Early evidence for direct and indirect effects of the infant rotavirus vaccine program in Queensland

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Rotavirus is the most common global cause of severe early childhood gastroenteritis and has a significant clinical impact.¹ In the pre-vaccine era, it was responsible for about 10 000 hospitalisations, 22 000 emergency department presentations and 115 000 general practice consultations annually in Australian children less than 5 years of age.²

To reduce this substantial disease burden, two rotavirus vaccines have been licensed for use in Australian infants: RotaTeq (Merck, Whitehouse Station, NJ, USA), a live multivalent bovine-human reassortant vaccine;³ and Rotarix (GlaxoSmithKline, Rixensart, Belgium), a single-strain live-attenuated human vaccine.⁴ Australian infants have been eligible for rotavirus vaccination via the National Immunisation Program since July 2007.⁵ Queensland children born on or after 1 May 2007 are eligible for three publicly funded doses of RotaTeq. Both vaccines were available on the private market from 2006, but, as with other recommended but non-funded vaccines,⁶ uptake is likely to have been modest.

The aim of our study was to examine the effect of introducing the publicly funded infant rotavirus vaccination program on disease notifications and on laboratory testing and results.

METHODS

To assess the impact of the first 18 months of the infant vaccination program in Queensland, we used two sources: routinely collected rotavirus notifications made to Queensland Health (2006–2008) and laboratory testing data from Queensland Health laboratories (2000–2008).

Notifications

Laboratory-confirmed rotavirus disease became notifiable in Queensland in December 2005, in accordance with the *Public Health Act 2005* (Qld). The notification case definition requires:

- detection of rotavirus in faeces by antigen detection; or
- detection of rotavirus by nucleic acid assay; or
- isolation of rotavirus.

ABSTRACT

Objective: To assess the impact of introducing a publicly funded infant rotavirus vaccination program on disease notifications and on laboratory testing and results.

Design and setting: Retrospective analysis of routinely collected data (rotavirus notifications [2006–2008] and laboratory rotavirus testing data from Queensland Health laboratories [2000–2008]) to monitor rotavirus trends before and after the introduction of a publicly funded infant rotavirus vaccination program in Queensland in July 2007.

Main outcome measures: Age group-specific rotavirus notification trends; number of rotavirus tests performed and the proportion positive.

Results: In the less than 2 years age group, rotavirus notifications declined by 53% (2007) and 65% (2008); the number of laboratory tests performed declined by 3% (2007) and 15% (2008); and the proportion of tests positive declined by 45% (2007) and 43% (2008) compared with data collected before introduction of the vaccination program. An indirect effect of infant vaccination was seen: notifications and the proportion of tests positive for rotavirus declined in older age groups as well.

Conclusions: The publicly funded rotavirus vaccination program in Queensland is having an early impact, direct and indirect, on rotavirus disease as assessed using routinely collected data. Further observational studies are required to assess vaccine effectiveness. Parents and immunisation providers should ensure that all Australian children receive the recommended rotavirus vaccine doses in the required timeframe.

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Duplicate-free data for the period 1 January 2006 to 31 December 2008 that were available on 9 January 2009 were analysed. We calculated the percentage change in the number of notifications in each age group in 2007 and 2008 compared with 2006.

Queensland Health laboratory testing

To compare rotavirus testing and positivity patterns before and after vaccine introduction, we examined statewide data from 33 Queensland Health laboratories for the period 1 January 2000 to 31 December 2008. We calculated the percentage change in number of tests performed and positive results for different age groups in 2007 and 2008, using mean annual figures from 2000 to 2006 as the baseline for comparison.

Using a hospital-specific, unique patient identification number we were able to identify rotavirus tests performed for the same individual in a single hospital. Where we could identify repeat tests within 7 days of a preceding test, these were collapsed into a single test record. If any of the individual rotavirus tests were positive, the single test

record was recorded as positive, and the date of testing was taken as the earliest date any rotavirus test was performed.

Between 2000 and 2008, there were changes to laboratory procedures for detecting rotavirus. Before March 2005, Queensland Health central laboratory used a monovalent immunoassay rotavirus antigen detection technique (VIDAS Rotavirus kit used on the VIDAS analyser [bioMérieux, Marcy-l'Etoile, France]) and an in-house polymerase chain reaction test to identify adenovirus in faecal specimens. From March 2005, testing for rotavirus and adenovirus in faecal specimens was combined using a bivalent immunochromatographic technique for antigen detection (VIKIA Rota-Adeno [bioMérieux, Marcy-l'Etoile, France]). After this date, any request for either rotavirus or adenovirus identification in faeces resulted in both viruses being tested.

Request slip audit

To assess changes in age group-specific testing behaviour, we audited the actual test

1 Percentage change in rotavirus notifications, tests performed* and tests positive* after introduction of a publicly funded infant rotavirus vaccination program in Queensland in July 2007

* Testing performed by Queensland Health Clinical and Statewide Services. † Percentage change in the number of rotavirus notifications in 2007 and 2008 compared with the number in 2006. ‡ Percentage change in the number of rotavirus tests performed in 2007 and 2008 compared with mean annual age group-specific values from 2000 to 2006. § Percentage change in the proportion of tests positive for rotavirus in 2007 and 2008 compared with age group-specific values from 2000 to 2006. ◆

requested by viewing a systematic sample of request slips for the first five specimens tested in each month of 2008 for two age groups: 0–23 months and ≥ 65 years. We compared relevant proportions using χ^2 tests and calculated associated *P* values.

Statistical analysis

Data were analysed using Stata software, version 9 (StataCorp, College Station, Tex, USA).

Ethics approval

Our project was approved as low-risk research⁷ by Queensland's Children's Health Services District Ethics Committee.

RESULTS

Notifications

During the 3-year period 2006–2008, 4786 rotavirus notifications were received by the Communicable Diseases Branch of Queensland Health. Most rotavirus notifications were for infants and children: 70% were aged less than 2 years and 81% less than 5 years. Males made up 52% of notifications. Queensland Health laboratories made 85% of all rotavirus notifications.

Annual rotavirus notifications have fallen since the introduction of public funding for universal infant vaccination: compared with 2510 notifications in 2006, there were 1189 notifications in 2007 (a 53% reduction) and 1087 notifications in 2008 (a 57% reduction).

(Box 1, a). In children less than 2 years of age, the reduction was 53% in 2007 and 65% in 2008, with reductions of similar magnitude in children aged 2–4 years (65% and 56%, respectively).

Queensland Health laboratory testing behaviour and results

Between 2000 and 2008, 41 166 rotavirus tests were performed in Queensland Health laboratories. Age or date of birth was not available for 91 requests (0.2%). Of the remaining 41 075 records, 12 282 were repeat tests performed on the same patient within 7 days of the preceding test. Collapsing these to a single test record removed 6409 records, leaving 34 666 in the dataset. Fifty-four per cent of laboratory tests were performed in children less than 2 years of age, and 73% in children less than 5 years of age. Fifty-four per cent of all tests requested were for males.

The number of tests performed and the proportion of all tests positive for rotavirus in Queensland had an annual winter–spring peak (Box 2). Comparing the mean annual number of rotavirus tests performed in the years 2000–2006 with values for 2007 and 2008 revealed variation between age groups: there was a fall in the number of tests performed for children aged less than 2 years (–3% [2007]; –15% [2008]) and aged 2–4 years (–18% [2007]; –5% [2008]), but an increase in tests performed for all older age groups (Box 1, b). The total number of tests increased from a mean annual figure of

3720 (over the period 2000–2006) to 4511 in 2007 and 4113 in 2008.

Before public funding of the universal infant vaccination program, the annual peak monthly value of the proportion of tests positive ranged from a low of 42% (September 2001) to a high of 58% (September 2006). After introduction of public funding, peak monthly values dropped to 24% (in both October 2007 and August 2008) (Box 2). In every age group (ie, including non-vaccinated age groups) there was a reduction in the proportion of tests that were positive in 2007 and 2008 compared with the proportion over the period 2000–2006 (Box 1, c). In children less than 2 years of age, reductions in the proportion of tests positive (relative to the proportion in 2000–2006) were 45% in 2007 and 43% in 2008.

Request slip audit

The audit of 2008 request slips showed that for patients in the oldest age group (≥ 65 years) there was less likely to be a specific request for rotavirus testing or adenovirus testing (which would also result in a rotavirus test as part of the dual test kit) than for those aged less than 2 years (63% [38/60] v 82% [49/60], respectively; *P* = 0.025). Further, comparing the oldest age group with the youngest, a larger proportion of rotavirus tests performed appeared to be done in response to a request for non-specific viral testing in the absence of either a specific rotavirus or adenovirus request (35% [21/60] v 13% [8/60], respectively; *P* = 0.006).

2 Monthly frequency of laboratory tests performed, results, and proportion positive for rotavirus, Queensland Health Clinical and Statewide Services, 2000–2008

DISCUSSION

These data, from two passively collected, potentially non-independent sources, show a fall, across all age groups, in rotavirus notifications and in the proportion of Queensland Health tests positive for rotavirus. These changes coincide with the commencement of the publicly funded, universal, infant rotavirus vaccine program in July 2007. Further, in the targeted age group (children less than 2 years of age) and in all children less than 5 years of age, there was a fall in 2007 and 2008 in the number of tests performed.

Concordant findings have been seen elsewhere: rotavirus activity was delayed by up to 4 months and diminished in size by more than 50% in the United States after the introduction of the RotaTeq vaccine,⁸ and there was evidence of vaccine effectiveness during a recent outbreak in the Northern Territory, where the Rotarix vaccine is used.⁹

Our Queensland data are an important addition to current findings, as they are among the first to show changes in rotavirus epidemiology in non-vaccinated age groups,¹⁰ providing good evidence for an equivalent indirect vaccine effect in older age groups. These local outcomes were achieved within 18 months of the program's commencement. Of the first two eligible birth cohorts in which coverage was measured, 75% of infants born in May–July 2007 and 80% of those born in August–September 2007 had received a complete three-dose vaccine course on assessment at 12

months of age (Mr Brynley Hull, Epidemiologist, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, personal communication). Improved benefits are anticipated as more birth cohorts are vaccinated and more courses completed.

Our only divergent finding was the increase in the number of tests performed for rotavirus in older age groups. The request slip audit showed that in the oldest age group there was less likely to be a specific request for rotavirus or adenovirus testing, and that the proportion of rotavirus tests done in response to a request for non-specific viral testing was higher. There has recently been an increased awareness of viral gastroenteritis outbreaks in hospitals, nursing homes and residential aged-care facilities.^{11,12} It may be that, in some circumstances, rotavirus testing is being done routinely on gastroenteritis specimens from older people, even though the overall number and proportion of specimens found positive is likely to be low.

Our data come from two passive, routinely collected sources. Both are likely to be reasonably representative of all regions in Queensland, and the data from 33 Queensland Health laboratories are likely to include nearly all testing done in rural and remote locations, which are not as well served by private pathology companies. It is worth keeping in mind that our results are produced from observational studies relating trends in rotavirus outcome data before and

after vaccine introduction: this is a less robust study design than other observational studies for assessing a causal relationship. The documented changes may represent secular trends — however, the results would represent unusual, persisting and extreme temporal variations. Further, the reductions seen coincide closely with vaccine introduction, and are in keeping with both US post-licensure data⁸ and vaccine efficacy studies showing a 98%–100% reduction in severe rotavirus gastroenteritis and a 73%–74% reduction in any rotavirus gastroenteritis.^{3,13} To support the role of vaccination in these locally improving trends, better quality observational studies are required, including efforts to estimate vaccine effectiveness using routinely collected data¹⁴ and during identified outbreaks.⁹ Australia, being in the unique position of having widespread and region-specific use of both currently licensed rotavirus vaccines, could further add to global research by routinely monitoring the field effectiveness of each vaccine, as well as regional differences in circulating genotypes, through the National Rotavirus Reference Centre.¹⁵

Our results, in conjunction with efficacy trial data and findings from the US, provide solid support for prompt direct and indirect effects following rotavirus vaccine use in Queensland. This should encourage parents and vaccination providers to ensure that all Australian children receive the recommended rotavirus vaccine course within the required timeframe.

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COMPETING INTERESTS

Stephen Lambert has been an investigator on industry-sponsored vaccine studies, has received support for conference attendance from GlaxoSmithKline and CSL, and been a member of vaccine advisory boards for GlaxoSmithKline and Novartis. Christine Selvey has previously received support from CSL to attend a local meeting. Michael Nissen has been an investigator on industry-sponsored studies and has received support from Wyeth and GlaxoSmithKline for conference attendance. Keith Grimwood was a member of a rotavirus vaccine advisory board and received support for conference attendance, lecture fees, and a research grant from GlaxoSmithKline, as well as a research grant from Merck. The research for this article was done entirely within the authors' roles in Queensland Health, and was not funded by any external grant or agency.

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REFERENCES

- 1 Grimwood K, Lambert SB. Rotavirus vaccines: opportunities and challenges. *Hum Vaccin* 2009; 5: 4-16.
- 2 Galati JC, Harsley S, Richmond P, Carlin JB. The burden of rotavirus-related illness among young children on the Australian health care system. *Aust N Z J Public Health* 2006; 30: 416-421.
- 3 Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; 354: 23-33.
- 4 Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; 354: 11-22.
- 5 Australian Government Department of Health and Ageing. Fact sheet: Australian Government funding of rotavirus vaccine. http://www.health.gov.au/internet/main/publishing.nsf/Content/rotavirus_vaccine.htm (accessed Apr 2009).
- 6 Gilbert GL, Gidding HF, Backhouse J, et al. Varicella seroprevalence and vaccine uptake in preschool children [letter]. *Med J Aust* 2005; 182: 42.
- 7 National Health and Medical Research Council, Australian Research Council and Australian Vice-Chancellors' Committee. National statement on ethical conduct in human research. Canberra: Australian Government, 2007. http://www.nhmrc.gov.au/PUBLICATIONS/synopses/_files/e72.pdf (accessed Apr 2009).
- 8 Centers for Disease Control and Prevention. Delayed onset and diminished magnitude of rotavirus activity — United States, November 2007–May 2008. *MMWR Morb Mortal Wkly Rep* 2008; 57: 697-700.
- 9 Graham J, Cook H, Roberts C, et al. An estimate of rotavirus vaccine efficacy following an outbreak of rotavirus gastroenteritis in Central Australia. *Northern Territory Dis Control Bull* 2008; 15: 8-13.
- 10 Lieberman JM, Huang X, Koski E, et al. Decline in rotavirus cases in the US after licensure of a live, oral rotavirus vaccine. 48th Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Annual Meeting of the Infectious Diseases Society of America; 2008 Oct 25–28; Washington, DC, USA: G1-G437.
- 11 Lyon MJ, Wei G, Smith GA. Epidemic viral gastroenteritis in Queensland coincides with the emergence of a new norovirus variant. *Commun Dis Intell* 2005; 29: 370-373.
- 12 Kirk MD, Roberts L, Horvath J. Understanding gastroenteritis in elderly residents of aged-care facilities [editorial]. *Med J Aust* 2008; 189: 476-477.
- 13 Block SL, Vesikari T, Goveia MG, et al. Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. *Pediatrics* 2007; 119: 11-18.
- 14 Torvaldsen S, McIntyre PB. Observational methods in epidemiologic assessment of vaccine effectiveness. *Commun Dis Intell* 2002; 26: 451-457.
- 15 Kirkwood CD, Cannan D, Bogdanovic-Sakran N, et al. Australian Rotavirus Surveillance Program: annual report, 2006–07. *Commun Dis Intell* 2007; 31: 375-379.

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