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Effectiveness of rotavirus vaccines in an Australian population: A case-control study

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ABSTRACT

Objective: Two rotavirus vaccines (RV1 and RV5) were included in the publicly funded National Immunisation Program in Australia from July 2007. The programme in Western Australia initially provided RV1 (at ages 2 and 4 months) and then switched to RV5 (at ages 2, 4 and 6 months) from July 2009. This retrospective case-control study was conducted to assess the effectiveness of rotavirus vaccine against laboratory confirmed and notified cases of rotavirus infection among children aged <5 years.
Methods: Case-subjects were identified as vaccine-eligible children (born from 1 May 2007) who were notified as having rotavirus infection during the period 2009–2011. The control group was vaccine-eligible children notified as having *Campylobacter* or *Salmonella* infection during the same period. Individual rotavirus immunisation status was ascertained from a population-based immunisation register. Full-dose and partial-dose vaccine effectiveness (VE) were calculated for both vaccines using the adjusted odds ratio (OR) of vaccination for cases versus controls (VE = (1 − OR)*100%).
Results: Overall, 282 cases and 883 controls were included. The adjusted VE for a full course of either rotavirus vaccine was 72% (95% CI: 56–82) and 71% (95% CI: 50–84) for partial vaccination (one dose of RV1 or one/two doses of RV5). The VE for a complete 3-dose course of RV5 was 82% (95% CI: 59–92) and for a full 2-dose course of RV1 was 73% (95% CI: 55–83).
Conclusions: RV1 and RV5 were both effective in preventing laboratory confirmed and notified rotavirus infections among children aged <5 years. Even incomplete courses of vaccination conferred good protection.

1. Introduction

Rotavirus is the foremost cause of severe gastroenteritis among children aged <5 years, resulting in substantial morbidity and mortality in both the developed and developing world [1]. Prior to the introduction of rotavirus vaccines, rotavirus accounted for 28% of all severe cases of gastroenteritis and diarrhoeal deaths globally, translating to >450,000 deaths and over two million hospitalisations [2,3]. In Australia, before the introduction of the rotavirus vaccine program, rotavirus was responsible for up to half of all diarrhoea-related hospitalisations in children <5 years old, resulting in an estimated 22,000 emergency department visits and 10,000 hospitalisations of children each year [4]. The annual direct medical cost associated with rotavirus infection among Australian children was estimated to be approximately $30 million [5]. Despite the high morbidity, mortality due to rotavirus is very low (<1 death per year) in Australia [6].

Currently, the World Health Organization recommends two live attenuated oral rotavirus vaccines – the 2-dose monovalent human rotavirus vaccine RV1 (Rotarix; GlaxoSmithKline Biologicals, Rixensart, Belgium), and the 3-dose pentavalent human-bovine reassortant vaccine RV5 (RotaTeq; Merck Vaccines, Whitehouse Station, NJ) for all young children [7,8]. Both vaccines have been licensed for use in Australia since June 2006 and all infants born

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since 1 May 2007 have been eligible for rotavirus vaccination funded by the National Immunisation Program (NIP) [9]. The programme in Western Australia (WA) provided RV1 at ages 2 and 4 months from July 2007, and then switched to RV5 at ages 2, 4 and 6 months from July 2009 [10]. Since 2008, uptake of rotavirus vaccine assessed at 12 months of age in WA has been shown to be around 78–85%.

In pre- and post-licensure studies, both RV1 and RV5 have demonstrated efficacy and effectiveness against rotavirus-associated acute gastroenteritis in developed and developing countries [11–17]. However, studies suggest that rotavirus vaccine effectiveness (VE) varies from region to region [17]. In Australia, declines in rotavirus-associated hospitalisations have been recorded, but studies have also shown differences in VE, depending upon the study setting [18–20]. To date, the rotavirus vaccination program has not been assessed in WA and no direct comparative data exists for these vaccines in Australia. Since WA changed from RV1 to RV5, the experience provides a unique opportunity to evaluate the effectiveness of RV1 and RV5 in the same population using the same methods. Thus, we assessed the VE of rotavirus vaccines (RV1 and RV5) against laboratory confirmed and notified rotavirus infections in children aged <5 years.

2. Methods

2.1. Setting and population

Western Australia (WA) is Australia's largest state by size, with a total land area of more than 2.5 million km^2. The landscape and climate varies from a tropical north, temperate south and arid and semi-arid mid-west and southeast regions. WA is divided into eight administrative health regions – Metropolitan (WA's capital city Perth – North and South), Kimberley, Pilbara, Midwest, Wheatbelt, Goldfields, South West and Great Southern. Approximately 3.4% of WA's population of 2.4 million identify as Aboriginal and/or Torres Strait Islander (hereafter referred to as Aboriginal) [21].

2.2. Data sources

Data on enteric disease notifications were extracted from the Western Australian Notifiable Disease Database (WANIDD) managed by the WA Department of Health. WANIDD is an intranet-based real-time application and database that stores information on all laboratory diagnosed notifiable infectious diseases in WA. Rotavirus became a notifiable disease in WA from 1 July 2006, primarily to gather data for evaluating the effectiveness of the then imminent national rotavirus vaccination program [22].

Immunisation data were obtained from the Australian Childhood Immunisation Register (ACIR). The Immunisation register is a national population-based database which includes all children enrolled in the national health insurance scheme (Medicare) and at the time of the study recorded details of all vaccines administered to children aged up to seven years. ACIR has now been renamed as the Australian Immunisation Register and records vaccination details for people of all ages in Australia.

2.3. Study design

We conducted a record-based retrospective unmatched case-control study to assess the effectiveness of RV1 and RV5 in preventing laboratory confirmed rotavirus gastroenteritis requiring medical attention (including general practice, emergency department visits and/or hospitalisation), among children aged <5 years.

2.4. Participants

2.4.1. Cases

Cases were children identified as having laboratory confirmed rotavirus infection from January 1, 2009 to December 31, 2011. Only children born on or after May 1, 2007 were included in the study.

2.4.2. Controls

Control children were chosen from among vaccine-eligible children (born on or after May 1, 2007) notified as having non-vaccine related diarrhoeal diseases of non-rotavirus origin. The control group consisted of children notified as having *Campylobacter* infection or *Salmonella* infection from January 1, 2009 to December 31, 2011. Inclusion criteria for the controls were identical to those for cases.

2.5. Immunisation status of the participants

Rotavirus immunisation status of the cases and controls were ascertained by referring to individual immunisation record on ACIR. For each vaccine dose, the vaccine type and date of administration were recorded. Vaccine doses were only considered valid if administered $\geq$14 days before the date of onset of disease (as recorded on WANIDD). The vaccination status of each child was recorded as being fully vaccinated if all recommended doses of vaccine were administered (2 doses for RV1 or 3 doses for RV5) $\geq$14 days before the disease onset date, partially vaccinated if the child had received at least one dose but less than the recommended doses, or unvaccinated.

Children aged less than 2 months at the time of disease onset were excluded as were children whose records were not available on ACIR. All analyses were restricted to only children who were older than the age recommended for completion of the rotavirus vaccinations (24 weeks old for RV1 and 32 weeks old for RV5) at the time of notification.

2.6. Statistical analysis

Univariate analyses were performed to compare the demographic characteristics between cases and controls. Pearson Chi-square tests were used to assess any differences between the categorical variables in both groups. Logistic regression models were used to calculate the unadjusted and adjusted odds ratio (OR) and 95% confidence intervals (CIs) of vaccination in cases compared with controls. The OR for vaccination with RV1 and RV5 (versus no vaccination) were estimated separately. For both cases and controls, RV1-only analyses were restricted to children born 1 May 2007 – 30 April 2009 and RV5-only analyses were restricted to children born on or after 1 May 2009. The multivariable model was adjusted for age (in years), sex, Aboriginal status and area of residence (metropolitan or non-metropolitan). VE was estimated from the OR using the formula VE = $(1 - \text{OR}) \times 100\%$ [23]. Secondary analyses were conducted to assess VE for partial vaccination (1 dose of RV1 or 1 or 2 doses of RV5), and VE by age group, region of residence and Aboriginal status. All analyses were performed using Stata™, version 12.1 (StataCorp).

2.7. Ethics committee approvals

Approval for this study was granted by the University of Western Australia Human Research Ethics Committee, Western Australian Department of Health Human Research Ethics Committee and the Western Australian Aboriginal Health Ethics Committee.

3. Results

A total of 522 rotavirus cases and 1214 *Salmonella* or *Campylobacter* controls were identified over the study period. Immunisation records could not be obtained for 81 (16%) rotavirus cases and 187 (16%) controls. Of the remainder, 282 cases and 883 controls were eligible to be included in the study (Fig. 1). Based on the child's date of birth, 208 cases and 539 controls were RV1 eligible, and 59 cases and 263 controls were RV5 eligible.

The median age at onset of disease for both the cases and controls was 17 months and the proportion identified as Aboriginal was similar (Table 1). Controls were more likely than cases to be male (59% v 52%; p = 0.04), and were less likely to reside in the metropolitan region of WA (64% vs 76%; p < 0.001). Among cases, 188 (67%) were fully vaccinated, 38 (13%) were partially vaccinated and 56 (20%) were unvaccinated. The number of controls fully, partially or not vaccinated were 706 (80%), 123 (14%), and 54 (6%) respectively. Aboriginal children were significantly less likely to be fully vaccinated than non-Aboriginal children (80% vs 90%; p < 0.001); vaccination status was not associated with gender or region of residence.

Compared to unvaccinated children, the adjusted VE against notified rotavirus infection among children fully vaccinated with either vaccine was 72% (95% CI: 56–82); the adjusted VE was 71% (95% CI: 48–84) for partial vaccination with either vaccine (Table 2). The point estimate of VE for fully vaccinated children was lower among those aged 12–24 months than those aged 6–11 months (VE 58% vs 88%), albeit with overlapping confidence intervals (Table 3). Similarly, the point estimates of VE among non-Aboriginal children were lower than that among Aboriginal children with overlapping confidence intervals, as was the estimate of VE among metropolitan compared with non-metropolitan children (Table 3).

VE for a full 2-dose course of RV1 was 73% (95% CI: 55–83) and for a full 3-dose course of RV5 was 82% (95% CI: 59–92) (Table 2). The VE was 67% (95% CI: 32–82) for 1 dose of RV1, 39% (95% CI: −157–85) for 1 dose of RV5 and 81% (95% CI: 39–94) for 2 doses of RV5 (Table 2). Similar to the overall analysis, point estimates of VE among non-Aboriginal children were lower than that among Aboriginal children in both RV1- and RV5-specific analyses, with overlapping confidence intervals (Table 3).

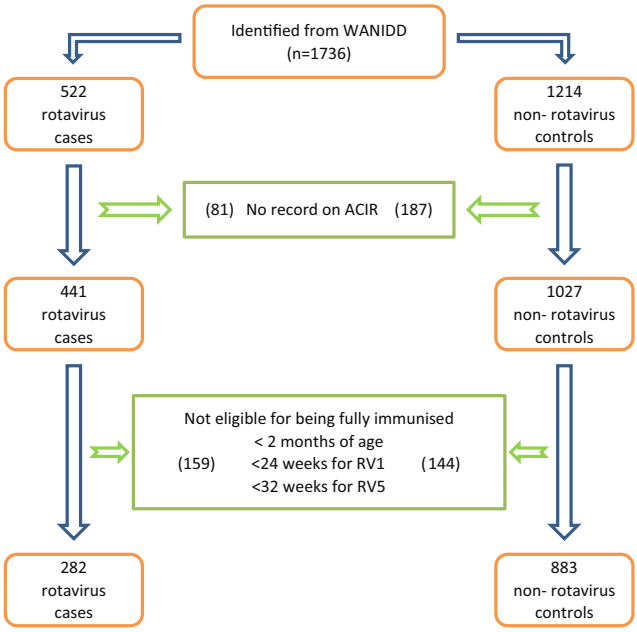

Fig. 1. Flow diagram showing enrolment and exclusion of participants (cases and controls).

Table 1
Demographic characteristics of rotavirus cases and non-rotavirus controls.

Characteristic	Rotavirus cases N = 282 n (%)	Non-rotavirus controls N = 883 n (%)	p-value
Median age in months	17 (IQR[a] 11–24)	17 (IQR[a] 12–26)	0.70
Sex			
Male	147 (52)	523 (59)	0.04
Female	135 (48)	360 (41)	
Aboriginal status			
Aboriginal	37 (13)	94 (11)	0.35
Non-Aboriginal	219 (78)	677 (77)	
Region of residence			
Non-metropolitan	68 (24)	315 (36)	<0.001
Metropolitan	214 (76)	568 (64)	

[a] IQR–Inter quartile range.

4. Discussion

Vaccination with either vaccine was shown to be protective against rotavirus infection requiring medical attention among children aged <5 years. This pattern corresponds with those observed in other parts of Australia where the introduction of rotavirus vaccination in the NIP has not only reduced the burden of gastroenteritis related hospitalisations in young children [16,24–26], but has also demonstrated a strong herd protective effect among older vaccine-ineligible children [16,18,24].

In our setting, a complete course of either rotavirus vaccine conferred a 72% (95% CI: 56–82%) protective effect against laboratory confirmed and notified rotavirus gastroenteritis. Furthermore, partial vaccination (1 dose of RV1 or 2 doses of RV5) conferred a similar protective effect. These VE estimates are comparable to the VE of the two vaccines estimated in other studies in developed countries where both vaccines are being used concurrently [27–29]. With regard to the individual vaccines, complete courses of both RV1 and RV5 exhibited a good protective effect against rotavirus gastroenteritis with an estimated VE of 73% (95% CI: 55–83) and 82% (95% CI: 59–92) for RV1 and RV5 respectively. Published VE reviews summarised the VE range of 76–85% for RV1 and 85–100% for RV5 in Australia and/or other developed countries [30,31]. Most of these studies focussed on rotavirus requiring hospitalisation whereas the present study included ambulatory participants accessing general practices, ED services as well as hospitalisations and this may account for the slightly lower VE point estimates in this study.

Despite the modestly lower point estimate of VE for RV1 compared to RV5 in this study, there was considerable overlap in the observed confidence intervals. Differences in the circulating strains of rotavirus in the community could potentially affect the VE estimates of RV1 and RV5. RV1 is a live, monovalent, attenuated oral rotavirus vaccine derived from the most common human rotavirus strain G1P [8,32]. This vaccine has demonstrated good efficacy against severe rotavirus gastroenteritis caused by serotypes G1, G3, G4 and G9, but possibly lesser protection against severe disease associated with G2 strains which are heterotypic to the vaccine strain [12]. Post-licensure studies have shown mixed results for the effectiveness of this vaccine against G2 associated strains and G2P [4] strains have emerged as the dominant circulating serotype in some settings using RV1 vaccine [20,33–35]. RV5 is a live, pentavalent (G1, G2, G3, G4, P [8]) human–bovine reassortant vaccine, and has been shown to be highly effective against G2P [4] (which is

Table 2
Effectiveness of rotavirus vaccine against notified rotavirus infection in WA (2009–2011) by vaccination status and vaccine type.

Immunisation status	Rotavirus cases n (%)	Non-rotavirus controls n (%)	Vaccine effectiveness % (95% CI)	
			Unadjusted	Adjusted[a]
RV1/RV5	***N = 282***	***N = 883***		
Unvaccinated	56 (20)	54 (6)	Ref.	Ref.
Partially vaccinated[b]	38 (13)	123 (14)	70 (50, 82)	71 (48, 84)
Fully vaccinated[c]	188 (67)	706 (80)	74 (61, 83)	72 (56, 82)
RV1[d]	***N = 208***	***N = 539***		
Unvaccinated	42 (20)	39 (7)	Ref.	Ref.
1 dose	22 (11)	59 (11)	65 (33, 82)	67 (32, 82)
2 doses	144 (69)	441 (82)	70 (51, 81)	73 (55, 83)
RV5[e]	***N = 59***	***N = 263***		
Unvaccinated	14 (24)	15 (6)	Ref.	Ref.
1 dose	5 (8)	8 (3)	33 (−154, 82)	39 (−157, 85)
2 doses	7 (12)	35 (13)	79 (36, 93)	81 (39, 94)
3 doses	33 (56)	205 (78)	83 (61, 92)	82 (59, 92)

[a] Adjusted for sex, age in years, Aboriginal status and region of residence.
[b] 1 dose of RV1 OR 1/2 doses of RV5.
[c] 2 doses of RV1 OR 3 doses of RV5.
[d] RV1-only analyses were restricted to children born 1 May 2007 – 30 April 2009.
[e] RV5-only analyses were restricted to children born on or after 1 May 2009.

Table 3
Effectiveness of complete course of rotavirus vaccine[a] against notified rotavirus infection in WA (2009–2011) by vaccine type, age, Aboriginal status and region of residence.

	RV1/RV5[a]		RV1		RV5	
	Cases/controls	Adjusted vaccine effectiveness% (95% CI)	Cases/controls	Adjusted vaccine effectiveness% (95% CI)	Cases/controls	Adjusted vaccine effectiveness% (95% CI)
Age group[b]						
6–11 months	69/177	88 (69, 96)	38/84	78 (2, 95)	27/79	95 (71, 99)
12–24 months	112/352	58 (20, 78)	88/187	54 (2, 79)	19/133	51 (−99, 88)
Aboriginal status[c]						
Aboriginal	28/77	83 (48, 95)	20/50	82 (32, 95)	8/19	86 (−35, 99)
non-Aboriginal	193/583	69 (48, 81)	151/363	60 (36, 80)	33/176	76 (27, 92)
Region of residence[d]						
Metropolitan	194/484	63 (37, 78)	150/301	59 (28, 77)	34/149	81 (49, 93)
Non-metropolitan	50/276	89 (71, 96)	36/179	88 (63, 96)	13/71	84 (20, 93)

[a] 2 doses of RV1 OR 3 doses of RV5.
[b] Model adjusted for sex, Aboriginal status and region of residence.
[c] Model adjusted for sex, age in years and region of residence.
[d] Model adjusted for sex, age in years and Aboriginal status.

partly heterotypic to RV5) in post-licensure studies [36]. Over the course of the study period, G2P [4] was identified as the most common strain in WA, representing nearly 66% of all specimens analysed [37]. Also, we note that VE analysis for RV1 included children up to age 4 years whereas VE analyses for RV5 only included children up to 2 years. Although the regression models were adjusted for age of the child at the time of disease onset, waning immunity could have had a differential influence on VE estimates for RV1 and RV5.

Historically, the burden of gastroenteritis in young children in WA has been higher in Aboriginal than in non-Aboriginal children, with approximately five times greater rotavirus-related hospitalisation rates in the Aboriginal group [6]. The reduction in gastroenteritis-related hospitalisations has been more modest among Aboriginal than non-Aboriginal Australian children [24]. We found no evidence of differences in VE among Aboriginal and non-Aboriginal children in WA, suggesting that reduced impact is more likely due to documented lower coverage rather than vaccine failure [38]. This finding underscores the importance of timely vaccination in Aboriginal children.

One of the main strengths of this study is that the controls were selected among children presenting with a clinically compatible illness (two common types of bacterial gastroenteritis), similar to the test-negative design for vaccine effectiveness studies described elsewhere [39]. The strength of this method is that it protects against ascertainment bias which might arise if a child's vaccination status is associated with patterns of either health seeking or testing behaviour. The choice of control group implicitly assumes that children with bacterial gastroenteritis are no more or less likely to be rotavirus vaccinated than other children in the source population; we were not able to confirm this is true although we have no specific reason to believe otherwise. Vaccination status was ascertained identically for cases and controls, using data systematically recorded on a comprehensive population-based immunisation register. Bias from misclassification of vaccination status was therefore unlikely.

Compared to clinical trial evidence, there are several limitations to the findings of this study. Not every child who presents to a general practitioner or the ED with symptoms of gastroenteritis undergoes rotavirus testing and so the included cases may not be representative of all rotavirus infections in the community. If only severe cases were tested, VE may be overestimated. Rotavirus antigen testing of faecal samples was conducted at different pathology laboratories in the state. Each laboratory has its own stool testing method and each method has its own sensitivity and specificity [40]. Any false positive results are likely to result in some underestimation of VE, while false negatives might also result in underestimation of VE if controls with culture confirmed bacterial

gastroenteritis coincidentally had undetected rotavirus infection. We note that there was no overlap in the time periods in which RV1 and RV5 were administered limiting our ability to directly compare VE estimates for RV1 and RV5. Changes in prevailing strains or in testing patterns over the study period, for example, might favour VE estimates for one vaccine over another.

In conclusion, two doses of RV1 and three doses of RV5 both appear effective for providing protection against clinically identified and notified rotavirus infection among WA children aged <5 years old. Even incomplete vaccination appears to confer moderately high protection. The benefits of timely immunisation with rotavirus vaccine in preventing rotavirus gastroenteritis should be emphasised and encouraged in the population.

5. Authorship

PF and RAG conceptualised and designed the study. RAG also provided advice on data cleaning. PF carried out the analysis and drafted the initial manuscript. RAG and TLS provided expert epidemiological and clinical advice and assisted with the interpretation and presentation of the results. All authors reviewed and revised the manuscript and approved the submitted final manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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