Early impact of rotavirus vaccination

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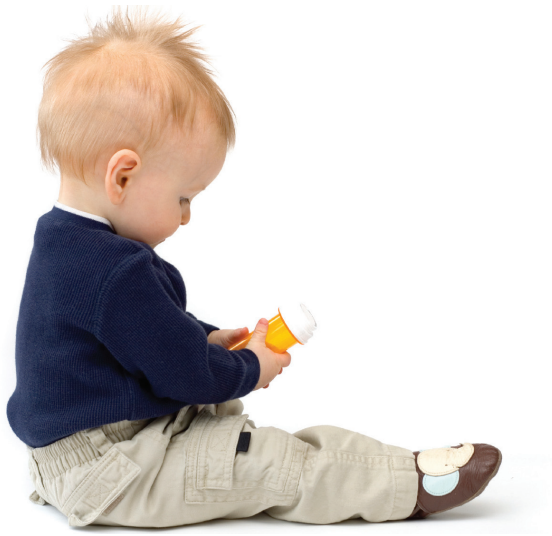
Background: Rotavirus is the most common cause of severe gastroenteritis in children and two vaccines to prevent rotavirus infection have been licensed since 2006. The World Health Organisation recommends the inclusion of rotavirus vaccination of infants in all national immunisation programs. **Aim:** To review current literature evaluating the global impact of rotavirus immunisation programs over the first two years of their implementation. **Methods:** A MEDLINE search was undertaken to identify relevant observational studies. **Results:** Eighteen relevant studies were identified which had been carried out in eight countries. Introduction of the vaccine was associated with a reduction in all-cause gastroenteritis hospitalisation rates of 12-78% in the target group and up to 43% in older groups ineligible for the vaccine. Hospitalisation rates for confirmed rotavirus cases ranged between 46-87% in the target group. Mortality from all-cause gastroenteritis was reduced by 41% and 45% in two countries studied. **Conclusions:** Early research evaluating rotavirus immunisation programs suggests significant decreases in diarrhoeal disease rates extending beyond the immunised group. Further monitoring will allow vaccine performance to be optimised and for the long-term effect of vaccination programs to be assessed.

Introduction

Rotavirus (RV) is the most common cause of severe diarrhoea in infants and young children. It has been reported to cause over two million hospitalisations and half a million deaths annually in children under five, with 85% of deaths occurring in low and middle income countries. [1] In recognition of the high burden of childhood morbidity and mortality, attempts to develop a vaccine against rotavirus have been underway since the early 1980s. Clinical trials of two oral vaccines in middle- and high-income countries demonstrated vaccine efficacy of 85-98% in preventing severe rotavirus gastroenteritis. [2]

The vaccines, RV1 (Rotarix - oral live-attenuated monovalent human rotavirus vaccine; Glaxo Smith Kline Biologicals, Rixensart, Belgium) and RV5 (RotaTeq - oral live human-bovine reassortment multivalent rotavirus vaccine; Merck & Co Incorporated, US) have since been licensed in over 80 countries, and national immunisation programs have commenced in several countries in the Americas, Australasia and Europe. [3] RV1 is a two-dose vaccine which the manufacturer states should be completed by the age of 24 weeks. RV5 is a three-dose vaccine which should be administered before 36 weeks. A previous vaccine, RotaShield (oral rhesus-human tetravalent reassortment vaccine; Wyeth-Ledarle, US) was licensed in 1998 but withdrawn less than a year later due to an association with intussusception.

Until recently no association had been found between either RV1 or RV5 and intussusception in clinical trials or the post-licensure period, [3] but evolving research has cast doubt on the assumption that the RV1 vaccine is entirely safe. Case-series and case-control analysis found a significantly increased risk of intussusception on days 1-7 following



the first dose of the vaccine in Mexico, but not in Brazil. However, the authors concluded that these findings were outweighed by the substantial benefits of rotavirus vaccination programs, and regulatory bodies reviewing the data have recommended that vaccination programs continue, with further monitoring of adverse events to be conducted. [4]

Despite the overwhelming need to address rotavirus rates in low income countries which bear the greatest burden of diarrhoeal disease and mortality, the World Health Organisation (WHO) initially recommended that rotavirus vaccines should only be included in national vaccination programs in countries "where data on vaccine efficacy suggest a significant public health impact." [5] There was concern that, as in the case of previous rotavirus vaccines and other oral vaccines (including polio and cholera), the vaccine may not be as effective in these settings due to a range of host and environmental factors. [6] These concerns were largely allayed by a large phase III trial of RV1 in Kenya and Malawi that found an overall efficacy of 61.2% against severe rotavirus gastroenteritis and 30.2% efficacy against severe gastroenteritis of any cause. [7] While these results were less dramatic than those demonstrated in middle- to high-income countries, they provide hope for a considerable reduction in childhood mortality related to diarrhoeal disease due to the burden of severe disease in similar settings. Studies in other low-income countries are ongoing. The WHO has since recommended the inclusion of rotavirus vaccination of infants into all national immunisation programs, with particular focus on countries where diarrhoeal deaths account for ≥10% mortality among children less than five years old. [5] The Global Alliance for Vaccines and Immunisation (GAVI) will provide financial support for eligible low-income countries to purchase rotavirus vaccines. [6]

Despite the encouraging data provided by the pre-licensure data presented above, continued research is essential to monitor the effectiveness of rotavirus vaccines in real world settings. It is not known how the vaccines will perform under routine public health use, including whether partial vaccination confers protection and whether sustained protection throughout childhood will be achieved. Other questions that remain include whether vaccination of infants will

confer herd immunity and have an indirect effect on older unvaccinated children, and how routine vaccination will impact on the epidemiology of disease including seasonality and serotype distribution. [8] The WHO has issued a policy to guide the monitoring of rotavirus vaccination programs, which advocates use of ecological methods including active surveillance systems (primary sources) or routinely collected data such as hospital discharge data (secondary sources) to assess the impact of the vaccine on the burden of disease in the population. It also suggests that a case-control design may be useful to assess vaccine effectiveness if baseline data is unavailable or if vaccine coverage is not yet high enough for ecological methods to show an impact of the intervention. [2] The first national immunisation programs were launched in 2006 and early evidence of the effectiveness and impact of RV1 and RV5 vaccines is emerging. This evidence will be analysed in this review.

The objective of this review article is to review current literature evaluating the global impact of rotavirus immunisation programs over the first two years of implementation.

Methods

A literature search was conducted using the MEDLINE database with search terms "rotavirus vaccine," "rotavirus vaccination," "RotaTeq" and "Rotarix." Reference lists of identified studies were also checked for relevant additional studies not identified by this search.

Inclusion criteria were:

- Setting: country where national rotavirus immunisation has been initiated
- Date: commencement of immunisation program preceding study period
- Methodology: ecological, surveillance or case control study
- Outcome measure: rotavirus or acute gastroenteritis (AGE) epidemiology (rates of notification, outpatient presentations, hospitalisations, mortality, laboratory results)
- Availability of English language article or translation.

Results were classified by outcome measure, country and data source, with the youngest subgroup for which data is available considered the target group as many of these children would have been eligible for vaccination. Any identified effect on older, unvaccinated age groups was also considered. Where vaccine coverage was recorded it refers to completion of the full vaccine course.

Results

Eighteen relevant studies were identified: seven conducted in the United States (US), six in Central America (Mexico, Nicaragua, Panama, El Salvador), two in Brazil, two in Australia and one in Austria. Studies were conducted between 2007 and 2010 following introduction of national immunisation programs in 2006-2007. Fifteen studies used an ecological methodology. Three were case-control studies. Ten studies were conducted where RV5 was used in local programs, seven assessed RV1 and one country used both vaccines.

The results of all studies, stratified by outcome measure, are presented in Table 1. The varying methodological methods and stage of implementation of the immunisation program prevent direct comparison of all results, so the evidence from each country is summarised below.

Table 1. *Gastroenteritis epidemiology following universal rotavirus vaccination.*

Outcome measure	% Reduction target group (age)	% Reduction in unimmunised (age)	Vaccine type, coverage rate	Study location	Study year	Data source [reference]
Mortality: AGE	41% (<1y)	29% (1-2y)	RV1, 51%	Mexico	2007	Secondary [9]
	45% (<1y)		RV1, 77%	Brazil	2008	Secondary [10]
Outpatient presentations: AGE	28% (<1y)	21% (1-4y)	RV5, 37%	Nicaragua	2007	Secondary [11]
	85% (<2y)		RV5, N/A	Houston, US	2008	Case-control [12]
	85% (<5y)		RV1, N/A	Alice Springs, Australia	2007	Case-control [13]
Hospitalisations: AGE	12% (<1y)	-5% (1-4y)	RV5, 37%	Nicaragua	2007	Secondary [11]
	37% (<5y)		RV1, 72%	Panama	2008	Secondary [14]
	40% (<2y)	36% (2-5y)	RV5, N/A	New York, US	2008	Primary [15]
	48% (<1y)	19% (1-4y)	RV1, 78%	Brazil	2007	Secondary [16]
	50% (<2y)	43% (2-3y)	RV5, 33%	US (18 states)	2008	Secondary [17]
	52% (<1y)		RV1, 74%	Mexico	2009	Primary [18]
	61% (<5y)		RV1, 61%	El Salvador	2009	Primary [19]
	78% (<5y)		RV1, N/A	Alice Springs, Australia	2007	Case-control [13]
Hospitalisations: rotavirus cases	46% (<2y)		RV5, N/A	Nicaragua	2007-08	Case-control [20]
	65% (<2y)		RV5, 75-80%	Queensland, Aus	2008	Secondary [21]
	72% (<18y)		RV5, N/A	Florida, US	2008-09	Primary [22]
	79% (<1y)		Mixed, 72%	Austria	2009	Primary [23]
	86% (<2y)	70% (2-3y)	RV5, N/A	New York, US	2008	Primary [15]
	87% (<18y)		RV5, 50%	Philadelphia, US	2007	Primary [24]
RV Notifications	65% (<2y)	56% (2-4y)	RV5, 75-80%	Queensland, Australia	2008	Secondary [21]
Proportion of positive laboratory results for rotavirus	43%		RV5, 75-80%	Queensland, Aus	2008	Secondary [21]
	58%		RV5, N/A	Florida, US	2008-09	Primary [22]
	69%		RV5, N/A	US	2007-08	Secondary [25]
	86%		RV5, N/A	US	2008-10	Secondary [26]

United States

Post-licensure surveillance began in the United States following the inclusion of RV5 in the national immunisation program in 2006. Analysis of hospital discharge information from 18 states in 2008 found a 45% reduction in AGE hospitalisations, comparable with the 59% reduction found in pre-licensure studies. [17] Similar findings emerged from active surveillance carried out in New York State, Philadelphia and Florida. [15,22,24] A case-control study in Houston found that a complete RV5 series provided 96-100% protection against severe disease requiring hospitalisation or intravenous hydration. This study also assessed partial courses, calculating vaccine effectiveness to be 69% for one dose of the vaccine and 81% for two doses. [12]

There was a 69% reduction in overall positive laboratory results for rotavirus in the 2007-8 season using national data, increasing to 86% by 2008-10. The effect of the vaccine on the seasonality of rotavirus infection was analysed in both of these studies finding that the epidemic season was delayed and substantially shorter than previous years preceding the immunisation program and that by 2009-10 it did not meet the threshold to define the start of the season. [25,26]

Australia

Australian states and territories implemented routine vaccination programs independently, which has resulted in both RV1 and RV5 being used across the country. Queensland introduced RV5 immunisation in infants in July 2007 and by 2008 rotavirus notifications in children less than two years old had declined by 65%. [21] Additionally, the proportion of positive tests had reduced by 43% as compared with 2006. [21] Significant reductions were also seen in older age groups. The Northern Territory began immunising infants with RV1 in late 2006 and a Central Australian rotavirus epidemic in 2007 provided an opportunity to evaluate vaccine effectiveness. The full vaccine course was found to be 78% protective against hospitalisation for gastroenteritis and 85% against confirmed cases of rotavirus. [13]

Central America

Mexico introduced RV1 universally in May 2007. Analysis of hospitalisation rates in 2008-9 found a 40% reduction in gastroenteritis admissions for children less than five years old, most pronounced in infants (89% of whom had been immunised). However, there was no change found among older children who were not immunised. [18] Another study found that diarrhoea-related mortality in infants was reduced by 41% and mortality in children one to two years old also decreased by 29% despite few of these children being eligible for vaccination. [9]

Nicaragua is a low-income country in Central America and was the first GAVI-eligible country to initiate universal rotavirus immunisation in 2006, with the vaccines provided by the manufacturer. Analysis of national data one year after introduction of RV5 vaccination, when 37% of infants had been immunised, demonstrated a 28% reduction in outpatient gastroenteritis presentations and 12% decline in hospitalisations for AGE in children less than one year old. A 21% reduction in outpatient presentations was also found in older children; however, there was a 5% increase in hospitalisations among children aged one to four years in 2007. [11] A case-control study in 2007-8 found vaccine effectiveness of 46% against rotavirus disease requiring admission or intravenous hydration, with stratification of severity identifying increased effectiveness against severe (58%) and very severe (77%) gastroenteritis. [20]

Panama is a middle-high income country which introduced RV1 vaccination nationally in 2006. By 2008, with 72% coverage, there was a 37% reduction in childhood gastroenteritis admissions and a blunting of the seasonal peak. [14]

El Salvador, a low-middle income country in the same region, had a reduction in rotavirus hospitalisation rates of 69% with 69% vaccine coverage. [19]

Brazil

Brazil began national immunisation with the RV5 vaccine in 2006 and assessed the impact of the program using national hospital discharge data in 2007. A 48% decline in AGE hospitalisations was found in infants, slightly greater than the findings of phase III clinical trials of the vaccine in Latin America (39%). Nineteen percent fewer hospitalisations in one to four year olds was also shown, and the greatest decline in both age groups was seen in areas of Brazil with the greatest vaccine coverage. [16] Mortality was assessed in a subsequent study which found that 45% fewer infants died of gastroenteritis in 2008 following initiation of rotavirus vaccination. [10]

Austria

Austria introduced national immunisation for rotavirus in July 2007, initially with RV5 then RV1. Sentinel surveillance found a decrease in hospitalisations for rotavirus gastroenteritis of 79% in the target population, with significant reductions seen in unimmunised children: 47% fewer cases among of children less than three months, 38% reduction among five to fifteen year olds. [23]

Discussion

These results represent the preliminary outcomes of national rotavirus immunisation programs and demonstrate real-world effectiveness of the two licensed rotavirus vaccines. Within three years of implementation, a significant reduction in the burden of diarrhoeal disease is evident among the infant population eligible to receive the vaccine. Confirmation that RV1 and RV5 provide significant protection against hospitalisation for AGE in a real-world setting suggests that substantial gains could be made in reducing the global burden of diarrhoeal disease once the vaccine is widely distributed.

Four of nine studies assessing hospitalisation relating to all-cause gastroenteritis had results comparable to the phase III clinical trials (reductions of 37-61% in the target population compared with 42-59% in the efficacy studies). Of the remaining two studies, one had much higher effectiveness (78%) as it carried out during a rotavirus epidemic; the other demonstrated a reduced impact (12%) but this was undertaken in a low-income country at a very early stage of the vaccination program when vaccine coverage was low.

Indirect effect

Several studies found a significant improvement in rotavirus rates in older, unimmunised age groups and suggested that this was an indirect effect caused by 'herd immunity,' or the overall reduction in transmission of rotavirus due to a proportion of the population being immunised. The magnitude of the effect on both populations exceeds any likely annual variation in gastroenteritis epidemiology, and together with the consistency of results across four continents, these findings suggest a significant indirect benefit to the broader population.

Countries such as the Netherlands concluded that universal rotavirus immunisation would not be cost-effective based on pre-licensure data, but recognised that the level of indirect protection is a major factor determining cost-effectiveness. [27] Therefore inclusion of this emerging data in economic modelling may influence national decision-making in regards to the need for rotavirus vaccination.

Vaccine coverage

It was not possible to compare the relationship between any outcome measures and vaccine coverage rates, as few studies were able to provide an accurate coverage rate during the early phases of the immunisation program. In the US there is an extensive lag time between vaccination and public reporting. Furthermore, the multi-dose regimens (two doses for RV1 and three doses for RV5;)complicate the reporting and comparison of immunisation status in other countries. [17] However, the magnitude of improvement in rotavirus rates in studies where vaccine coverage was likely to be low suggests that a degree of protection from partial vaccination may be occurring. This is particularly relevant in developing countries where up to one-third of

the burden of severe disease occurs in infants under six months who are not fully vaccinated. Further research is required to address the role of partial vaccination. [20]

Rotavirus season

The impact of the vaccination program on seasonality of rotavirus disease was found in several studies, with blunting of the seasonal pattern seen. In some cases such as Mexico in 2008-9, there was no apparent 'season' at all. Changes in these epidemiological patterns demonstrate an appreciable impact on the previously predictable rotavirus pattern in temperate areas throughout winter and spring.

Vaccine strains

None of the studies were able to assess whether introduction of the vaccine had led to alteration in the prevalent circulating strains of rotavirus; however, this will need to be evaluated in the longer term as the effectiveness of current vaccines may be affected by serotype replacement. The considerable variability in study methods prevented comparison of the impact of the two vaccines RV1 and RV5. A Cochrane review recommended new trials be conducted with head-to-head comparison of the two vaccine types. [3]

Developing countries

A major concern following the pre-licensure clinical trials, largely conducted in middle- to high- income countries, was whether the vaccine would be as effective in developing countries, where 85% of deaths from diarrhoeal disease occur. Trials in Africa demonstrated significant improvement in rates of diarrhoeal disease, though not as impressive as those in the original trials. [7] The post-licensure monitoring data reviewed in this study similarly shows that while rotavirus vaccination has led to improvements in diarrhoeal disease in Central and South American countries, the improvement is to a lesser degree than in developed countries. Successful integration of rotavirus into Nicaragua's childhood immunisation program and achievement of >80% vaccine coverage provides an encouraging precedent for other developing countries to introduce the vaccine. [11,20] Another review has assessed the impact of the vaccine in both developing and developed countries with similar conclusions: while vaccination programs appear to be less effective in impoverished populations, there is a greater absolute reduction in severe disease and significant improvement in public health can be expected where universal rotavirus vaccination is introduced. [28]

Study limitations

There are several limitations of the observational and ecological studies included in this review which will be briefly discussed. Studies based on secondary data sources have the potential to introduce bias because private hospitals or laboratories were not included in government data collection and there may have been interhospital differences in practices to test for rotavirus, admit patients or classify cases. Use of sentinel hospitals does not capture the entire target population; however in most cases they have been designed to cover the majority of the target population (for example, paediatric referral hospitals). All studies suggested a positive impact from the vaccination programs; however without access to unpublished data it is difficult to determine whether publication bias has contributed to this finding.

Many studies used all-cause gastroenteritis as a surrogate for rotavirus disease, with rotavirus known to cause 30-50% of all AGE hospitalisations in children. [2] However this methodology does not control for variability in the circulation of other gastroenteritis causing pathogens, or trends in other factors influencing diarrhoeal disease such as sanitation, water or nutrition.

While study limitations mean that it is not possible to definitively conclude that rotavirus immunisation was responsible for the decline in gastroenteritis rates, the dramatic change following introduction of immunisation in eight countries, as analysed in this study, provides strong evidence that rotavirus vaccination programs are having an appreciable impact on the burden of diarrhoeal diseases.

Future monitoring

Many of the studies utilised routinely collected data for which historical information was available for comparison as this method has minimal additional costs. However, broader use of active surveillance is important to accurately evaluate the impact of vaccine programs and potentially to identify ways to improve the effectiveness of the program to have the greatest impact on the morbidity and mortality of diarrhoeal disease. [29]

Conclusions

National rotavirus immunisation programs have been initiated in several countries since two vaccines were licensed for use in 2006. Research has emerged from eight countries evaluating the impact of the first two years of these programs in a real world setting. All studies found improvements in outcomes of diarrhoeal disease in the target population, with the greatest protection found against severe rotavirus gastroenteritis. A significant indirect effect was also detected in the unvaccinated population in some studies, which may improve the cost effectiveness of vaccination programs. Active surveillance methods are recommended to monitor the impact of rotavirus vaccination programs; however routinely collected data can provide useful information in resource-poor settings. Further research is required to establish the effectiveness of partial vaccination and the effect of vaccination programs on circulating rotavirus strains.

Conflict of interest

None declared.

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