Short reports

Rotavirus surveillance in Australia

Kate A Ward, Peter B McIntyre, Carl D Kirkwood, Paul W Roche, Mark J Ferson, Paul G Van Buynder, April R Roberts-Witteveen, Alison M Kesson, Vicki L Krause, Jeremy M McAnulty

Background

Rotavirus

Globally, rotavirus is the most common cause of severe gastroenteritis in early childhood[1] infecting almost all children by five years of age. Rotavirus is estimated to be responsible for more than 600,000 deaths per year in these children with 85% occurring in low-income countries.[2]

In Australia, an estimated 10,000 hospitalisations and one death occur annually in children under 5 years, mostly in children aged under two years.[3] Among those under one year, hospitalisation rates are five times greater in Indigenous Australians compared with non-Indigenous children.[4] In addition to hospital admissions, 22,000 emergency department visits attributable to rotavirus are estimated to occur annually.[3] Direct medical costs in Australia are estimated at over $30 million.[3]

Rotaviruses are primarily spread by the faecal-oral route. Symptoms include diarrhoea, vomiting and fever. In severe cases acidosis, electrolyte abnormalities, severe dehydration and death can occur. Infection can be asymptomatic, especially in infants aged under three months. Diagnosis is usually confirmed by detection of rotavirus in stool samples.[5]

Rotaviruses are RNA viruses. They are classified into serogroups (A–G) with most human infections caused by Group A. They can be further subdivided into G and P serotypes by the VP7 and VP4 outer proteins of the virus (e.g. G1-4, G9, P[4], P[8]).[5]

In Australia, from 1 July 2005 to 30 June 2006, national rotavirus serotype surveillance data indicated that serotype G1 was the most dominant serotype representing 40% of all strains. Serotype G1 continues to be the most frequently reported serotype worldwide and has been the most common Australian serotype, for all but two years since 1999. From July 2001 to June 2003, serotype G1 was replaced by G9 as the most dominant serotype. Substantial geographical variation in prevalent serotypes has also been identified within Australia.[6] This geographical and temporal variation in strains along with the diversity of strains capable of causing severe disease in children in Australia has potential implications for vaccine effectiveness should the prevalent strains diverge from those primarily targeted by the available vaccines.

Two vaccines have been recently developed. Rotarix® (GlaxoSmithKline) is a live attenuated G1P[8] human rotavirus, which provides cross protection against most other serotypes when administered in two doses, one to two months apart.[7] Rotateq® (Merck) is a live pentavalent human-bovine (WC3 strain) reassortant rotavirus vaccine providing protection against five human serotypes G1, G2, G3, G4 and P[8] when administered in three doses four to ten weeks apart.[8]

In 2006, Rotateq was licensed for use in the United States of America (USA) and Rotarix was licensed for use in the United Kingdom. Both vaccines have been shown to be highly efficacious against severe rotavirus disease with 85% efficacy for Rotarix,[7] and 98% efficacy for Rotateq.[8]

Rotarix and Rotateq were licensed in Australia in 2006. Both vaccines have been available on the private market since June 2006 and Rotarix was publicly funded for babies in the Northern Territory from August 2006. Rotavirus vaccination has been included in the National Immunisation Program, commencing from 1 July 2007, with all infants born after 1 May 2007 eligible for vaccination. Victoria, South Australia and Queensland have included Rotateq in their vaccination program while the remaining jurisdictions have elected to use the Rotarix vaccine.

Surveillance

According to published US Centers for Disease Control and Prevention (CDC) guidelines,[9] the public health importance of a disease can be measured using the following parameters:

- frequency of disease;
- severity of disease;
- inequities associated with disease;
- costs;
- preventability (or amenability to public health intervention); and
- public interest.

Prior to establishing a surveillance system for any condition, it is crucial to identify specific aims and ensure that any system is adequately sensitive and specific to achieve these aims.

The aims of surveillance vary depending on the health condition of interest, and may include to:

- control the spread of disease (with public health follow up for each case);
- estimate the burden of disease;
- monitor trends in the burden over time;
- assess the effectiveness of interventions (e.g. vaccines);
- monitor changes in disease characteristics over time (e.g. change in serotypes, strains);
- enhance understanding of the epidemiology and clinical course of the disease;
- provide a basis for epidemiologic research; and
- inform policy makers.

Following the identification of surveillance system aims, further consideration needs to be given to the specific analyses that will be conducted, the importance of timeliness and the potential public health actions in response to surveillance data. Finally, the resources (including funding and personnel) that would be required to operate the system must be allocated and key stakeholders consulted prior to its introduction.

Rotavirus surveillance

Aims

Based on the above criteria, the following is a list of possible aims of rotavirus surveillance in Australia with a brief discussion surrounding each aim.

Control the spread of disease

Laboratories and doctors are likely to identify only a small proportion of all rotavirus cases (Figure). Public health follow-up on individual cases for rotavirus will therefore not be a feasible or appropriate method to control the spread of rotavirus.

Estimate the burden of a disease, monitor trends in the burden of disease over time and provide a basis for epidemiologic research

Given that many rotavirus cases do not make contact with a health provider, the burden of rotavirus infection must be estimated.

Laboratory counts of patients who test positive for rotavirus depend on the number of tests done that is influenced by a number of factors including physician practice and access to laboratory facilities. While access to laboratory testing may remain stable within regions, other more unpredictable changes such as physician practices following the introduction of the vaccination and epidemics of gastroenteritis infection due to norovirus, may influence testing requests (Table). Thus interpreting trends over time in positive laboratory tests for rotavirus requires caution, especially at the national level.

Assuming that moderate to severe cases of rotavirus make contact with the hospital system, monitoring rotavirus coded hospitalisation data and mortality from all gastroenteritis-related codes over time could broadly detect changes in the burden of severe rotavirus.

Case surveillance could direct future scientific studies with clearly defined hypotheses and study population e.g. an increase in incidence in certain groups or geographic areas may warrant further research. With the introduction of the vaccine and expected decline in cases, outbreaks will provide an increasingly valuable opportunity to assess vaccine effectiveness.

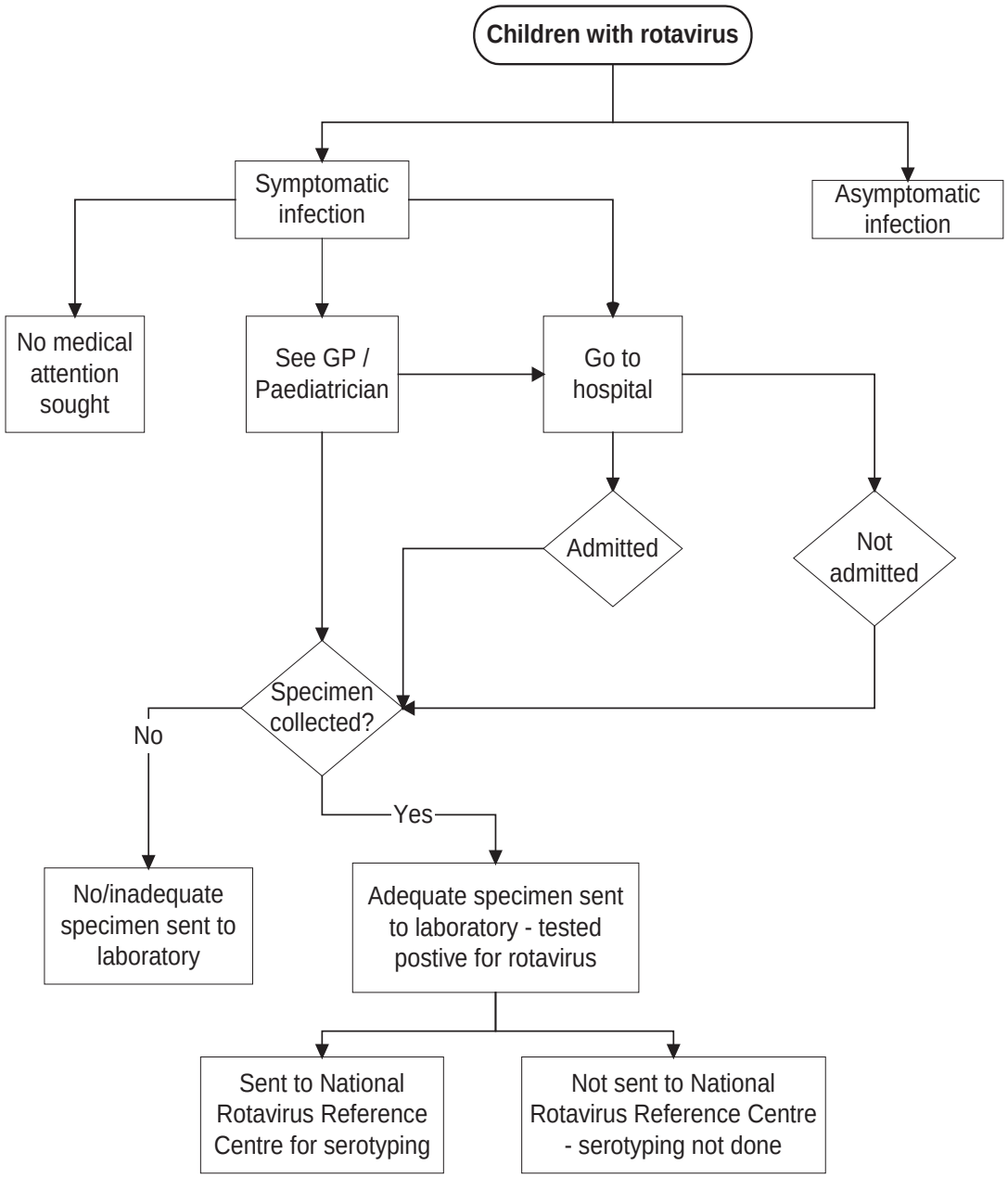
Assess the effectiveness of vaccines

The two rotavirus vaccines have undergone rigorous safety and efficacy trials each involving approximately 70,000 children.[7,8] While public funding is not contingent on national effectiveness data, evaluating the impact of any rotavirus vaccination program is worthwhile to ensure maximum impact of the vaccination. The absence of a stable national baseline of rotavirus notification patterns and rates prior to vaccine introduction and the fact that laboratory data reflect only a proportion of the true incidence of rotavirus disease makes it difficult to assess the impact of vaccination at the national level. The opportunity cost of investing public health resources into individual case follow-up to determine vaccine status must be considered at the jurisdictional level. Specific scientific studies to better assess vaccine efficacy in defined populations may be appropriate and feasible under some circumstances, especially in areas of high incidence such as the Northern Territory.[10] Australia may have the unique opportunity to compare the two vaccines, given that individual jurisdictions have chosen different vaccines.

Monitor changes in serotypes over time

The National Rotavirus Reference Centre has documented temporal and geographical variations in strain type in isolates sent from participating laboratories throughout Australia since 1999. Given the

Figure. Diagram of children infected with rotavirus captured by laboratory surveillance



introduction of a vaccine in subgroups of the population, understanding the impact of vaccination on circulating serotypes is important. The prevalent strains of rotavirus have been shown to vary substantially in the absence of vaccine pressure so interpretation of changes following vaccine introduction is complex and likely to require a long time period. To maximise the usefulness of such data, the National Rotavirus Reference Centre must receive specimens from a sufficiently large and representative sample across the country.

Enhance understanding of the epidemiology of the disease

Laboratory and hospitalisation data following vaccine introduction will add to the available descriptive epidemiological data from the pre-vaccine period. Analysis of additional risk factors including indigenous status would require follow-up of individual cases.

Table. Potential sources of data for rotavirus surveillance

	Advantages	Limitations
Mortality data	Mortality due to any gastroenteritis-related codes could be evaluated	Mortality extremely low in Australia therefore not likely to be very informative source of data
	Captures most severe cases	Biased sample given that only the most severe cases will die
	Additional resources required for data analysis and reporting	Delays in accessing data (approximately 1 month)
		Potential coding/ cause of death assignment errors
Inpatient statistics data	Has been shown in Australia to provide a good source of information on moderate to severe disease over time (of primary importance for vaccination)	Limited to rotavirus cases associated with moderate to severe disease
	Specific in the inpatient data collection code for rotavirus already collected	Potentially underestimate cases if rotavirus ICD code not assigned[4]
	Captures sex, age, aboriginality and length of time in hospital	Hospital practices/admission rates may change over time
	Can be used to help assess the economic burden of rotavirus	Variations in admission practices between jurisdictions complicates national summary data
	Additional resources required for data analysis and reporting	Delays in accessing data (available within six months)
Laboratory data – sentinel (e.g. LabVISE) or all laboratories	Timely	Only represent a proportion of all rotavirus cases (moderate to severe disease)
	Accurate	May be variations in testing practice over time (especially considering the introduction of a vaccine)
		Can be influenced by other factors e.g. epidemic season of norovirus can result in increased in all virus testing
		Additional resources required for data entry, reporting and analysis
Emergency department (ED) surveillance	Timely	Low specificity: only captures data on ED presentations that are allocated a provisional diagnosis of gastrointestinal disease. Laboratory results not usually available in ED setting
	Resource intensive to set up but minimal additional resources required once established as reports can be automated	Data not captured nationally
Sentinel GPs	More representative sample than hospital data	Resource intensive to maintain
	Vaccine information available	
Institutional outbreak reports	Identifies outbreak, which enables public health intervention	Incomplete reporting as reliant on institution notifying public health unit
	No additional resources required as data already collected by OzFoodNet	

Current rotavirus surveillance systems in similar countries

United States of America

Rotavirus is not a notifiable disease in the USA. The CDC recommendations for national surveillance systems for rotavirus infections include national hospital discharge databases for rotavirus diagnoses and laboratory reports from sentinel laboratories. A system of sentinel laboratories has also been established by the CDC to monitor the prevalence of rotavirus serotypes over time. Special studies (e.g. case control and retrospective cohort studies) are planned to assess vaccine effectiveness at state and local levels.[11]

United Kingdom

Rotavirus is not a notifiable disease in England or Wales. Surveillance is based on routine laboratory reports to monitor secular trends.[12] Ad hoc disease burden studies have estimated the proportion of acute gastroenteritis that is attributable to rotavirus using data from laboratories, general practitioners, hospital admissions and deaths.[13]

Canada

Rotavirus is not a notifiable disease in Canada. Surveillance is based on laboratory data reported through the National Enteric Surveillance Program.

These data represent a subset of infections and are meant to monitor trends rather than provide an estimate of incidence. Ad hoc cohort studies have been conducted to estimate the burden of rotavirus in Canada. Prospective hospital based studies will be used to assess vaccine effectiveness in the future.[14]

Current rotavirus surveillance systems in Australia

In Western Australia (since 2006), Queensland (since 2005) and the Northern Territory (since 1994), all laboratory-confirmed cases of rotavirus infection are notifiable conditions, which are reported to the health department under public health legislation. On the basis of notifications to health departments in 2006, there were 605 cases (rate = 311/100,000) in the Northern Territory and 2,508 cases (rate = 64/100,000) reported in Queensland. Laboratory surveys in New South Wales suggest that just over 1,000 (rate = 18/100,000) stool samples tested positive for rotavirus in 2006.

The National Rotavirus Reference Centre in Melbourne currently collects specimens from nine collaborating centres in New South Wales, the Northern Territory, South Australia, Victoria and Western Australia in order to characterise rotavirus strains causing annual epidemics of severe diarrhoea in young children. Participating laboratories predominantly test specimens from hospitalised children.

Potential data sources in Australia include death registry data (although this is limited by small numbers), inpatient statistics for all gastroenteritis and episodes coded as due to rotavirus, emergency department presentations and institutional outbreak reports. Hospital and mortality data are delayed and are currently only analysed by researchers on an ad hoc basis.

Laboratory diagnoses and sentinel general practice presentations are two potential data sources for rotavirus surveillance but such data are not currently collected nationally. The advantages and limitations of these data sources are discussed in the Table.

Monitoring adverse events

Extensive safety data exists for both rotavirus vaccines[7,8] and post licensure studies are underway in the USA. While intussusception was identified as an adverse event of the older rotavirus vaccine licensed in 1998 in the USA[15] (prompting its later withdrawal), no association with intussusception has been found for the two new rotavirus vaccines. The existing reporting through the Adverse Drug Reactions Advisory Committee can be used to monitor any adverse events associated with rotavirus vaccines but has substantial limitations, as it is a passive reporting system. In 2007, to coincide with the introduction of rotavirus vaccines into Australia, the Australian Paediatric Surveillance Unit commenced a national study to monitor intussusception incidence in children aged less than 24 months.

Summary

Rotavirus is a cause of significant morbidity in children aged under five years in Australia. Clinical trials have shown that two available vaccines are highly efficacious in the prevention of severe diarrhoea and hospitalisation due to rotavirus. A national rotavirus vaccination program was initiated in Australia in July 2007.

Apart from immunisation, current tools are unlikely to be effective in controlling the spread of rotavirus in the wider community. Routine surveillance has limited value in assessing vaccine effectiveness.

The available evidence indicates that surveillance is likely to be useful for (and therefore aim to):

1. Detect changes in the rotavirus serotypes to track whether prevalent strains match the available vaccine. This requires the National Rotavirus Surveillance Program to test a representative sample of rotavirus cases across Australia.
2. Monitor trends in the burden of rotavirus over time using data on positive laboratory tests stratified by jurisdiction and hospitalisations from all gastroenteritis-related codes and those coded as due to rotavirus. Mortality data are likely to be of limited value but are important to evaluate over a longer time period.
3. Provide a basis for further epidemiologic research.

Recommendations

1. States and territories should consider mandating laboratory reporting of patients with rotavirus infection under public health legislation to broadly monitor the burden due to rotavirus and facilitate collection of representative specimens for the National Rotavirus Reference Centre.
2. States and territories should ensure representative samples are submitted to the National Rotavirus Reference Centre for serotyping.
3. The National Rotavirus Reference Centre will continue to distribute annual reports to laboratories for circulation to stakeholders.
4. The Surveillance Branch of the Australian Government Department of Health and Ageing and the National Centre for Immunisation Research and Surveillance should regularly monitor mor-

tality, hospitalisation data already collected and additional laboratory data, for changes in the burden of rotavirus over time.

5. Special studies that address specific research questions such as vaccine efficacy in certain groups may be undertaken by jurisdictions with the interest and capacity to do so, especially for groups at special risk such as Indigenous children in high incidence areas.

Author details

Ms Kate Ward, Trainee Public Health Officer[1]
Professor Peter B. McIntyre, Director[2,3]
Dr Carl D Kirkwood, Senior Research Fellow[4]
Dr Paul W Roche, Epidemiologist[5]
Professor Mark J Ferson[6,7]
Associate Professor Paul G Van Buynder, Director[8]
Mrs April R Roberts-Witteveen[5,9]
Associate Professor Alison M Kesson, Head of Infectious Diseases and Microbiology[10]
Associate Professor Vicki L Krause, Director[11]
Dr Jeremy M McAnulty, Director[1]

1. Communicable Diseases Branch, NSW Health, North Sydney, New South Wales
2. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Westmead, New South Wales
3. Discipline of Paediatrics and Child Health and School of Public Health, University of Sydney, New South Wales
4. Enteric Virus Research Group, Murdoch Childrens Research Institute, Parkville, Victoria
5. Surveillance Policy and Systems Section, Australian Government Department of Health and Ageing, Canberra, Australian Capital Territory
6. Director, Public Health Unit, South Eastern Sydney Illawarra Health, Randwick, New South Wales
7. Conjoint Professor, School of Public Health & Community Medicine, University of NSW, Kensington, New South Wales
8. Communicable Disease Control, WA Department of Health, Subiaco, Western Australia
9. Masters of Applied Epidemiology Scholar, Australian National University, Acton, Australian Capital Territory
10. The Children's Hospital at Westmead and Discipline of Paediatrics and Child Health, The University of Sydney, New South Wales
11. Centre for Disease Control, Department of Health and Community Services, Casuarina, Northern Territory

Corresponding author: Ms Kate Ward, Communicable Diseases Branch, NSW Health, Locked Mail Bag 961, North Sydney NSW 2059. Telephone: +61 2 9391 9279. Facsimile: +61 2 9391 9189. Email: kward@doh.health.nsw.gov.au

References

1. Parashar UD, Bresee JS, Gentsch JR, Glass RI. Rotavirus. *Emerg Infect Dis* 1998;4:561–570.
2. Parashar UD, Gibson CJ, Bresse JS, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis* 2006;12:304–306.
3. 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.
4. Newall AT, MacIntyre R, Wang H, Hull B, Macartney K. Burden of severe rotavirus disease in Australia. *Paediatr Child Health* 2006;42:521–527.
5. Glass RI, Parashar UD, Bresee JS, Turcios R, Fischer TK, Widdowson MA, et al. Rotavirus vaccines: current prospects and future challenges. *Lancet* 2006;368:323–332.
6. Kirkwood CD, Cannan D, Bogdanovic-Sakran N, Bishop RF, Barnes GL, National Rotavirus Surveillance Group. National Rotavirus Surveillance Program annual report, 2005–06. *Commun Dis Intell* 2006;30:434–438.
7. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11–22.
8. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z; et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23–33.
9. Centers for Disease Control and Prevention. Updated Guidelines for evaluating public health surveillance systems. *MMWR Recomm Rep* 2001;50 (RR13):1–35 Available from: http://iier.isciii.es/mmwr/preview/mmwrhtml/rr5013a1.htm
10. Schultz R. Rotavirus gastroenteritis in the Northern Territory, 1995–2004. *Med J Aust* 2006;2;185:354–356.
11. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP) *MMWR Recomm Rep* 2006;55(RR12):1–13. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5512a1.htm
12. Health Prevention Agency. Rotavirus surveillance data from England and Wales. Available from: http://www.hpa.org.uk/infections/topics_az/rotavirus/data.htm
13. Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. *Vaccine* 2007;25:3962–3970.
14. Landry L. Rotavirus disease in Canada. *7th Canadian Immunization Conference;* 3–6 December 2006. Winnipeg, Manitoba, Canada. Available from: http://www.phac-aspc.gc.ca/cnic-ccni/2006/pres/_pdf-mon-lun-dec04/PM/B-Hall-B-Rotavirus/Landry_Rotavirus-disease-in-Canada_Imm-Conference-2006.pdf
15. Centers for Disease Control and Prevention. Suspension of rotavirus vaccine after reports of intussusception—United States, 1999 [published erratum appears in *MMWR Morb Mortal Wkly Rep* 2004;53:879]. *MMWR Morb Mortal Wkly Rep* 2004;53:786–789.