

# Surveillance of viral pathogens in Australia

For many years, a sentinel laboratory system, the Laboratory Virology and Serology Reporting Scheme (LabVISE) has been collecting data on viral pathogens of public health importance in Australia. This report is one in a series of articles focussing on the epidemiology and public health aspects of viruses and viral groups under surveillance by LabVISE, which are of current public health interest.

## Rotavirus

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### Introduction

Since the discovery of rotaviruses in 1973, at the Royal Children's Hospital in Melbourne,<sup>1</sup> they have been recognised as a leading cause of severe and acute diarrhoeal illness in young children throughout the world. The global burden of rotaviral disease was recently estimated as 111 million cases requiring home care, 25 million cases requiring medical attention, one million requiring hospitalisation and 440,000 deaths in children aged less than five years, annually.<sup>2</sup> In the United States of America (USA), rotaviral infections are responsible for an estimated 500,000 physician visits, 50,000 hospitalisations and 20 to 40 deaths per year.<sup>3</sup> In Australia, it has been estimated that rotavirus infection is the cause of diarrhoea in 10,000 of the nearly 20,000 children admitted to hospital each year with severe diarrhoea.<sup>4</sup>

In this report, surveillance data for rotavirus infections in Australia are analysed from four sources: the Laboratory Virology and Serology Reporting Scheme (LabVISE), the National Hospital and Morbidity database, the Northern Territory notifiable diseases data and the Australian Rotavirus Surveillance Programme. The importance of surveillance data for future rotavirus vaccine development is discussed.

### Molecular biology and nomenclature

Rotaviruses comprise a genus within the family Reoviridae that includes viruses that inhabit both the respiratory and enteric systems of birds and mammals. Initially, members of this family were considered 'orphan viruses', as they were not associated with any disease in humans, and it was this combination of properties that led to their being named reoviruses (**R**esp, **e**nteric, **o**rphan, – viridae).

The rotavirus is named for its 'spoked wheel' appearance in electron micrographs of negatively stained faecal extracts. The double-stranded RNA can be separated into 11 segments by gel electrophoresis. Six of the genes code for structural proteins (VP1–4, VP6, VP7) and five for non-structural proteins. Six groups of rotavirus (A, B, C, D, E, F) are recognised based on differences in serology and genetic patterns. Group A is common in humans, Group B is uncommon in infants, but has caused large epidemics in adults in China while Group C appears to be uncommon in humans (Chin, 2000).<sup>5</sup> All six groups of rotavirus occur in animals and birds.

Variations in the two proteins making up the outer layer, viral protein 4 (VP–4, or P (protease-sensitive) and viral protein 7 (VP–7, or G (glyco-protein) are used to further classify rotaviruses. In a similar manner to the classification of influenza virus strains, serotypes of Group A rotaviruses are defined by the characteristics of the two outer proteins (e.g. G1, G2, or P1, P2) and the two in combination are used to identify particular serotypes (e.g. G1,[P1A]).<sup>6</sup>

The mode of transmission of rotaviruses is predominantly by a faecal oral route, although airborne transmission has been postulated, particularly in nurseries, child day care centres, and hospital wards. Infected infants shed virus in large numbers ( $>10^{12}$  particles/ml faeces) for four to seven days after the onset of disease. Chronic shedding of virus by healthy adults or partially immune infants may provide a reservoir of infection. Public water supplies may also be a source of infection.<sup>7</sup> Within hospital nurseries rotavirus may be endemic with a single strain circulating for years<sup>8,9</sup> and nosocomial infections are common. A recent study of an outbreak of a novel rotaviral strain in a neonatal hospital unit was shown to be associated with persistence of the virus on hard surfaces and with lapses in infection control practices.<sup>10</sup>

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## Pathology and clinical outcomes

Following ingestion, the virus infects mature absorptive epithelial cells lining the small intestine where they replicate, followed by lysis of infected cells. There is a depression of lactase enzyme in the damaged intestinal mucosa, which increases gut osmolarity and results in watery diarrhoea and lactose malabsorption that may persist for 10 to 14 days.<sup>7</sup> Fever, vomiting and watery diarrhoea are the major clinical signs of rotavirus infection. In a neonatal intensive care setting, rotaviral infection may manifest as more frequent production of watery or bloody stools.<sup>11</sup> Re-infections that occur in childhood and adult life are common but are usually associated with mild enteric symptoms or are asymptomatic.

The key treatment of rotaviral diarrhoea is replacement of fluids and electrolytes. The promotion in developing countries of oral fluid replacement therapy in children with diarrhoea has been critical in saving many lives. The oral rehydration mixtures consist of pre-weighed glucose, sodium, potassium, chloride and base in appropriate proportions to replace electrolyte losses, increase the uptake of water and provide calories.<sup>7</sup>

## Epidemiology

Globally nearly all children experience a primary rotavirus infection by the age of five years. One in five will have visited a clinic, one in 65 will have been hospitalised and one in 293 will die of rotaviral infection. Eighty-two per cent of deaths due to rotaviral infection occur in developing countries.<sup>2</sup>

Infection in children less than three months is uncommon, possibly due to the protective effect of maternal antibodies,<sup>12</sup> although breast-feeding has not been clearly shown to reduce the incidence or severity of rotaviral disease. However, a recent study in Italy noted an attack rate of rotaviral infection of 10.6 per cent in hospitalised breast-fed infants aged 1 to 18 months compared with an attack rate of 32.4 per cent in non-breast-fed infants.<sup>13</sup> Susceptibility to rotaviral infection in children may increase as the gut epithelium matures.<sup>7</sup>

Prospective studies in Australia, Mexico, Africa and elsewhere have shown that primary infection with rotavirus gives little or transient protection against re-infection, but does protect against clinically severe diarrhoea after reinfection.<sup>9,14,15</sup> Reinfection with rotavirus occurs into adult life, but infections are usually asymptomatic or cause mild disease presumably because of the immunity gained in early childhood. Epidemics associated with rotavirus infection have occurred in nursing homes for the elderly.<sup>16</sup> Intestinal secretory IgA antibodies

directed to the VP4 and VP7 proteins of the viral outer coat play a critical role in immunity to rotaviral infection by preventing viral attachment and entry into the intestinal epithelium.<sup>17</sup> A recent review has concluded that serum anti-rotaviral antibodies are a correlate of protective immunity when present at sufficient levels.<sup>18</sup>

There is a strong association of rotaviral infections with the winter seasons in temperate climates, while in tropical climates cases occur year round. The reasons for the seasonal epidemics in winter are uncertain, but may reflect increased opportunity for transmission within families and longer survival of the virus in the environment during colder months.<sup>19</sup>

## Prevention of rotaviral disease

### Passive immunisation and probiotics

Treatment of acute rotaviral diarrhoea by oral administration of antibodies to rotavirus has been investigated. Despite numerous studies on the use of oral administration of rotaviral immunoglobulin preparations, a recent Cochrane review was unable to identify randomised control trials to assess the efficacy of this approach in low birth weight babies.<sup>20</sup> The passive administration of bovine milk antibodies containing high titres of neutralising antibodies to human rotaviral strains was shown to have significantly reduced the duration of excretion of rotavirus from infected children.<sup>21,22</sup> In immunodeficient children passive administration of antibodies may also reduce chronic rotaviral diarrhoea.<sup>7</sup>

An alternative approach has been to administer the non-pathogenic *Lactobacillus* GG bacteria to modulate the diarrhoeal disease caused by rotaviral infection. A randomised trial of *Lactobacillus* GG therapy has shown reductions in the frequency and duration of rotavirus diarrhoea in children with acute respiratory infection being treated with antibiotics.<sup>23</sup> However, *Lactobacillus* GG therapy in hospitalised infants failed to prevent nosocomial rotaviral infection.<sup>24</sup>

## Vaccines

In view of the high disease burden and high mortality rates in the developing world from rotaviral infection, a rotavirus vaccine is the only control measure likely to have a significant impact on the incidence of the disease. The World Health Organization has given a high priority to the development of a safe and effective rotaviral vaccine.<sup>25</sup>

The first licensed vaccine against rotavirus, a live rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV, known also as RotaShield), was released for use in the United States of America in 1998. The RRV-TV was an oral vaccine designed to provide protection against the four major human serotypes G1, G2, G3 and G4. Extensive trials had demonstrated a vaccine efficacy of up to 91 per cent in preventing hospitalisation for severe diarrhoeal disease and a three dose regimen (at 2, 4, and 6 months) was recommended for all healthy infants in the USA.

A retrospective review of RRV-TV vaccine effectiveness in the prevention of hospitalisations in infants under three years for rotaviral related illness, demonstrated a reduction in attack rates from 0.34 per 100 child years in unimmunised infants, to 0.2 per 100 child years in partially, or to zero per 100 child years in fully, RRV-TV immunised children. This implied a protective effectiveness of 70 per cent and that one episode of rotaviral diarrhoea requiring hospitalisation was prevented for every 64 infants fully vaccinated.<sup>26</sup>

Nine months after the release of the vaccine, when at least one million doses had been administered, the vaccine program was suspended. Fifteen reports of intussusception (a bowel obstruction resulting from the infolding of one segment of the intestine within another) had been reported, with 13 occurring within one week of receiving the first dose of RRV-TV.<sup>27</sup> Although the risk of intussusception due to RRV TV vaccination was low (about 1 in 11,000), trials of new vaccines will need to exclude this rare but serious complication. There will be a need for post-licensure surveillance of intussusception.

In addition, two further human-animal rotavirus based reassortant vaccines are undergoing clinical trials. Merck have completed extensive trials of pentavalent bovine (WC3)-based vaccine incorporating serotypes G1–G4 and P8 specificity.<sup>28</sup> The National Institutes of Health, USA, have developed a bovine (UK) based reassortant vaccine, incorporating G1–G4 antigens and capable of including G5, G8, G9 and G10 antigens as required.<sup>29,30</sup>

Several live attenuated rotavirus vaccine candidates are currently in human trials around the world. These include the attenuated human monovalent live vaccine 89–12 (Rotarix) which is currently undergoing phase III trials in several countries, including the USA and South America. The vaccine efficacy in a recent follow up study in the USA has been estimated at 76 per cent against rotaviral gastroenteritis, 83 per cent against severe rotaviral disease and 100 per cent against rotaviral disease requiring medical intervention.<sup>31</sup>

A naturally attenuated human neonatal rotaviral strain RV3 has been tested recently in a limited phase II trial in Australia. Three oral doses at 3, 5 and 7 months induced immune responses in 46 per cent of recipients and partial protection (54%) against rotaviral disease in a subsequent epidemic.<sup>32</sup>

An estimate of the cost effectiveness of a rotaviral vaccine in Australia was undertaken in 1999. The analysis was based on the RRV-TV vaccine in a universal program and concluded that such a program would be cost-neutral. The authors acknowledged that uncertainties about vaccine and delivery costs made any cost effectiveness estimates difficult.<sup>33</sup>

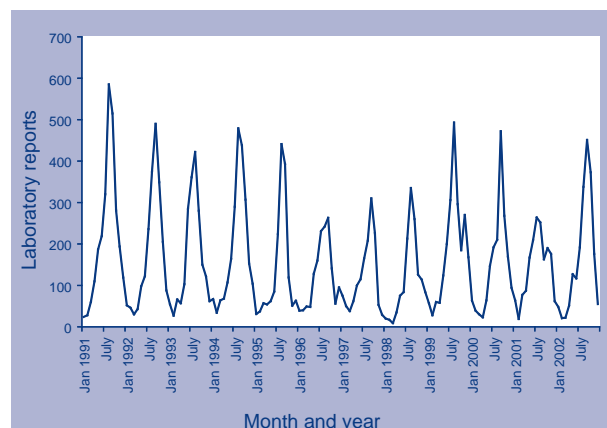
### *Surveillance of rotavirus in Australia*

#### **Laboratory Virology and Serology Reporting Scheme**

Laboratories perform a central role in the definitive diagnosis of rotaviral disease. Since 1991, between 13 and 26 sentinel laboratories have voluntarily notified the Department of Health and Ageing each month of isolations of viruses of public health importance. From 1991 to 2002, between 1,372 and 2,642 reports of rotavirus were received annually, with the largest numbers of reports from New South Wales (32%).

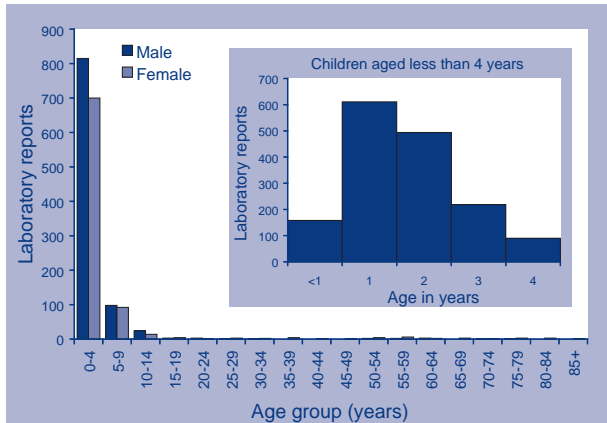
The number of reports received by the Laboratory Virology and Serology Reporting Scheme (LabVISE) are a product of the number and location of reporting laboratories; hence in the 12 year period, 1991 to 2002, only 77 reports were received from the Northern Territory (reported by interstate laboratory as there is no Northern Territory laboratory reporting to LabVISE). LabVISE data on rotavirus show that in Australia there is an annual winter epidemic, with a peak in reports every August or September (Figure 1).

**Figure 1. Laboratory reports to LabVISE of rotavirus infection, Australia, 1991 to 2002, by month of specimen collection**



The age and sex of rotavirus cases reported to LabVISE in 2002 are shown in Figure 2. The male to female ratio was 1.1:1. The largest number of reports was for children aged 0 to 4 years (77% of all reports), among whom the highest rates were in children aged one year (31% of all reports).

**Figure 2. Laboratory reports to LabVISE of rotavirus, 2002, by age and sex**



**National Hospital Morbidity Database**

The National Hospital Morbidity Database (NHMD) is compiled by the Australian Institute of Health and Welfare from data supplied by the state and territory health authorities. The NHMD is a collection of summary records for patients admitted to public and private hospitals in Australia in the years 1993–94 to 2000–01. The total number of records for 2000–01 was 6.14 million. Almost all hospitals in Australia are included: public acute, public psychiatric hospitals, private acute and psychiatric hospitals, and private freestanding day hospital facilities.

Data from the NHMD for rotaviral hospitalisations for rotaviral enteritis are shown in the Table as ‘separations.’ This term is used to refer to the episode of care, which can be a total hospital stay (from admission to discharge, transfer or death), or a portion of a hospital stay beginning or ending in a change of type of care (for example, from acute to rehabilitation). ‘Separation’ also means the process by which an admitted patient completes an episode of care by being discharged, dying, transferring to another hospital or changing type of care.

Data from the two most recent years are shown in the Table. Rotaviral enteritis was recognised as the primary diagnosis in between 3,000 and 4,300 separations in Australian hospitals. These represented between a quarter and a third of all separations for viral gastroenteritis. Of hospital separations for rotaviral enteritis, 94 per cent were in children aged less than five years. Patients admitted for rotaviral enteritis were hospitalised for two to three days on average and accounted for between eight and 11,000 hospital bed days.

**Rotavirus surveillance in the Northern Territory**

In the Northern Territory, infection with rotavirus has been a notifiable disease since 1994. The number of notifications and the rates of rotaviral disease in Indigenous and non-Indigenous populations are shown in Figure 3.

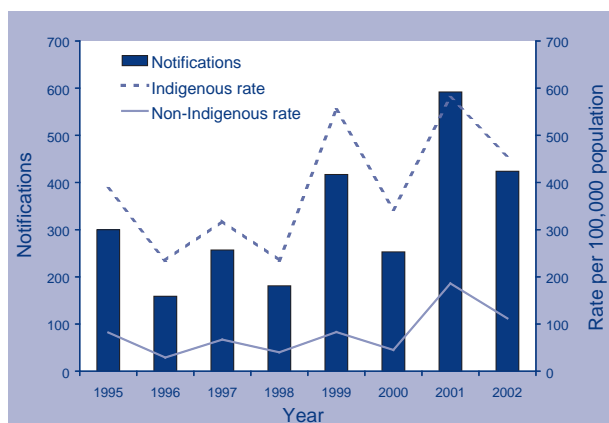
**Table. Separation, patient day and average length of stay for rotaviral enteritis, Australia, 1998–99 and 1999–00\***

Separations	1998–1999	1999–2000
AO8 Viral and other specified intestinal infections	13,026	14,110
AO8.0: Rotaviral enteritis	3,043	4,306
(percentage of separations under AO8)	(23%)	(31%)
Separations in < 1 year olds	809	1,018
Separations in 1 to 4 year olds	2,055	3,032
Percentage of rotaviral separations in infants aged less than 5 years	94.5%	94%
Total patient days for rotaviral enteritis (all ages)	8,194	11,029
Average length of stay for rotaviral enteritis (all ages)	2.7	2.6

\* Source Australian Institute of Health and Welfare National Hospital Morbidity Database.

The magnitude of the annual rotaviral epidemic varies year by year with biennial peaks.<sup>34</sup> The Northern Territory contains both tropical regions around Darwin and hot arid regions around Alice Springs. Neither area experiences consistent seasonal peaks in rotaviral activity.<sup>35</sup> The rate of rotaviral enteritis in Indigenous Australians in the Northern Territory was between three and eight times the rate in the non-Indigenous population (Figure 3).

**Figure 3. Notifications of rotaviral enteritis and rates per 100,000 population in Indigenous and non-Indigenous populations, Northern Territory, 1995 to 2002**



Source: Data supplied by Dr Peter Markey, Centre for Disease Control, Darwin.

These surveillance data were also used to analyse an outbreak of G9-associated rotavirus in Central Australia, in which over 500 cases of childhood diarrhoea were notified.<sup>34</sup> The impact of this outbreak, unprecedented in Australia, placed an extreme demand on the Central Australian health services.<sup>36</sup>

**Australian Rotavirus Surveillance Program**

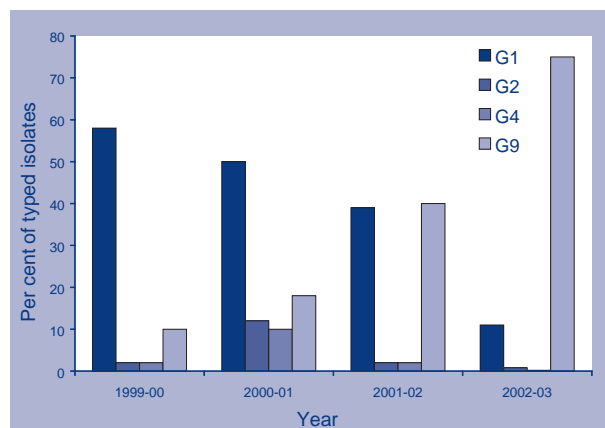
A 13-year survey (1980–1993) of children hospitalised with acute gastroenteritis at the Royal Children’s Hospital in Melbourne identified Group A rotavirus in 40 per cent of children, and 55 per cent of children aged between 12 and 23 months. The study also found that rotavirus was responsible for 19 per cent of acute gastroenteritis in children aged under six months. This implies that any vaccine must be able to be given early in life, or a significant number of events in infants will not be prevented.<sup>37</sup> Rotavirus appeared to be largely responsible for the seasonal increase in cases during the winter epidemics.

This work prompted a national survey in eight Australian cities of rotavirus isolates from children aged less than five years admitted to hospital for acute gastroenteritis between 1993 and 1996.

Admissions for gastroenteritis averaged just under 20,000 per year nationwide, and 50 per cent could be attributed to rotavirus infection. This study showed a predominance of the G1 serotype in all centres. Subsequent work demonstrated outbreaks of rotaviral enteritis in the Northern Territory in 1993–04 due to unusual rotaviral strains, including a G8 strain with some ‘bovine’ characteristics.<sup>38</sup>

From June 1999, a national rotavirus surveillance program was initiated to undertake the characterisation of rotavirus strains causing severe diarrhoea in Australian children. The program was designed to monitor changes in the prevalence of rotaviral serotypes prior to the anticipated introduction of a rotaviral vaccine into Australia. The Australian Rotavirus Surveillance Program, funded by the Commonwealth Government has documented rotaviral serotypes circulating in Australia over the past four years (Figure 4).

**Figure 4. Changes in prevalence of serotypes of subgroup A rotavirus, Australia, 1999 to 2002**



The major finding is the appearance and rapid increase in the prevalence of the G9 serotype.<sup>39</sup> National rotavirus surveillance has shown serotype G9 to be the dominant type for the past two reporting periods (2001–02 to 2002–03). In Darwin in 2001–02 the G9 serotype made up 95 per cent of serotypes and was the serotype responsible for a major outbreak in 2001 in the Northern Territory (described above), while in Perth and Melbourne the G1 serotype was still the most prevalent serotype (72 and 48% of reports, respectively). Since then, in 2002–03, G9 has become the most common serotype throughout Australia, and was dominant in all seven contributing centres.

Internationally, the emergence and spread of the G9 serotype has been documented in several countries since 1995<sup>39,40</sup> and should now be considered the fifth globally important serotype along, with serotypes G1 to G4.<sup>6</sup> Continued surveillance of the circulating Group A serotypes is essential preparation for the introduction of new rotaviral vaccines.

### The future of rotavirus surveillance in Australia

The current surveillance systems capturing data on rotaviral infection in Australia each contribute complementary data essential for public health action. LabVISE provides basic information on the annual epidemics of rotaviral disease, largely from hospitalised children in south-eastern Australia. LabVISE data on rotaviral infections in the Northern Territory is inadequate. The LabVISE system is not sensitive enough to detect year to year variations in the size and extent of the annual epidemics.

The inclusion of rotavirus infection in the Northern Territory notifiable diseases surveillance system however, is able to identify the extent of disease activity in the communities most affected by the disease. These data are useful in describing the variation in the size of annual epidemics, outbreaks of disease and the burden of rotaviral disease in Indigenous communities.

The National Hospital Morbidity Database provides some estimates on the hospitalisation costs associated with rotaviral enteritis on a national basis. Delays in these data limit their usefulness for surveillance purposes. Hospitalisation data is important for the analysis of the cost effectiveness of any future rotaviral vaccine program.

The Australian Rotavirus Surveillance Program has documented rapid and significant changes in the relative prevalence of different serotypes of Group A rotaviruses and the variation in the geographical distribution of serotypes across the country. It is important to maintain a central laboratory capable of detection and characterisation of new rotavirus strains as they emerge. Future rotavirus vaccines may require updating if they do not cross-protect against commonly found strains. These data are essential to policy makers in future decisions about the introduction of a rotaviral vaccine to Australia.

In combination, these four surveillance systems provide important information about rotaviral disease in Australia. Should a rotaviral vaccine be introduced, either as a universal childhood vaccine or targeted to Indigenous children, none of the present surveillance systems would be adequate to measure the vaccine effectiveness in disease control. The future of rotaviral surveillance depends largely on whether or not vaccines are introduced. Meanwhile the current systems are important in monitoring the epidemiology of the rotaviral disease, and for informing decisions about the introduction of any new vaccine in Australia.

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