

# Impact of rotavirus vaccination on childhood gastroenteritis



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**Rotaviruses are the most common cause of severe childhood gastroenteritis worldwide. The recent development of safe and effective rotavirus vaccines means that the global health and economic burden of rotavirus disease can now be reduced.**

## Disease burden and impact

By age five years, virtually all children will have had at least one rotavirus infection. Each year, rotaviruses cause more than 450,000 deaths in children aged under five years, comprising over a third of worldwide deaths due to diarrhoea and 5% of all deaths in this age group<sup>1</sup>. Most deaths occur in low- and middle-income countries<sup>1</sup>.

Whilst deaths from rotavirus infections are rare in high-income countries, the incidence of disease is similar to children from lower income countries. This results in a substantial health system and economic burden, especially as rates peak each winter and spring during the annual respiratory virus season. For example, in the pre-vaccine era in Australia there were approximately 10,000 hospitalisations, 22,000 emergency department presentations and 115,000 general practice consultations for rotavirus annually among children aged under five years<sup>2</sup>. Importantly, Indigenous Australians have substantially higher rates of disease than the general population, with approximately five times the

hospitalisation rate during infancy and a longer average length of stay<sup>3</sup>.

Despite most severe disease outcomes occurring in low- and middle-income countries, most measured costs are direct medical costs and lost parental wages in high-income countries. The pre-vaccine era annual health care and societal cost in the United States was estimated at US\$893 million for 2004<sup>4</sup>, while in Australia direct medical costs were A\$30 million in 2005–2006<sup>2</sup>.

## Licensed vaccines

Rotaviruses can be classified according to two surface proteins, VP7, a glycoprotein (G-protein), and VP4, a protease-cleaved protein (P-protein). Both are targets for neutralising antibodies. However, cross-protection amongst different G and P-types might also be mediated by immune responses to shared epitopes amongst several viral proteins. Globally, G1-G4 and G9 are the most common VP7 genotypes, while P[4], P[6] and P[8] are the most prevalent VP4 genotypes<sup>5</sup>.

Two licensed vaccines are available currently. Each was developed according to different biological principles to achieve protection. Both are live-attenuated, orally administered vaccines, but vary in their virus components and schedule (Table 1). The human strain rotavirus vaccine (RV1; Rotarix®, GlaxoSmithKline) contains

a single, live, attenuated human rotavirus strain, which is intended to induce both homotypic and heterotypic protection. In contrast, the pentavalent rotavirus vaccine (RV5; RotaTeq®, Merck & Co Inc/CSL Biotherapies) contains five human-bovine reassorted rotavirus strains and relies more heavily upon inducing homotypic protective immunity.

Rotavirus vaccines were included in the publicly funded Australian National Immunisation Program in July 2007, with an earlier introduction in the Northern Territory in October 2006. Both vaccines have strict administration timetables (Table 1). Catch-up dosing is not recommended as safety data in older age groups are lacking, with a theoretically increased risk of intussusception if doses are given beyond the recommended age limits. Both rotavirus vaccines can be administered safely with other routinely delivered childhood vaccines.

## Efficacy

Trials to determine the efficacy of RV5 and RV1 have been undertaken in several countries (Table 2). Although no direct comparisons can be made between the two vaccines because of differences in subject populations and clinical endpoints, both vaccines appear to perform similarly against different rotavirus strains in various settings. Vaccine efficacy in high- and middle-income (Latin American) countries was highest against severe

rotavirus gastroenteritis, providing 83–98% protection in the first rotavirus season post-vaccination and maintaining similar levels of protection against severe disease over the following one-to-two seasons<sup>8–12,16</sup>. The definition of ‘severity’ varied according to study, but included severity grading according to one of two different clinical scoring scales (Vesikari or Clark)<sup>17</sup>, or the need for overnight admission to hospital or rehydration therapy. In addition, both vaccines also provided 74–87% protection against rotavirus diarrhoea of any severity in the first rotavirus season post-vaccination<sup>8,9</sup>, and decreased ‘all-cause’ gastroenteritis hospitalisations by 39–72%<sup>8,9,11,12</sup>.

In contrast, vaccine efficacy was initially reduced and poorly sustained in middle- and low-income African and Asian settings. Protection provided by RV1 against severe rotavirus gastroenteritis disease during infancy was 77% (95% confidence interval [CI]: 56,88) in South Africa and 49% (95% CI: 19,68) in Malawi<sup>13</sup>. Meanwhile RV5 field trials in Africa and Asia demonstrated efficacy against severe disease of 64% (95% CI: 40,79) and 51% (95% CI: 13,73) in the first year of life, and 20% (95% CI: -16,44) and 45% (95% CI: 1,71) in the second year of life, respectively<sup>14,15</sup>.

The findings from Malawi demonstrate the important distinction between efficacy and impact. While relative efficacy was lower in Malawi compared to South Africa, the absolute impact in

Table 1. Properties and dose schedule of currently licensed oral live-attenuated rotavirus vaccines.<sup>6</sup>

	RV1	RV5
Trade name	Rotarix®	RotaTeq®
Origin	1 human strain G1P[8]	5 human-bovine reassortment strains with human serotypes G1, G2, G3, G4, and P[8]
Biological principles*	Heterotypic immunity	Homotypic immunity
Presentation	Oral liquid stored at 2–8°C	Oral liquid stored at 2–8°C
Number of doses	2 (1.5 mL per dose)	3 (2 mL per dose)
Administration	1st dose: 6 to <15 weeks 2nd dose: ≥4-week interval at 10 to <25 weeks	1st dose: 6 to <13 weeks, next doses at 4- to 10-week intervals, completed by <33 weeks

\* RV1 relies upon a single, human-derived rotavirus strain inducing protective heterotypic immunity against all other strains, while RV5 uses 5 bovine-human reassortant strains to induce serotype-specific (homotypic) immunity against the most commonly circulating strains (G1P[8], G2P[4], G3P[8], G4P[8] and G9P8) worldwide.

Table 2. Rotavirus vaccine efficacy for severe gastroenteritis in the first year of life across high-, middle- and low-income countries (modified from WHO<sup>7</sup> with permission).

Setting	Efficacy	Main country where phase III trials performed
High-income	96–98%	North America <sup>8</sup> , Western Europe <sup>8,9</sup> , Singapore <sup>10</sup> , Taiwan <sup>10</sup> and Hong Kong <sup>10</sup>
Middle-income	72–85%	Latin America <sup>11,12</sup> , South Africa <sup>13</sup> , and Vietnam <sup>14</sup>
Low-income	46–64%	Ghana <sup>15</sup> , Kenya <sup>15</sup> , Mali <sup>15</sup> , Malawi <sup>13</sup> and Bangladesh <sup>14</sup>

terms of severe rotavirus gastroenteritis cases prevented, was greater in Malawi (6.7 vs 4.2 cases prevented per 100 vaccinees) due to a higher disease burden and year-round circulation of the virus<sup>15</sup>. Thus, despite lower efficacy, the potential impact of rotavirus vaccine reducing morbidity and mortality is greatest in low-income countries. Reasons for lower immunogenicity and efficacy of live-attenuated oral rotavirus vaccines in low-income settings remain unknown. These are, however, likely to involve multiple host and environmental factors such as interference by maternal antibodies in blood and breast-milk, coexistent enteric infections, chronic illness, malnutrition and difficulties maintaining the cold chain<sup>18</sup>.

### Post-licensure effectiveness and impact

Since 2006, rotavirus vaccines have been licensed in over 125 countries and included in the national vaccination schedules of 28 predominantly high- and middle-income countries worldwide<sup>19</sup>. A detailed review of published post-licensure studies is beyond

the scope of this article. Tables 3 and 4 summarise a selection of major studies describing the effectiveness and impact of rotavirus vaccines respectively across high- and middle-income countries. Both vaccines appear to have direct and indirect effects on rotavirus disease patterns, with the real-world findings broadly consistent with the efficacy studies for different settings. As with efficacy studies, comparisons of effectiveness estimates are limited by differences in study design, including selection of controls, setting and period of observation.

Studies on RV5 vaccine effectiveness in high-income settings report effectiveness of 89–100% against hospitalisation for rotavirus gastroenteritis<sup>24–26</sup>. In contrast, mixed results were found for RV1 effectiveness in Australia. Two studies undertaken during outbreaks predominantly affecting Aboriginal children in Central Australia found effectiveness against hospitalisation for infants to be 85% during a G9P[8] outbreak, but in a subsequent outbreak of a non-vaccine related strain G2P[4], the vaccine was found only to provide a significant protective effect in a subset

Table 3. Major post-licensure studies on effectiveness of rotavirus vaccines against rotavirus hospitalisation and/or emergency department visits among children under five years of age across high- and middle-income countries.

Setting	Effectiveness (%)	Country where study undertaken
<b>RV1</b>		
High-income	19–85%	Australia <sup>20,21</sup> (largely Indigenous population)
Middle-income	76%	Brazil <sup>22</sup> and El Salvador <sup>23</sup>
<b>RV5</b>		
High-income	89–100%	Australia <sup>24</sup> , France <sup>25</sup> and United States <sup>26</sup>
Middle-income	43%	Nicaragua <sup>27</sup>

Table 4. Major post-licensure studies on impact of rotavirus vaccines across high- and middle-income countries.

Setting	Coverage	Comparison of 2–3 years post-vaccine introduction vs pre-vaccine era
<b>Impact on RV hospitalisations or ED visits</b>		
<b>High income</b> Australia <sup>28</sup> , Belgium <sup>29</sup> , USA <sup>30,31</sup>	Up to 90%	74–90% decline in children <2 years of age 41–80% decline in children 2<5 years of age
<b>Impact on 'all-cause' AGE hospitalisations</b>		
<b>High income</b> Australia <sup>28</sup> , USA <sup>30,31</sup>	Up to 82% for 12-month-olds	29–50% decline in children <5 years of age
<b>Middle income</b> Brazil <sup>32</sup>	Up to 81% of children <1 year of age	17% decline in children <5 years of age
<b>Impact on diarrhoea-related mortality</b>		
<b>Middle income</b> Brazil <sup>32</sup> , Mexico <sup>33</sup>	Up to 89% of children <2 years of age ≥1 dose	22–46% decline in children <5 years of age

Abbreviations: AGE, acute gastroenteritis; ED, emergency department; RV, rotavirus.

of infants with disease complicated by acidosis<sup>20,21</sup>. Interestingly, in middle-income Latin American countries, both vaccines provided 43–76% protection against rotavirus hospitalisation from various strains, including G2P[4], but as in Central Australia, this effectiveness waned after infancy<sup>22,23,27</sup>.

Introducing rotavirus vaccines into national immunisation schedules has been associated with substantial and significant declines in morbidity and mortality. Reductions of up to 46% of diarrhoea-related mortality in children under five years have been found in Latin American countries<sup>32,33</sup>. Declines in health care utilisation for both rotavirus and ‘all-cause’ gastroenteritis have been described across Europe, United States, Australia and Brazil<sup>24,28–32</sup>. In an Australian study, a reduction of 87% in nosocomial infections was identified following vaccine introduction<sup>34</sup>. Whilst the impact is greatest among children under two years of age, herd protection is believed responsible for reductions among largely unvaccinated age groups by presumably reducing transmission opportunities within the community<sup>24,27–31,34,35</sup>. Common across European, the United States and Australian settings, have been delays in onset with loss of seasonality and attenuation of the annual winter/spring rotavirus epidemics<sup>29,31,34</sup>.

## Intussusception

The first licensed rotavirus vaccine, RotaShield (Wyeth Laboratories) was withdrawn controversially after it was found to be associated with an increased risk of intussusception. The excess risk was approximately 1 case in 10,000 vaccine recipients<sup>36,37</sup>. Subsequently, the large-scale phase III safety trials undertaken in middle and high countries involving more than 140,000 subjects, found no elevated risk of intussusception during the 42-day and 30-day periods after vaccination, with RV5 and RV1, respectively<sup>8,10,12</sup>. In Australia, post-marketing surveillance reported no overall increase in intussusception with either vaccine, although there was some evidence of increased risk in infants aged 1 to <3 months within seven days (RV5: RR 5.3, 95% CI 1.1,15.4; RV1: RR 3.5, 95% CI 0.7,10.1) and within 21 days (RV5: RR 3.5, 95% CI 1.3,7.6; RV1: RR 1.5, 95% CI 0.4,3.9) of receiving dose 1 of either vaccine<sup>38</sup>. A post-licensure case-control study involving surveillance at 69 hospitals in Mexico and Brazil found RV1 was associated with a short-term risk of intussusception in approximately 1 in 51,000 to 68,000 vaccinated infants<sup>39</sup>. However, in the context of these countries, the absolute number of deaths and hospitalisations averted greatly exceeded those associated with RV1 vaccination. The risk-benefit analysis found RV1 resulted in an annual excess

of 96 cases of intussusception and five associated deaths, but prevented approximately 80,000 hospitalisations and 1300 deaths from diarrhoea each year across Mexico and Brazil<sup>39</sup>. A recent review assessing the current vaccines has led the World Health Organization to reaffirm its recommendation that rotavirus vaccines should be used globally<sup>40</sup>. Further evidence of rotavirus vaccine safety has come from recent large cohort studies in the United States, which included follow-up of children who received almost one million RV5 doses. Whilst these studies found no increased intussusception risk within 30 days of any RV5 dose received, they would still theoretically fail to detect a risk of intussusception of less than one in 50,000 vaccinated children<sup>41,42</sup>.

## Future

Whilst high- and middle-income countries have largely benefited from rotavirus vaccines, it is in lower-income African and Asian countries where greatest gains are to be made. With donor support, the Global Alliance for Vaccines and Immunization plans to introduce rotavirus vaccine into more than 40 low-income countries by 2015<sup>43</sup>. Nevertheless, rotavirus vaccine efficacy needs to be improved in low-income countries. Development of rotavirus vaccines administered at birth may be particularly important in these settings where primary infection occurs early in life and access to health care and routine immunisation services is poor.

Ongoing surveillance is needed to ensure the expected benefits are being achieved, to monitor changes in rotavirus epidemiology, including duration of protection, and to ensure the continued safety and effectiveness of current vaccines<sup>19</sup>. Whilst there is no substantial evidence to date of new strains emerging or a sustained shift in circulating strains occurring attributable to vaccine introduction<sup>19,44</sup>, ongoing surveillance is necessary to monitor rotavirus strain diversity, and the effectiveness of vaccines against them. Meanwhile, widespread implementation of rotavirus vaccines will help reduce the global morbidity and mortality associated with childhood diarrhoea.

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## Biographies

**Professor Keith Grimwood** is Director of the Queensland Children's Medical Research Institute and is an infectious diseases physician at the Royal Children's Hospital, Brisbane. In addition to rotaviruses, his research interests include common viral respiratory infections and lung infection in CF and non-CF bronchiectasis.

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**Dr Sarah Sheridan** is an advanced trainee in public health medicine and is a PhD candidate at the Queensland Children's Medical Research Institute and the School of Population Health, University of Queensland.

## Declaration of interest

Keith Grimwood has been a member of a Rotavirus Advisory Board and received support for conference attendance, lecture fees and a research grant from GlaxoSmithKline; he has also received a research grant from Merck.

Stephen Lambert has been an investigator on research studies funded by Merck, CSL Ltd, and GlaxoSmithKline, although none involving rotavirus vaccines. He has received support for conference attendance and honoraria for advisory board activities from CSL Ltd and GSK.

Sarah Sheridan has no interests to declare.