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EXPERT REVIEWS

Human rotavirus vaccine (*Rotarix*): focus on effectiveness and impact 6 years after first introduction in Africa

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A decade after licensure of the human rotavirus vaccine (HRV), a wealth of evidence supports a reduction of rotavirus (RV) gastroenteritis-associated mortality and hospitalizations following HRV inclusion in national immunization programs. Nevertheless, the majority of real-world data has been generated in high- or middle-income settings. Clinical efficacy trials previously indicated RV vaccine performance may be lower in less-developed countries compared with wealthier counterparts. Using recently published data from Africa, we examine the effectiveness and impact of HRV in resource-deprived areas, exploring whether vaccine performance differs by socioeconomic setting and the potential underlying factors. HRV vaccine effectiveness in early adopting African countries has proven to be similar or even superior to the efficacy results observed in pre-licensure studies.

Keywords: Africa • developing countries • RIX4414 vaccine • Rotavirus vaccine • vaccine effectiveness • vaccine impact

Rotavirus (RV) infects nearly all children by the age of 5 years, irrespective of socioeconomic background [1]. The clinical presentation of RV disease ranges from transient, mild diarrhea to severe episodes of acute fever, vomiting and watery diarrhea. At its most serious, RV gastroenteritis (RVGE) results in rapid dehydration, which, in the absence of oral or intravenous rehydration therapy, can result in circulatory collapse and death [2,3].

In developed countries, where access to good healthcare facilities is near universal and often state subsidized, deaths from RV are rare, estimated at approximately 200 deaths per year in Europe, for example [4]. In these settings, the burden of RVGE predominantly manifests as an increase in hospitalizations and outpatient visits, resulting in a substantial economic and social burden [4,5]. In contrast, in less-developed countries, RV mortality rates can be high. In the pre-vaccine era, the latest estimates (in a scenario of natural declination) were 453,000 deaths worldwide per year from RV infection, of which over half occurred in Africa [6].

Improved sanitation and hand washing have had limited impact on fully preventing the spread of this fecal–oral transmitted virus, as evidenced by the burden of RVGE in highly developed areas [4,5,7]. Thus, it is now widely accepted that vaccination presents the most effective option for controlling this pathogen [8]. The WHO recommends that RV vaccination is included in all national immunization programs (NIPs), to be prioritized in countries with high rates of RV-associated mortality [8].

There are currently two widely licensed RV vaccines, both of which are live, attenuated and orally administered. Human rotavirus vaccine (HRV; *Rotarix*® [GlaxoSmithKline, Rixensart, Belgium]) is a two-dose vaccine based on a single RV strain of the most commonly observed human genotype, G1P[8]. *RotaTeq*® (Merck and Co., Inc., PA, USA and Sanofi Pasteur MSD SNC, Lyon, France) is a three-dose, human–bovine reassortant vaccine (HBRV) containing five different strains. A number of other vaccines are in development (recently

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reviewed by O'Ryan *et al.* [9]) or have been regionally licensed.

As of March 2015, 75 countries have included RV in their NIPs [10]. Ten years post-licensure, this is a remarkable achievement, although many children remain without access to RV vaccination. Despite almost half of all national vaccine introductions occurring in Global Alliance for Vaccines and Immunisation (Gavi)-eligible countries [10], relatively few studies have assessed the field effectiveness of RV vaccination in these lower-income settings. This article will review the currently available data on the impact and effectiveness of HRV in African countries in the context of the wider global picture; it is only from this broader understanding that we can begin to comprehend the complex interplay of study setting and vaccine performance.

Study design for assessing vaccine performance in routine clinical practice

Demonstrable improvements in health outcomes, as assessed by vaccine impact and effectiveness studies, are an important validation of RV vaccines beyond efficacy trials, providing the most emphatic argument to decision-makers to invest in new vaccination programs. There are principally two types of methodology used to assess the real-life impact of public health efforts to reduce the burden of RVGE: ecological (impact) and case–control (effectiveness) studies. Ecological studies assess vaccine impact by monitoring trends over time in gastroenteritis (GE) and RV disease burden in conjunction with vaccine coverage rates. These studies may measure a variety of parameters, ranging from cases of all-cause GE (AGE) mortality to RVGE-specific notifications. The impact of a vaccine will be a function of vaccination coverage rates in the region. Subsequently, vaccine impact is expected to be seen primarily in infants <12 months of age in the first year of vaccine rollout, and in incrementally increasing age groups for successive years. As well as being subject to vaccine uptake, ecological studies are not able to distinguish vaccine effect from a decline in disease burden due to other factors.

Case–control studies provide an alternative to ecological studies. These studies compare the frequency of vaccination exposure among patients with RV with the background frequency in a control cohort who are free from the disease. In the case of RVGE, suitable control groups can be RV-negative diarrhea patients, non-diarrhea patients or disease-free community participants. Recruiting children with non-RV diarrhea represents the closest possible matching of cases to controls, but may be over-representative of children vulnerable to gastrointestinal disease, for example, the malnourished. Inclusion of non-diarrheal patients mitigates for this bias, but may still conceal underlying weakness or susceptibility to disease found in hospitalized children, or differences in healthcare utilization between socioeconomic groups. Matched controls taken from the community facilitate comparison with well children and are considered most representative of the 'at-risk' population. The inclusion of two different sets of controls can help with the interpretation of case–control studies in the presence of such potential confounding factors. Case–control studies offer the advantage of being able to assess vaccine effectiveness irrespective of coverage rates, and against specific RV strains.

Summary of effectiveness & impact of HRV in high- & middle-income countries

Given the link between vaccine efficacy, as assessed in Phase III randomized, controlled clinical trials, and study setting, it is pertinent also to evaluate the real-world effectiveness and impact of RV vaccination in a variety of settings. The impact and effectiveness of HRV in high- and middle-income settings has been reviewed in detail elsewhere [11]. Case–control studies from high-income European countries report HRV effectiveness of approximately 90% against RVGE hospitalization [12,13], and 75% against all RVGE requiring medical attention [14], which is similar to the efficacy results obtained during the clinical development program. Effectiveness studies from upper-middle-income Brazil found two doses of HRV to be 65–96% effective against RVGE hospitalization, depending on the age group studied [15]. Effectiveness of HRV against RVGE hospitalization was also similar in two lower-middle-income countries, Bolivia and El Salvador, at 77% and 76%, respectively [16,17]. In terms of vaccine impact, there have been over 80% reductions, after introduction of RV vaccine into NIPs, in RVGE hospitalizations in children aged <12 months reported from both high- and middle-income countries [18–23]. In addition, a noted reduction in RV cases among non-vaccinated older children, suggestive of herd protection with HRV, has been demonstrated in culturally and economically diverse countries, including Austria [24], Belgium [19], Brazil [23,25] and El Salvador [18]. At the most severe end of the disease spectrum, robust evidence suggests that RV vaccination can save lives. Pediatric AGE mortality rates have fallen significantly following HRV inclusion in NIPs in Mexico [26,27], Brazil [25,28,29] and Panama [30]. Demonstrating the human value of vaccination, in the 3 years following HRV introduction in Brazil, 1500 and 130,000 fewer RV deaths and hospital admissions among children <5 years, respectively, are estimated to have occurred [29].

Impact & effectiveness of RV vaccination in Africa

Africa represents a particular challenge for delivering new vaccine programs and achieving universal coverage. Very few African countries have independently introduced RV vaccine, with the majority of vaccine introductions supported through Gavi funding (Figure 1). As well as financing vaccine dose purchasing, Gavi also supports new vaccine introductions by providing tertiary assistance to strengthen healthcare delivery systems, cold-chain establishment and training of healthcare professionals. In 2011, Sudan was the first country in Africa to introduce RV vaccines with Gavi support (following the earlier, independently financed, introduction of RV vaccines in South Africa in 2009) [31]. Of the 28 countries of the African continent that have already introduced RV vaccines into their national immunization schedules, 22 have selected to administer HRV and six have selected to give HBRV (Figure 1) [10].

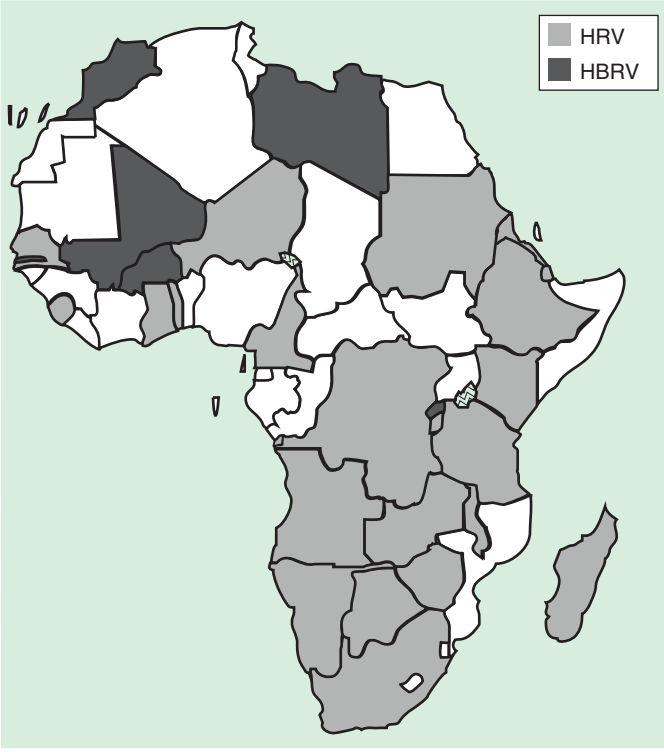

Figure 1. African countries (by geographic region) introducing rotavirus vaccines into their national immunization schedules.
Countries introducing HRV: Angola, Botswana, Burundi, Cameroon, Republic of Congo, Djibouti, Eritrea, Republic of Ethiopia, Ghana, Kenya, Madagascar, Malawi, Namibia, Niger, Senegal, Sierra Leone, South Africa, Sudan, Tanzania, Togo, Zambia, Zimbabwe. Countries introducing HBRV: Libya, Mali, Morocco, Burkina Faso, The Gambia, Rwanda. Underline indicates countries that did not receive GAVI-funding [10].
HBRV: Human–bovine reassortant vaccine; HRV: Human rotavirus vaccine.

Compared with other new vaccines, widespread access to RV vaccination has been achieved at a relatively fast pace, with reported coverage rates in African countries ranging from 78% in Botswana to 99% in Rwanda just a few years post-introduction (December 2014 data) [32].

There are currently no published studies on the impact and effectiveness of HBRV in Africa. Data on HRV use in Africa are currently available from three countries, spanning a wide cross-section of study settings. Tables 1 and 2 summarize the impact and effectiveness data currently available from these African countries using HRV. Results from impact studies (Tables 2) are grouped by country income (as defined by the World Bank [33]), WHO RV mortality quartile [34] and principal impact measure(s); this information is supplemented by details of study design and vaccine coverage rates (where available).

South Africa

South Africa represents an 'early adopter' of HRV, having introduced HRV in August 2009 on a recommended 6- and 14-week two-dose schedule [35]. Despite being one of the more socioeconomically developed countries in Africa, with a gross national income (GNI) per capita of US$12,530 (2013), South Africa is constituted of a diverse range of regions at varying levels of development, and subsequently offers data from studies conducted in areas that could be classified as low- to high/middle-income [33,36,37].

A multicenter prospective ecological surveillance study evaluated hospital admission rates during two RV seasons in 2010 and 2011 at three sentinel sites, representing three distinct settings: a large tertiary referral hospital in Soweto (an urban area located on the outskirts of Johannesburg), a community hospital in the north of Pretoria serving a peri-urban population, and two hospitals (one regional referral hospital and one district-level hospital) in the rural Bushbuckridge district [35]. Johannesburg and Pretoria, located in the Gauteng Province of South Africa, are both listed in the world's 300 largest metropolitan economies, each reporting gross domestic product per capita of >$16,000 in 2014. Nevertheless, despite of being one of the least impoverished regions of the country, 23% of the population in Gauteng still live in poverty [38]. Bushbuckridge is a town in the Mpumalanga province of South Africa where more than half of the population lives in poverty (52%) [38]. Across all study sites, nearly three-quarters of all RV diarrheal hospitalizations prior to vaccine introduction were of children aged <1 year (Figure 2A) [35]. Post-vaccine introduction, there was a reported 38–43% and 61–69% reduction in AGE and RVGE, respectively, in children aged <12 months compared with 2009 data (Figure 2B, C). This impact was achieved despite modest vaccine coverage estimates for the districts studied (two doses: all study sites 41% [range 40–45%], April 2010; all study sites 72% [range 56–78], April 2011), reflecting both the high proportion of diarrhea attributable to RV at peak season times and the overall impact RV vaccine can have in these high disease burden settings (Table 2 & Figure 2).

A separate case–control study evaluated the effectiveness of RV vaccination between April 2010 and October 2012. Participants were enrolled from a number of the same hospitals reported in the ecological study above, representing a cross-section of urban, peri-urban and rural settings in South Africa. Two doses of HRV were 57–63% effective against RVGE hospitalization for children aged 18 weeks to 23 months, with little difference observed regarding the control group against which vaccine effectiveness was evaluated (Table 1) [39].

Vaccine effectiveness against admission to hospital was similar in both the first (54–66%) and second (60–61%) years of life (Table 1) [39]. The observation that the field effectiveness of HRV appears to be sustained in the 12- to 23-month age group is in contrast to the vaccine efficacy study conducted in South Africa, where HRV efficacy against severe RVGE appeared to decline in the second year of life (Table 3) [40,41].

Important differences in study design preclude direct comparison of RV performance between efficacy and effectiveness studies. Efficacy is calculated from a prospective cohort of subjects and is based on a first-event analysis, while effectiveness studies identify cases and controls retrospectively from the population.

Table 1. HRV vaccine effectiveness (case–control studies) in African countries.

Study (year)	Main outcome measure(s)	Setting and method of comparison	Vaccine effectiveness (%) (95% CI)	Age group	Ref.
South Africa (vaccine introduced August 2009) **Dose schedule 6 and 14 weeks**					
Groome *et al.* (2014)	RVGE hospitalization	Multi-center case–control study performed between April 2010 and October 2012 enrolling children aged <2 years, using both RV-negative and respiratory controls. HIV infection rate: Cases, 8% RV-negative controls, 11% Respiratory controls, 3%	2-doses: 57% (40–68) (RV-negative controls) 63% (45–75) (respiratory controls) 2 doses: 54% (32–68) (RV-negative controls) 66% (46–79) (respiratory controls) 2 doses: 61% (35–77) (RV-negative controls) 60% (21–80) (respiratory controls)	18 weeks–23 months 18 weeks–11 months 12–23 months	[39]
Malawi (vaccine introduced May 2012) **Dose schedule 6 and 10 weeks**					
Bar-Zeev *et al.* (2015)	RVGE hospitalization	Single hospital case–control study performed between October 2012 and June 2014 enrolling vaccine eligible children, using RV-negative and non-diarrhea controls. HIV infection rate: Cases, 4% RV-negative controls, 5% Community controls, not reported	2 doses: 64% (24–83), RV-negative controls 63% (23–83), non-diarrhea controls	Age-eligible children	[50]

CI: Confidence interval; RV: Rotavirus; RVGE: Rotavirus gastroenteritis.

The efficacy study in South Africa was not powered to evaluate efficacy specifically during the second year of follow-up and was further limited by a low attack rate in both the vaccinated and control cohorts, with only nine cases of RVGE detected in a cohort of 686 infants. As a consequence of the low incidence of RVGE in both the placebo and vaccine group, vaccine efficacy in the second year of life could not be accurately determined (estimated vaccine efficacy 40% [95% confidence interval (CI): −204–87]) [41]. Due to its retrospective nature, the case–control study was able to identify 151 cases in children aged 12–23 months, allowing for statistically significant between-group differences to be determined between the RV group and uninfected controls [39].

In addition, there are important differences between the vaccine administration schedule used in the efficacy study and the recommended schedule for RV vaccination in South Africa that forms the backdrop to the effectiveness study. Infants in the efficacy study were randomized 1:1:1 to receive either placebo, two doses of HRV at 10 and 14 weeks or three doses of HRV at 6, 10 and 14 weeks. Therefore, of those vaccinated, half would not have received their first vaccine dose until 10 weeks of age. It has been reported that 4–13% of infants in South Africa are infected by RV before 9 weeks of age, and it is of note that this age group comprises 3% of all RVGE hospitalizations in middle- and low-income countries [42,43]. As a consequence, vaccination after this time would leave infants unprotected and vulnerable to circulating RV. South Africa introduced HRV on a two-dose schedule at 6 and 14 weeks of age, and it is assumed that the majority of infants included in the effectiveness study would have received the vaccine accordingly, providing early protection before infants are exposed to the virus.

As well as demonstrating protection for vaccinated children into the second year of life, the vaccine impact study highlights an age-related protective herd effect for unvaccinated children in South Africa. Reductions in RVGE and AGE hospitalization were detected in 2010 in children aged 12–<24 months who would have been too old to be vaccinated [35]. These findings echo the fall in RVGE cases and mortality in older unvaccinated children upon HRV introduction in Mexico, Australia and several European countries with RV included in their universal mass vaccination programs [19,22,24,26,44]. These observations add to the body of evidence that the positive impact of RV vaccination could be amplified in real-life clinical settings due to indirect effects.

The studies reviewed here provide insight into the impact and effectiveness of RV vaccination against a potentially clinically relevant background of high (but falling) rates of infant human immunodeficiency virus (HIV) infection (programs for

Table 2. HRV impact (ecological studies) on RV- and all-cause diarrhea hospitalizations in African countries.

First author (year)	Main outcome measure(s)	Setting and method of comparison	Vaccine impact (%) (95% CI)	Age group	Estimated coverage	Ref.
Upper-middle-income countries with high child mortality and very high adult mortality						
South Africa (vaccine introduced August 2009) **Dose schedule 6 and 14 weeks**						
Msimang *et al.* (2013)	All-cause diarrheal hospitalizations	Hospital-based surveillance study based at three sentinel sites representing urban, peri-urban and rural settings, and including both community and referral hospitals	32% reduction, 2010 33% reduction, 2011	<5 years	2 doses, infants <1 year: 41% 2010 72% 2011	[35]
			38% reduction, 2010 43% reduction, 2011	<1 year		
	RVGE hospitalizations		54% reduction, 2010 58% reduction, 2011	<5 years		
			61% reduction, 2010 69% reduction, 2011	<1 year		
Lower-middle-income countries with high child mortality and high adult mortality						
Ghana (vaccine introduced May 2012) **Dose schedule 6 and 10 weeks**						
Enweronu-Laryea *et al.* (2014)	All-cause diarrheal hospitalizations	Hospital-based surveillance study of enrolled children aged <5 years, comparing hospitalization rates before and after the implementation of RV vaccination, 2008–2014	52%, reduction from 2011 to 2012 16% reduction from 2012 to 2013	<5 years	Nationwide coverage: 42–56% in 2012 73–93% in 2013	[48]
Low-income countries with high child mortality and high adult mortality						
Malawi (vaccine introduced October 2012) **Dose schedule 6 and 10 weeks**						
Bar-Zeev *et al.* (2015)	RVGE hospitalizations	Hospital-based surveillance comparing hospitalization rates from 1 January to 30 June 2012 preceding vaccine introduction compared with the equivalent calendar periods in 2013 and 2014	49% increase from 2012 to 2013 15% decrease (ns) from 2012 to 2014	<5 years	5.2% in 2013 18% in 2014	[50]
			5.8% increase (ns) from 2012 to 2013 43% reduction from 2012 to 2014	Age-eligible infants	26% in 2013 92% in 2014	

CI: Confidence interval; ns: Non-significant; RV: Rotavirus; RVGE: Rotavirus gastroenteritis.

the prevention of mother-to-child transmission have reduced HIV prevalence in infants from 9.6% in 2008 to 2.8% in 2011) [45]. The case–control study reviewed here was not powered to evaluate vaccine effectiveness by HIV infection. Nevertheless, HIV exposure without subsequent infection has been identified as a potential childhood risk factor for diarrheal disease, perhaps due to the withdrawal of the protective effects of breastfeeding by HIV-infected mothers [46]. Of the HIV uninfected children included in the study, 98% had a known HIV-exposure status; of these, 31% of children were HIV-exposed but uninfected and 69% were HIV-unexposed and uninfected. Similar effectiveness of two doses of RV vaccine was demonstrated for HIV-exposed-uninfected children and HIV-unexposed-uninfected children [39]. The finding that RV demonstrates protection against RVGE irrespective of HIV exposure will be pertinent across the wider Sub-Saharan region where many babies are HIV exposed, with infection prevalence as high as 37% among females [47].

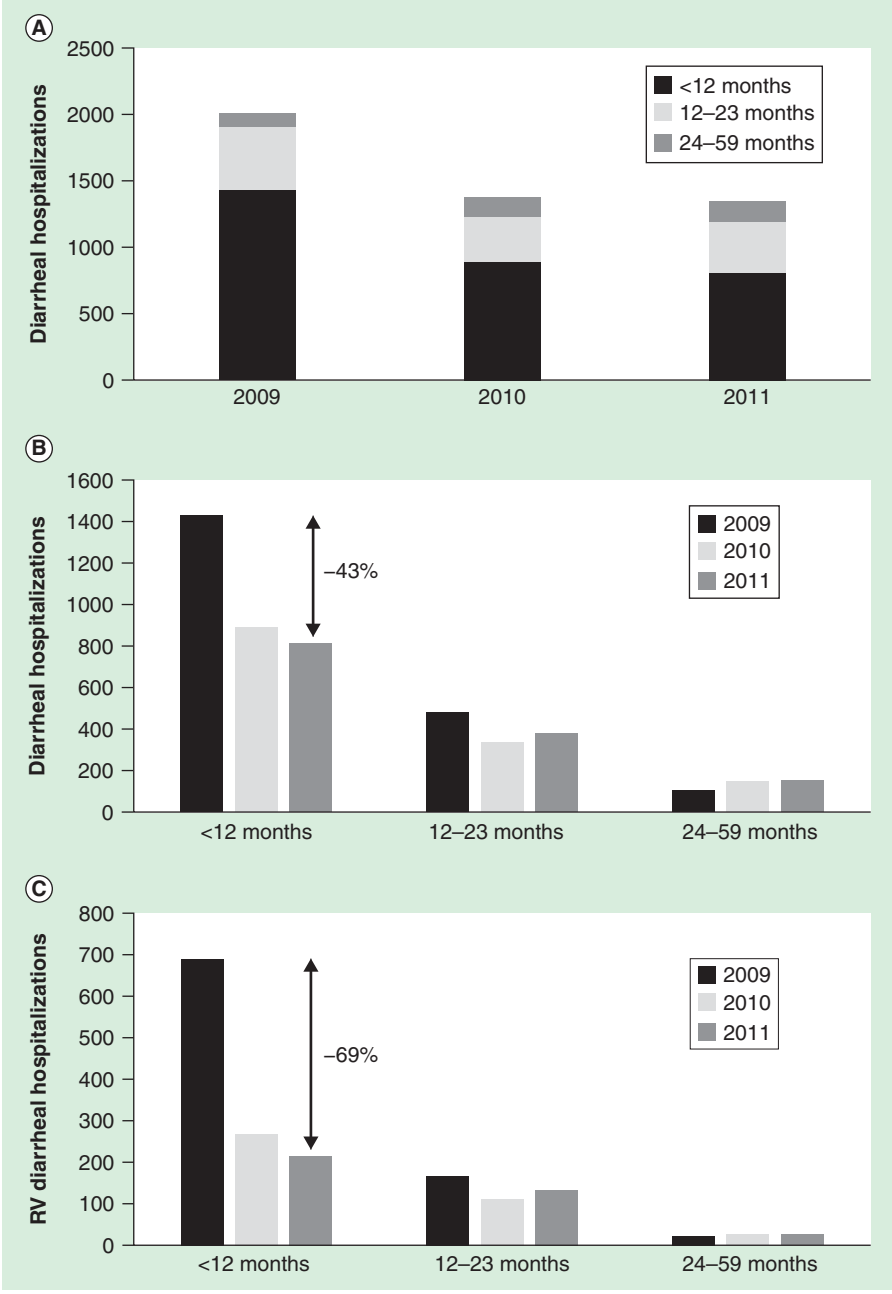

Figure 2. Impact of HRV vaccination on diarrheal disease burden in South Africa. **(A)** Number of total diarrheal hospitalizations by age proportion. **(B)** Number of diarrheal hospitalizations, **(C)** number of rotavirus hospitalizations, by age group, 2009–2011, in South Africa.
RV: Rotavirus [35].

Ghana

Ghana, a lower-middle-income country with a GNI per capita of $3900 (2013) [33,36], has been performing RV surveillance from the capital, Accra, since 2008, as part of a WHO-sponsored collaboration [48]. In May 2012, HRV was introduced into the expanded program on immunization, given at 6 and 10 weeks of age [49]. Based on surveillance data from two pediatric referral hospitals, and in the context of coverage rates of 42–56% in 2012 and 73–93% in 2013, child hospitalizations from all-cause diarrhea fell substantially following vaccine introduction, by 51.6% from 2011 to 2012 and by a further 16.2% from 2012 to 2013 (Table 2) [48]. The proportion of diarrheal hospitalizations attributable to RVGE fell from 49.7 to 27.8% in the pre- and post-vaccination eras, respectively. Over the same time periods, the proportion of children aged <11 months hospitalized with RV-confirmed GE declined from 72.6 to 45.7%. The majority of the burden of RV disease (87%) was in children aged <18 months during the pre-vaccination period. Therefore, due to low case numbers and the relatively short post-vaccine duration, this study was unable to evaluate indirect protection of older unvaccinated children.

Malawi

Malawi is an impoverished country in Sub-Saharan Africa with a GNI per capita below $800 (2013) [33,36]. Overall levels of child mortality are high in this setting [34]. Blantyre, the largest city in the country, hosted clinical trials during the licensure program of HRV, reporting an efficacy rate of 49% against severe RVGE in the first year of life [48]. Gavi supported the introduction of HRV into Malawi's NIP in October 2012 on a 6- and 10-week schedule, offering an ideal opportunity to assess the translation of efficacy into impact and effectiveness in a single setting [50].

Despite the relatively recent introduction into the vaccination program, RV coverage rates in age-eligible children in Blantyre were 26% in 2013, rising to 92% by 2014 [50]. In an impact study conducted in Blantyre between October 2012 and June 2014, an important reduction in RV hospitalizations – 43.2% in children aged <12 months, compared with 2012 – was noted, suggesting that RV vaccination can have a rapid and substantial impact in such settings (Table 2) [50]. The same authors also conducted a case–control study to assess vaccine effectiveness in Blantyre. Vaccination rates were compared in laboratory-confirmed diarrheal cases against both RV test-negative controls and community controls. The effectiveness of two doses of HRV against acute RVGE was 63–64%, depending on the control group used in the analysis (Table 1) [50]. For severe disease (Vesikari

Table 3. HRV efficacy against severe RVGE and effectiveness against RVGE hospitalization in studies conducted in African countries.

	Study (year)	First year	Second year	Overall 2-year period	Ref.
South Africa	Efficacy Madhi *et al*. (2010), Madhi *et al*. (2012)	77% (56–88)	40% (−204–87)	59% (1–83)	[40,41]
	Effectiveness[†] Groome *et al*. (2014)	66% (46–79)	60% (21–80)	63% (45–75)	[39]
Malawi	Efficacy Madhi *et al*. (2010), Cunliffe *et al*. (2012)	49% (19–68)	18% (−59–56)	38% (9.8–57)	[40,51]
	Effectiveness[‡] Bar-Zeev *et al*. (2015)	NA	NA	63% (23–83)[§]	[50]

[†]Case–control study design using respiratory controls.
[‡]Non-diarrhea controls.
[§]Vaccine effectiveness calculated for the 6-month January–June period across 2013 and 2014.
CI: Confidence interval; NA: Not available; RVGE: Rotavirus gastroenteritis.

score ≥11), HRV effectiveness was slightly higher, at 68% for both control groups.

Similar to the experience with HRV in South Africa, vaccine effectiveness was notably higher in Malawi than previous estimates of the efficacy of the vaccine in the country (Table 3). As discussed earlier for South Africa, this observation may be explained by differences in the vaccine schedules used in the two types of study. HRV was introduced into Malawi's Expanded Program on Immunization, to be given with oral polio vaccine (OPV) at 6 and 10 weeks. In contrast, a later vaccine schedule was given to half of the vaccine recipients in the clinical efficacy study (one group received three doses of vaccine at 6, 10 and 14 weeks and one group received two doses of vaccine at 10 and 14 weeks), leaving 4 additional weeks in which 50% of vaccine recipients were vulnerable to RV infection prior to the first dose [50,51].

Furthermore, the reported vaccine effectiveness estimates are based on administration of the indicated two-dose HRV schedule, whereas the original efficacy studies pooled data from infants receiving two or three doses of HRV. The use of a three-dose vaccine schedule was included in clinical trials to overcome previous experience with HRV vaccines, where lower efficacy was observed in less-developed settings compared with developed countries [52]. It is reassuring to note that the vaccine effectiveness studies here demonstrate a high protective effect of HRV in the first 2 years of life using a two-dose schedule.

Preliminary data from Malawi are as yet unclear as to whether a herd effect is seen in this setting [50].

Serotype-specific effectiveness by setting

It is clear that HRV offers protection beyond the vaccine strain (G1P[8]), with both efficacy and effectiveness studies demonstrating robust protection against a range of homotypic and heterotypic RV types worldwide (Box 1) [53–55]. Nevertheless, there may be some degree of variation in the strength and/or nature of protection afforded by the vaccine against more phylogenetically divergent RV types.

The case–control study conducted in South Africa examined HRV performance by vaccine serotype. Vaccine effectiveness was high against the dominant, partially heterotypic, strain G12P[8] (71% [95% CI: 55–82]) and against any homotypic or partially heterotypic strains (62% [95% CI: 45–74]) and slightly lower against any fully heterotypic strains (52% [95% CI: 20–72]) (Figure 3) [39]. The study findings from Malawi were similar: two-dose HRV effectiveness was highest against G1 types and slightly lower for G2 and G12 strains (Figure 3) [50].

Safety of RV vaccines

No review of RV vaccination is complete without due consideration of vaccine safety, specifically regarding intussusception. All RV vaccines are rigorously monitored during the clinical development program, and post-licensure, for signs of an associated risk with the condition. This specific caution is warranted following previous experience with the tetravalent rhesus-human reassortant vaccine (RRV-TV) *Rotashield*® in the 1990s, which was withdrawn from market after such an association was found [56,57].

The incidence of intussusception increases from the age of 2 months, peaking between the ages of 4 and 6 months, after the recommended age for RV vaccination [58]. A literature review estimated intussusception incidence in Africa to be 56 per

Box 1. Definition of homotypic and heterotypic protection.

- Homotypic protection (derived from the Greek 'homós', meaning 'same') is the ability of a vaccine to protect against rotavirus strains that contain at least one of the G- or P-types contained in the vaccine strain (i.e., in the case of HRV protection against a G1P[x] or GxP[8] strain).
- Heterotypic protection (derived from the Greek 'héteros', meaning 'different') is the ability of a vaccine to protect against rotavirus strains that share neither the G- nor P-type(s) in the vaccine strain(s).

	Strain	Vaccine effectiveness, %	95% CI
Africa			
Homotypic or partially heterotypic			
South Africa [Groome *et al.* 2014]	G12P[8]	*71*	*55–82*
	Any serotype	*62*	*45–74*
Malawi [Bar-Zeev *et al.* 2015]	G1	*82*	*42–95*
		78	8–95
Heterotypic			
South Africa [Groome *et al.* 2014]	Any serotype	*52*	*20–72*
Malawi [Bar-Zeev *et al.* 2015]	G2†	*53*	*–28–83*
		61	–29–88
	G12‡	*53*	*–99–89*
		61	–208–95

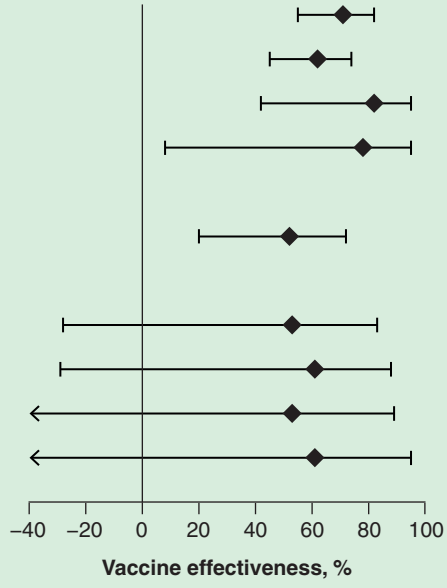

Figure 3. HRV strain-specific effectiveness in Africa during the first two years of life.
Italicised text denotes RV-negative controls, non-italicised text indicates non-diarrhea controls [39,50].
†G2P[4] and G2P[6] were the dominant G2 types identified.
‡G12P[6] was the dominant G12 type identified.
CI: Confidence interval.

100,000 in children aged <1 year, which was comparable to the calculated worldwide incidence of 74 per 100,000 [58]. Determining a true epidemiological picture of intussusception in Africa can be challenging due to limited access to diagnostic equipment, and while the majority of countries worldwide rely predominantly on radiographic modalities for diagnosis of intussusception, 65% of reported cases in Africa were diagnosed based on clinical findings or surgery [58].

The low natural incidence of intussusception in the age range for vaccination requires large numbers of cases to be monitored to detect any possible causal association [57]. Extensive post-marketing surveillance studies performed in the US and Australia have detected a small increased risk of intussusception of RV vaccines (HRV and HBRV) in the range of up to 6 cases per 100,000 infants vaccinated, mostly within 7 days of dose 1 vaccination, and to a lesser extent dose 2 [59]. This potential risk is supported by a recently published meta-analysis of five surveillance-based studies into confirmed cases of intussusception, indicating a relative risk of 5.4 (95% CI: 3.9–7.4, three studies) for HRV and 5.5 (95% CI: 3.3–9.3, three studies) for HBRV during the 7 days post-dose 1. During the 7 days post-dose 2, the relative risk of intussusception was 1.8 (95% CI: 1.3–2.5, four studies) for HRV and 1.7 (95% CI: 1.1–2.6, three studies) for HBRV [60]. The similarity in risk with both licensed vaccines suggests that intussusception appears to be a class effect of RV vaccination. However, a post-marketing surveillance study conducted in Australia did not find an overall excess in cases of intussusception in children between 1 and <9 months of age, despite the increased risk of developing intussusception within 7 and 21 days of vaccine receipt [61]. These observations suggest that any temporal increase in intussusception presentation in younger children triggered by vaccination may be counterbalanced by a subsequent decrease in recorded cases in older age groups. It may be that RV vaccination triggers the premature development of intussusception in children who would have developed intussusception at a later age. It is to be noted that the same study found no difference in clinical outcomes between children who developed intussusception within 21 days of vaccination and those who developed intussusception more than 21 days after vaccination [61]. The overall benefits of RV vaccination in terms of prevention of mortality, hospitalization and the requirement for medical attention, as demonstrated in clinical studies, far exceed the risk of intussusception [8].

Exploration of why vaccine performance varies by setting

It still remains clear that vaccine efficacy and vaccine effectiveness against RVGE is lower in the most resource-deprived areas compared with the rich countries of the industrialized world. The reasons for lower efficacy and effectiveness compared with more developed settings have often been postulated to stem

from a variety of factors that may affect vaccine immunogenicity and effect, including concurrent OPV administration [62]; enteric co-infections and the gut microbiota [63]; malnutrition [52]; breastfeeding [64]; genetic susceptibility to RV infection and disease [65,66]; high levels of natural immunity at younger ages owing to high natural infection [42,43]; and younger age of first infection [67].

It is characteristic of live, oral vaccines to demonstrate greater efficacy in developed countries than in less-developed countries, a phenomenon that has been speculated to occur with OPV vaccine and with the earlier RRV-TV formulation of RV vaccine [52,68]. A trend for lower immune response to RV vaccines has been observed when co-administered with OPV, a vaccine frequently used in less-developed settings instead of inactivated polio virus vaccine (IPV) due to the risk of circulating wild-type polio, but which is rarely used in developed settings [62]. Immunogenicity studies in South Africa recorded a higher anti-RV antibody seroconversion rate post-dose 1 when HRV was co-administered with IPV compared with co-administration with OPV [69]. This difference in seroconversion rates tended to be overcome with a second vaccine dose given at 14 weeks (with the first dose given at 10 weeks), and to a slightly lesser extent for infants given their second dose at 10 weeks (with the first dose given at 6 weeks). After the second HRV dose, there was no statistically significant difference in anti-RV antibody titers between the vaccine groups in this study. Despite the diminution of first-dose RV vaccine immunogenicity with OPV observed in South Africa, vaccine efficacy using a 2-dose 6-13-week schedule was similar between Latin American studies administering HRV with or without concurrent OPV [70,71]. Both the efficacy studies [40,51] and the effectiveness studies in Malawi and South Africa [35,39] involved concomitant HRV and OPV administration. Thus, OPV interference may partly explain reduced efficacy in some less-developed regions, but this is currently uncertain.

It has been suggested that high levels of neutralizing immunoglobulin A antibodies in breast milk can interfere with vaccine immunogenicity [64]. Even at low titers, neutralizing antibodies against RV can reduce vaccine strain titers by up to 80% [72]. However, more recent studies have challenged the contribution of breastfeeding to antibody response or conversion rate [73]. Despite differing proportions of infants receiving breast milk, vaccine effectiveness was similar in Malawi (>90% breastfed during study participation) and South Africa (approximately 37% formula-fed only), suggesting that difference in vaccine effectiveness cannot be explained by breastfeeding practices alone [39,50].

The age of first RV infection is perhaps the most convincing explanation for discrepancies in vaccine efficacy and effectiveness between more-developed and less-developed settings. RV vaccines are expected to be most effective when administered to RV-naïve infants, before natural immunity is induced by an episode of RVGE. The age of first RVGE episodes has been linked to the GNI of a country, with higher levels of early infection found in low-income countries compared with middle/high-income countries [43]. For example, in Malawi, the majority (77%) of RV infections occur in children aged <1 year [67]. This is in contrast to European countries where the peak of infection occurs in the 6- to 23-month age group [74]. Indeed, comparisons between Phase II and III efficacy studies with HRV are supportive of a higher incidence of RVGE in unvaccinated children in Africa than in Europe during the first year of life [42]. At the country-specific level in Africa, pre-dose 1 (approximately 6 weeks of age) anti-RV seropositivity rates were similar between South Africa (12.2% [11/90]) and Malawi (10.4% [7/67]), but after the completion of the last placebo dose (8–21 weeks of age) there was an apparent difference in the seropositivity rates in South Africa and Malawi (18.8% [172/917]) vs 38.0% [176/463]) [42]. Therefore, age of first RV infection is an important consideration for the timing of vaccination schedules. In settings with high levels of early natural infection, an early vaccination schedule before the onset of natural disease, and high compliance with the first dose, is crucial for the full protective effect of vaccination to be realized.

Vaccine success may be limited by exogenous factors inherent in less-developed settings. The rationale for RV vaccination is predicated on the protective effect of natural RV infection against future RV disease; Velazquez *et al.* found that, in Mexican children, two natural RV infections confer 83% efficacy against all-severity RVGE, regardless of serotype, and virtually 100% protection against moderate-to-severe RVGE [75]. This premise does not appear to apply in all settings and situations. A study performed in a deprived setting in India found that a first and second RV infection was only 39% and 52% protective against subsequent RV events, respectively [76]. In the same study, a first RVGE event did not reduce the severity of a second infection, while severity did decrease between a second and third infection [76].

In areas of poor sanitation, increased fecal–oral bacterial exposure has been postulated to affect the gut microbiota, altering the immune response to orally-delivered vaccines [63]. Therefore, immunity arising as a result of natural infection(s) and vaccination is likely limited to some extent by the degree to which a child's defenses are stretched by their environment.

Outstanding questions still to be addressed

RV vaccines have great potential to combat the high mortality from RVGE in less-developed settings, potentially saving an estimated 300,000 infant and child lives each year [77]. Despite these high expectations of RV vaccination, there are no data as yet on reductions in mortality from RVGE in the post-vaccine era in Africa.

Hospitalization rates are an important proxy for assessing the prevalence of severe diarrheal disease. Despite varying vaccine coverage rates and the contribution from other enteric pathogens, substantial reductions in hospitalization rates from all-cause diarrhea have been observed in a variety of settings in Africa, indicating the high disease burden from RV-specific GE in this region. Hospitalizations from RVGE in Malawi declined dramatically in the years immediately following RV introduction, with the most pronounced reductions observed in age-eligible children aged <12 months.

Differences in circulating strains in Africa give perspective on the suitability of RV vaccines to protect against future secular trends in strains. Previously, HRV demonstrated efficacy against diverse strains in Africa [78]. Real-world data from South Africa and Malawi support this trend for vaccine performance against non-vaccine serotypes, with HRV demonstrating 62–82% effectiveness against homotypic or partially heterotypic strains and 52–61% effectiveness against fully heterotypic strains [39,50]. Due to overlapping CIs in the vaccine effectiveness point estimates, further evidence is required before it can be determined if there is any meaningful strain-specific variation in HRV performance.

The benefit of RV vaccination may also extend into older unvaccinated age groups by interrupting transmission of the virus through the vaccinated infant population. Herd effect may be difficult to quantify or prove, but preliminary evidence exists that supports the benefits of RV beyond the age-eligible population in other regions of Europe and Latin America. Whether herd effect increases the value of RV vaccination in Africa – a region noted for the early age of first RV infection and high transmission rates – is yet to be documented, although impact data from South Africa suggest this is a possibility. If substantiated, herd effect is another important factor to consider in the economic evaluation of the cost–benefit of RV vaccine introduction.

Vaccine performance should continue to be evaluated for other African countries as more data are released from this region. The African RV Surveillance Network has been set up to monitor RV disease burden and to track the impact of RV vaccination in early-adopting countries. This initiative is expected to increase the release of data on RV impact in these settings, which should further inform policy-makers on the value of RV vaccines [79,80].

There are some limitations to the studies reviewed here. Temporal fluctuations in RVGE disease burden complicate assessment of the relationship between changes in disease trends and implementation of vaccination programs; therefore, studies carried out over a number of RV seasons represent the strongest evidence to support the hypothesis that vaccination is responsible for observed trends. For many of the countries reviewed here, HRV is a relatively recent addition to the vaccine schedule; as such, the studies coming out of these countries give only a preliminary indication of the potential impact of this vaccine, and further monitoring and reporting of long-term changes in disease levels is warranted. More extensive longitudinal analysis of disease trends in the pre-vaccine versus post-vaccine era will also delineate reduced RV incidence attributable to vaccination from exogenous factors that may also have decreased the disease burden (for example, improvements in child nourishment or access to clean water). Countries have been classified by income level based on gross domestic product or GNI, which are only a proxy of a country's economic status and a crude measure of healthcare expenditure and people's access to healthcare services. Comparison by country-level income status may not reflect the often substantial variability in socioeconomic status at the local level that is likely to affect vaccine performance.

Conclusion

Data from the first countries to adopt HRV vaccination in Africa and other less-developed settings across the world are highly promising and strongly supportive of the health benefits to be gained from RV vaccination. In addition, the vaccine impact and effectiveness studies reviewed here reveal additional benefits of RV vaccination in Africa, including sustained effectiveness during the first 2 years of life, which could not have been foreseen based on earlier efficacy studies conducted in the region and worldwide. These data are encouraging for other countries from a similar setting who may be considering introducing RV vaccination. The establishment of robust surveillance networks in the African region will further contribute to the body of evidence evaluating the benefits of RV vaccination.

Expert commentary

RV vaccines represent an important advance in vaccinology of the past two decades. The pivotal Phase III clinical trials of the two vaccines currently licensed worldwide, HRV and HBRV, demonstrated high efficacy against moderate-to-severe RVGE and acceptable safety profiles against intussusception. Now Phase IV trials have elucidated the real-world potential of RV vaccination for reducing the burden of RVGE disease. The observed lower efficacy/effectiveness in less developed environments is most probably a multifactorial consequence of early and repeated exposure to high inoculums of RV, overburden of the immune system from co-infections, some degree of oral poliovirus vaccine competition and possibly some breastfeeding interference, among other factors. Nevertheless, the effectiveness observed in African countries is an encouraging early indicator of the potential for these vaccines to fulfill the goal of reducing childhood rotaviral disease in those areas of the world with the greatest risk of diarrhea mortality and severe morbidity. There continues to be some space for improvement in effectiveness, potentially through adjustment of vaccine schedules for early completion and avoidance of co-administration; the feasibility of this approach in resource-limited countries may be an important limitation. The broad protection offered by RV vaccines beyond vaccine serotypes suggests that RV vaccination will continue to remain effective in the face of evolving trends in strain prevalence [81]; vaccine serotype circulation will need to be monitored in order to detect possible unexpected serotype shifts, a phenomenon that has not been observed to date. Ten years after rotavirus vaccine licensure, the overall RV vaccination strategy continues to be promising, especially after the good news that is being provided from low-resource regions such as Africa.

Five-year view

Increased vaccine use in low-resource countries should continue to occur during the next 5 years as a significant number of countries have not yet adopted RV vaccination. A novel vaccine candidate, derived from a pediatric strain isolated in India, was licensed in 2014 in India (ROTAVAC™, Bharat Biotech), and is likely to be adopted in this country. Phase IV evaluations of this vaccine will be required to determine its effectiveness in

real-world settings and safety profile. Adjustment of vaccine schedules may be implemented in low-resource areas if deemed effective, including earlier doses, separation from polio vaccines and spacing with breastfeeding practice, among others. However, pragmatic scheduling decisions to facilitate widespread vaccine access may need to supersede the optimization of individual vaccine delivery. Although not expected within the next 5 years, new vaccine candidates targeting more than one enteric pathogen, possibly administered parenterally, may become available for early clinical research trials. Conversely, including additional serotypes in an oral vaccine formulation does not seem to be a current priority based on the heterotypic effectiveness observed with RV vaccines. Continued surveillance of the genetic epidemiology of RV in conjunction with ongoing vaccine effectiveness monitoring will determine whether additional serotype formulations become warranted in the future.

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Key issues

- There are currently two widely licensed live, attenuated orally administered rotavirus vaccines. *Rotarix*® (human rotavirus vaccine [HRV]) – a two-dose vaccine based on a single RV strain of the most commonly observed human genotype, G1P8, and *RotaTeq*® a three-dose, human–bovine reassortant vaccine (HBRV) containing five different strains.
- As of March 2015, 28 countries in Africa have included RV vaccination in their NIPs (22 using HRV and six using HBRV). In 2009, South Africa became the first African country to introduce RV vaccines, and the first Gavi-funded RV vaccination program in Africa was rolled out in Sudan in 2011.
- Few studies have assessed the field effectiveness of HRV vaccination in lower-income settings; three African countries (South Africa, Ghana and Malawi) have now performed impact and effectiveness studies.
- There are two common methodologies used to assess the real-world performance of RV vaccines: Ecological (impact) studies, which monitor outcome trends over time, and case–control (effectiveness) studies, which compare the frequency of vaccination exposure among patients with RV disease and RV disease-free controls.
- European countries report HRV effectiveness of approximately 90% or more against RV gastroenteritis (RVGE) hospitalization compared with 76–96% in upper-middle-income and 76–77% in lower-middle-income countries.
- Current coverage rates in African countries range from 78% in Botswana to 99% in Rwanda.
- South Africa introduced HRV in August 2009 on a 6- and 14-week two-dose schedule. Three studies have reported 38–43% and 61–69% reduction in all-cause GE and RVGE, respectively, in children aged <12 months compared with 2009 data. Field effectiveness of HRV appears to be sustained in the 12- to 23-months age group.
- Ghana introduced HRV in May 2012 on a 6- and 10-week schedule. Surveillance data from two pediatric referral hospitals reported a decline in child hospitalizations from all-cause diarrhea by 51.6% from 2011 to 2012, and by a further 16.2% from 2012 to 2013. The proportion of diarrheal hospitalizations attributable to RVGE fell from 49.7–27.8% and for the <11 month olds from 73% to 46%.
- Malawi introduced HRV in October 2012 on a 6- and 10-week schedule. Pre-licensure clinical trials in Blantyre reported 49% efficacy against severe RVGE in the first year of life. A post-licensure impact study reported a 43.2% reduction in RV hospitalizations in children aged <12 months, while effectiveness of two doses of HRV against acute RVGE was approximately 64%.
- Similar to the experience with HRV in South Africa, vaccine effectiveness was notably higher in Malawi than previous estimates of the efficacy of the vaccine in the country.
- Efficacy and effectiveness studies have demonstrated robust protection against a range of homotypic and heterotypic RV types worldwide; nevertheless, there may be some degree of variation in the strength and/or nature of protection afforded by the vaccine against more phylogenetically divergent RV types.
- Determining a true epidemiological picture of intussusception in Africa will be challenging due to limited access to appropriate diagnostic equipment.
- The age of first RV infection is perhaps the most convincing explanation for discrepancies in vaccine efficacy and effectiveness between more developed and less developed settings.
- Data on reductions in mortality from RVGE in the post-vaccine era are still lacking in Africa.
- Whether herd effect increases the value of RV vaccination in Africa is yet to be documented, although impact data from South Africa suggest this is a possibility.
- Studies utilizing data from the African RV Surveillance Network initiative are expected to increase our current knowledge on RV impact in these settings.

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