Rotavirus diarrhea and Aboriginal Children

Rotavirus is the most common cause of paediatric gastroenteritis worldwide. In Australia, Aboriginal children are at the greatest risk of severe disease. The continual changes in dominant strains pose challenges to vaccine success. However, early evidence suggests that rotavirus vaccination will be successful in reducing the impact of rotavirus disease on Australia’s most susceptible population.

Rotaviruses were first discovered in humans in 1973, when they were identified by electronmicroscopy in duodenal epithelial cells and in diarrheal faeces from young children admitted to the Royal Children’s Hospital, Melbourne, for treatment of severe, acute diarrhoea. Within 6 months, similar particles had been visualised in young children hospitalised in the UK, Canada, Singapore and, eventually, worldwide. The discovery of “rotaviruses” as important causes of severe diarrhoea in young children was quickly linked to descriptions in the literature implicating morphologically similar viruses as causative agents of epidemic diarrhoea of infant mice (EDIM) and scours in newborn calves (Nebraska calf diarrhoea virus – NCDV). Eventually rotaviruses were found as causes of diarrhoea in the young of many other mammalian and avian species. All were identified as non-enveloped, 70nm diameter viruses, with a wheel-like appearance (rota is Latin for wheel) and they were classified as belonging to the Genus Rotavirus, within the family Reoviridae (Figure 1).

Rotaviruses contain 11 segments of double-stranded ribonucleic acid (RNA), that can be separated by gel-electrophoresis into 11 genes, coding for six structural proteins and six non-structural proteins implicated in replication. Rotaviruses were initially subdivided into “electropherotypes”, based on migration of these RNA gene segments. Epidemiological studies show a great diversity of electropherotypes, often coexisting within the same outbreak, but changing from year to year. Genetic and serological assays can now identify two outer coat proteins VP7 (a glycoprotein) and VP4 (a protease-sensitive protein) that stimulate neutralising antibodies and form the basis for classification of rotaviruses into VP7 (G types) and VP4 (P types). To date, 15 G types and 25 P types have been identified in humans and animals. In humans, 5 G types (G1, G2, G3, G4 and G9) in association with 3 P types (P[4], P[6], P[8]) are responsible for >90% of all disease.

A pilot study of Aboriginal children hospitalised for diarrhoea in 1974, in widely separated Aboriginal communities in Kalgoorlie, Western Australia (WA), Alice Springs, Northern Territory (NT) and Brewarrina, New South Wales (NSW) identified rotaviruses (then referred to as orbivirus-like particles) in children in each location. A more extensive study of 92 children with gastroenteritis admitted to Alice Springs Hospital in 1976 showed rotavirus infection in 54% of children, compared with Shigella (9%), Salmonella (1%), enteropathogenic E. coli (11%), astroviruses 9% and parasites (12%). This was convincing...
evidence of the importance of rotavirus in the causation of severe acute diarrhoea in young Aboriginal children.

At that time morbidity and mortality due to gastroenteritis in young Aboriginal children was 10-15 times higher than in white Australian children. Numerous surveys, in Queensland, WA and the NT, have emphasised the major contribution of acute diarrhoea to morbidity, mortality and the development of malnutrition in Aboriginal children 7,9,10. In the Darwin rural district, one in three children under 2 years old were hospitalised annually with diarrhoea. Study of birth cohorts of Western Australian Aboriginal and non-Aboriginal children aged 0-2 years showed that Aboriginal children had significantly higher rates of hospitalisation for gastrointestinal infections than non-Aboriginal children 9. Current studies still implicate rotavirus infection in approximately 50% of young Aboriginal children with severe diarrhoea.

We have been collaborating with the laboratories in Alice Springs and Darwin to monitor occurrence of severe rotavirus infection in Aboriginal children since 1976. The age group most at risk of severe diarrhoea are infants under 12 months of age, compared with Australian urban centres, where the majority of children admitted to hospital are 12-24 months old 11. Annual peaks of rotavirus disease usually occur during colder months in Alice Springs, but are less predictable in tropical Darwin. The dominant rotavirus serotypes change each year and differ from strains identified concurrently in other Australian centres. Peaks of disease are interspersed with variable periods when limited severe rotavirus disease is detected.

Large epidemics have occurred every 2 to 4 years, associated with dominant strains in 1976 – G3P[8], 1982 – G1P[8] and 1986 – G4P[8] (Figure 2). It is possible that the dominant strains are escape mutants selected by “between epidemics” replication in adults, who possess pre-existing rotavirus neutralising antibodies, as postulated for influenza 12. Alternatively, new strains can arise from reassortment as shown for the multiple-gene rotavirus reassortant (G2P[4]) causing an epidemic in Central and Northern Australia in 1993-1994 18. The identification of occasional unusual strains such as G6P[14], G8P[14] 17 and frequent differences between strains present in Alice Springs and those in other urban centres have the potential for the generation of unusual reassortant strains 19.

Major epidemics can have a similar impact to that of a natural disaster. For example, “in May 2001, one of the largest outbreaks of rotavirus in living memory swept through Central Australia” 19; it was caused by a G9P[8] strain, new to the NT and that may have originated in Perth 20. The first case presented at Alice Springs on 17 January, 2001, followed rapidly by the simultaneous appearance of the disease in widely separated remote communities of NT, in Darwin and in Western Queensland. At the peak of the epidemic in Alice Springs, 246 children (mostly <4 years old) presented to the emergency department and 137 were hospitalised during 1 month, with severe dehydration and acidosis (Figure 3).

Management of the outbreak was complex and involved the removal of non-infected children from the hospital to avoid nosocomial transmission, deferral of elective procedures (including operations), conversion of a day surgery unit to a paediatric ward, recruitment of additional nurses from Darwin and rapid replenishment of supplies (IV poles, IV fluids and nappies). Although many children suffered from severe disease, none died.

The discovery of rotaviruses in 1973 and the demonstration of their major involvement in the causation of severe, acute gastroenteritis and high mortality in young children worldwide, led to initiatives by the World Health Organization (WHO) to encourage the development of an effective live oral vaccine 21-23. The strategy for vaccine administration to infants <3 months old was based on two separate longitudinal studies of natural rotavirus infection in infants in Melbourne and in Mexico 24, 25. Both studies showed that primary infection, even in newborn babies, protected against severe symptoms on reinfection.

Initially a naturally attenuated bovine rotavirus (RIT) was trialled as a vaccine in young children in Finland, with encouraging results 22 but proved disappointing when trialled later in Peru and The Gambia. A tetravalent (G1, G2, G3, G4) simian reassortant vaccine (Rotashield), proved highly effective in the prevention of rotavirus diarrhoea, but was withdrawn after a rare association with development of intussusception was identified. Two new
vaccines – an attenuated human serotype GIP[8] strain (Rotarix, GSK) and a pentavalent (G1, G2, G3, G4, P[8]) bovine-human reassortant mixture (RotaTeq, Merck) – have now been shown to be safe immunogenic and 80-100% effective in preventing severe rotavirus gastroenteritis due to common human serotypes. Trends towards efficacy against other serotypes have also been identified. Efficacy of these rotavirus vaccines in developing countries in Asia and Africa still needs to be established.

At present, hospitalisation rates of Aboriginal children with rotavirus gastroenteritis remain high and are 3-8 times those for non-Indigenous children. Rotavirus infection accounts for approximately 50% of hospital admissions of Aboriginal children for treatment of severe gastroenteritis in NT and Darwin, representing 117/1000 children (<5 years) in NT compared with a median of 15/1000 children in other states. In addition, the duration of stay of Aboriginal children is much longer (9.15 days) than for non-Aboriginal children (2.2 days). The importance of rotavirus infection was recognised in the NT when the disease became notifiable in 1994. Vaccination to prevent rotavirus disease could provide substantial savings to the healthcare system.

The licensing and availability of effective live oral rotavirus vaccines in Australia resulted in a decision by the NT government to make one of these vaccines (Rotarix) available free of charge to all infants born after 1 August 2006. Rotarix and RotaTeq were both added to the Pharmaceutical Benefits Scheme and became part of the Australian National Immunisation Program from July 2007. The vaccines selected in each state varied. Rotarix is used in NT, NSW, Tasmania, Australian Capital Territory and in WA (until May 2009). RotaTeq is used in Victoria, South Australia and Queensland. No excess of serious adverse events (including intussusception) have been associated with either vaccine during the first 6 months of use. There is early evidence of decline by 53% (2007) and by 65% (2008) in rotavirus notifications for <2-year-old children in Queensland. Additionally, Rotarix vaccination has shown a protective efficacy of 77.7-84.5% in Central Australian children exposed to a widespread outbreak of G9P[8] infection in 2007.

Conclusion
Rotavirus disease is a major cause of morbidity in Aboriginal children, with large outbreaks due to different genotypes occurring regularly. Early evidence indicates the introduction of a rotavirus vaccine has the potential to have a significant impact on severe disease in a population that is most vulnerable.

References

Professor Ruth Bishop is a Senior Principal Research Fellow (Hon) with the Murdoch Childrens Research Institute, advising on rotavirus vaccine development. She is Co-Director of WHO Collaborating Centre for Child Health and has an interest in rotavirus vaccine development and introduction.

Dr Kirkwood heads the enteric virus research laboratory, in the Murdoch Childrens Research Institute, which is housed at the Royal Children’s Hospital, Melbourne. His research interests involve understanding the role of enteric viruses in gastrointestinal disease.