effective but effectiveness dropped to 19% (95% CI: −78%, 65%) in children 12 months of age and older. A similar pattern of declining effectiveness in older children was also seen in Malawi which introduced monovalent rotavirus vaccine in October 2012 with 2 doses given at 6 and 10 weeks of age.[23] Among all vaccine-eligible children, vaccine effectiveness was 62% (95% CI: 28%, 80%) against rotavirus hospitalizations in Malawi but when stratifying by age, the vaccine was 86% (95% CI: 59%, 95%) effective in children <12 months of age and 32% (95% CI: −139%, 80%) in children 12–23 months of age. In January 2013, Tanzania also introduced monovalent rotavirus vaccine with a 2 dose schedule at 6 and 10 weeks of age. In three hospitals in northwest Tanzania, at least one dose of rotavirus vaccine was 53% (95% CI: −14%, 81%) effective against rotavirus hospitalizations in children 5–23 months of age.[24] When the analysis was restricted to more severe disease outcomes, at least one dose of vaccine was 66% (95% CI: 9%, 87%) effective in children requiring IV rehydration and 70% (95% CI: 14%, 90%) effective against moderate-to-severe rotavirus disease (Vesikari score ≥11). Rotavirus vaccine effectiveness increased with increasing Vesikari score, consistent

with clinical trial data that rotavirus vaccines are more efficacious against diarrhea of greater severity.[3, 4]

Rotavirus Vaccine Impact

Rotavirus vaccines have had a tremendous impact on all-cause diarrhea and rotavirus hospitalizations in countries that have introduced the vaccine in sub-Saharan Africa. An evaluation in the 15 countries in the WHO East and Southern sub-region that participate in the WHO-coordinated African Rotavirus Surveillance Network found that the proportion of diarrhea hospitalizations due to rotavirus among children <5 years of age decreased following rotavirus vaccine introduction and the magnitude of decrease increased as vaccine coverage increased.[25] Furthermore, the proportion of rotavirus hospitalizations that had severe dehydration decreased following rotavirus vaccine introduction as did the proportion of rotavirus hospitalizations that occurred in children <1 year of age. In countries in this sub-region that have not yet introduced rotavirus vaccine, the proportion of diarrhea hospitalizations due to rotavirus remained stable over the surveillance period.

Similar changes in rotavirus hospitalizations were documented in the individual country evaluations of rotavirus vaccine impact included in this Special Issue with significant declines in the proportion of diarrhea hospitalizations due to rotavirus ranging from 23% −76% among children <5 years of age and often with larger declines of 27%−82% seen in children <1 year of age.[22, 24, 26–33] These declines were sustained up to four years in some early vaccine introducing Gavi-eligible countries although some variability in the proportion of diarrhea hospitalizations due to rotavirus from year to year were observed. [23, 30, 32, 33] A decrease in rotavirus positivity was also observed among unvaccinated infants in Malawi suggesting indirect effects of the vaccination program.[23] Declines in older age groups who were not yet vaccine age-eligible were mixed with some countries seeing small decreases [26] but other countries reported no changes or increases in rotavirus hospitalizations in older children in some years.[31, 32]

Changes in rotavirus epidemiology were observed in many countries following rotavirus vaccine introduction including a delay in the start of the rotavirus season[24, 26, 34], a blunting of seasonal peaks[22, 26–30, 32, 34], and a shorter duration of the season[24]. An increase in the median age at rotavirus hospitalization or a decrease in the proportion of rotavirus hospitalizations occurring in children <12 months of age was observed in many countries following vaccine introduction [23, 27, 28, 30, 33], but not in all countries [26].

Declines of 30%−39% in the proportion of total hospitalizations among children <5 years of age due to diarrhea were also observed in many countries with larger declines of 36%−54% observed among children <1 year of age.[29–31] However, trends in all-cause diarrhea hospitalizations were not always clear due to the non-specificity of diarrhea hospitalizations when reviewing hospital ward registries.[35] Similar to trends seen in rotavirus hospitalizations, the proportion of all-cause diarrhea hospitalizations that occurred in children <12 months of age also decreased following rotavirus vaccine introduction.[26, 28]

Circulating Rotavirus Genotypes

A diversity of circulating genotypes with yearly fluctuations were seen in many countries pre- and post-rotavirus vaccine introduction with no clear pattern or genotype uniformly emerging following vaccine introduction in most countries with reported genotyping data.[28, 36–39] However, some significant temporal changes in circulating genotypes were observed in South Africa combined with a significant reduction in overall disease.[40] Longer term surveillance will be needed to determine if strain evolution occurs after rotavirus vaccine introduction. Of note, a previous meta-analysis of global data showed that both Rotarix and RotaTeq provide protection against a range of vaccine-type and non-vaccine type strains.[41]

Cost-Effectiveness of a Rotavirus Vaccination Program

A cost-effectiveness analysis of the rotavirus vaccination program in Ghana found that continued rotavirus vaccination will be highly cost-effective even after Ghana assumes full responsibility for purchasing the vaccine after transitioning from Gavi support with a societal cost per DALY averted of $238-$332 and a cost per case averted of $27-$38.[42] Over the first 20 years following vaccine introduction, the rotavirus vaccination program in Ghana will avert over 2.2 million rotavirus cases and 8,900 deaths and avert $6-$9 million in treatment costs.

Summary

The evaluations included in this Special Issue of *Vaccine* provide further evidence of the tremendous health impact and effectiveness of rotavirus vaccination in sub-Saharan Africa. Countries that have introduced rotavirus vaccine into their national immunizations program have documented a decline in the proportion of diarrhea hospitalizations due to rotavirus and a decline in total hospitalizations due to diarrhea among children <5 years of age. The greatest declines were seen in children <1 year of age and the burden of disease may therefore be shifting to children >1 year of age. Vaccine effectiveness was similar to that seen in the clinical trials with some evidence of waning immunity after the first year of life. No single genotype has emerged as dominant in vaccine introducing countries. Rotavirus vaccine was shown to be high cost-effective in Ghana and will likely remain so even after Gavi support ends.

One commonality among many of the evaluations in this Special Issue is that many used an existing rotavirus surveillance platform to monitor trends in rotavirus hospitalizations over time and to serve as a platform upon which to build a vaccine effectiveness evaluation using standardized methods.[43, 44] These studies exemplify the importance of continuous, robust surveillance both before and after rotavirus vaccine introduction to document the impact of the vaccination program. In many settings, rotavirus surveillance was supplemented with a review of hospital discharge data for acute gastroenteritis hospitalizations. As rotavirus infection accounts for such a large proportion of acute gastroenteritis hospitalizations prior to vaccine introduction, monitoring trends in all-cause acute gastroenteritis also offers a broad perspective for rotavirus vaccine impact evaluations and a resource efficient complement to active rotavirus surveillance to monitor impact of vaccination.

Despite the promising findings reported in this Special Issue, further work still remains for evaluating rotavirus vaccines in sub-Saharan Africa. Nigeria and the Democratic Republic of Congo are on the threshold of rotavirus vaccine introduction and generating similar data on rotavirus vaccine performance in these countries with large birth cohorts will demonstrate that rotavirus vaccines can be successfully implemented in countries with complex immunization programs. Additional data on rotavirus vaccine effectiveness and impact is also needed from Francophone countries in Africa and countries with weaker immunization programs. Continued surveillance to document the long-term impact of rotavirus vaccination on disease trends and circulating rotavirus strains remains important. Several countries in Africa have noted a decline in in-hospital diarrhea deaths following rotavirus vaccine introduction but evidence of vaccine impact on overall diarrhea mortality among children under 1 and under 5 years of age is extremely limited. Rotavirus vaccine impact on overall diarrhea mortality could be investigated through population-based Health and Demographic Surveillance Systems. Earlier this year, a third rotavirus vaccines (ROTAVAC, Bharat Biotech) was pre-qualified by WHO and if any country in Africa introduces this vaccine into its national immunization program, monitoring its performance would be a priority as this vaccine has not been widely evaluated globally. Finally, as rotavirus disease declines in the region, it is important to assess how rotavirus vaccine introduction impacts overall diarrhea disease epidemiology, including etiology changes.

The evaluations conducted in the African region can serve as a model for other regions such as Asia where wide-scale rotavirus vaccine introductions are just beginning and surveillance is ongoing as part of the WHO-coordinated Global Rotavirus Surveillance Network. Furthermore, as countries begin transitioning from Gavi support, the findings of these studies provide evidence of the impact and effectiveness of rotavirus vaccination programs under conditions of routine use.

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