Epidemiology of rotavirus gastroenteritis

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Infantile gastroenteritis and the resulting dehydrating diarrhoea is a major cause of morbidity in developed countries and of mortality in many developing countries. Since their original description in 1973, rotaviruses have emerged as the single most important cause of diarrhoea in infants and young children requiring admission to hospital for treatment of gastroenteritis. A desire to reduce the significant morbidity associated with rotaviruses led to the development of a live attenuated vaccine, recently made available for trials in this country. Concurrently, advances in adequate typing systems allowing characterisation of virus from different geographic areas and from sequential infections in populations followed longitudinally have increased our understanding of the epidemiology of this most important group of viruses.

Knowledge of the epidemiology of rotavirus would be important in the planning of any vaccine programme contemplated for this country.

The gastroenteritis associated with rotavirus has consistently been described as more severe than that caused by other agents. The pathophysiology is felt to be loss of absorptive capacity in the small intestine. The incubation period is 48 hours, with viral excretion preceding the onset of symptoms. There is often early vomiting followed by explosive and watery diarrhoea lasting 5-7 days. Virus is usually shed from the 3rd-8th days. Although IgM antibody appears on the 5th day and stays elevated for about three weeks, IgG antibody does not appear until 2-4 weeks after infection.

Cross-sectional seroepidemiological surveys have shown high antibody levels in the newborn (due to transfer of passive antibody from mother), falling over the first six months of life, peaking again from 2-3 years. High geometric mean titres are then maintained until the age of 40 when levels begin a gradual decline.

Children aged 6-24 months seem most susceptible to clinical illness following rotavirus infection with peak incidence in most series at 9-12 months. Sequential rotavirus illness can occur in the same child, although such illnesses are characteristically due to different serotypes. A large prospective study in Washington reported 3.7 episodes of rotavirus gastroenteritis per 1000 infants per epidemic year with 2.2 episodes/1000/year in the 12-24 month age group. Rotavirus was implicated in 50% of hospitalised episodes of diarrhoea in children under the age of two. A prospective study from Copenhagen similarly found rotavirus to be the most frequent pathogen in children hospitalised with gastroenteritis. Incidence was highest under the age of 12 months, with twice as many cases between 6-12 as between 0-6 months.

Both series noted a decline in incidence of hospitalisation and outpatient visits with age, and a predominance of males among hospitalised patients.

Transmission of rotaviruses is assumed to be faecal-oral and probably varies with climate, population density and local habits. In temperate climates, rotavirus gastroenteritis peaks in the cooler months, as illustrated by the series from Copenhagen where 85% of isolations occurred from January-April. A similar seasonal trend was noted in Tecumseh. In contrast, this virus is seen year round in most tropical climates.

In prospective follow-up of children from 20 day-care centres in Houston, rotavirus was recovered exclusively from children under the age of 3, with a secondary attack rate of 15%. A subsequent prospective study in Arizona day-care centres found rotavirus significantly more often in children under 12 months, compared to those 13-36 months of age (p<0.001). Intra-familial transmission was emphasised by a series from New Zealand: 28 families exposed to a child with rotavirus were studied prospectively. 75% of siblings under the age of 12 acquired rotavirus, in contrast to control families (exposed to non-rotavirus gastroenteritis) where there were no secondary cases of diarrhoea. Even 33% of adults exposed to rotavirus through index children experienced serological conversions, although their infections were more likely to be mild or subclinical.

The rotavirus genome consists of 11 segments of double stranded RNA. Rotavirus is identified initially by electron microscopy and blocking ELISA on stool samples. Three major forms of serological classification of strains have emerged. Reactions of sera against major inner capsular antigen distinguish at least two subgroups. Neutralisation by
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hyperimmune sera distinguishes 2–5 serotypes. The large variety of genomic patterns exhibited by human rotaviruses has permitted the identification of long and short electropherotypes by migration patterns of nucleic acid in gel on silver staining. Strains showing long pattern on electrophoresis tend to correspond to subgroup 1 and serotype 2.

Prevalence of subgroups in an area tends to vary from year to year. In Washington, the rate of isolation of serotype 2 decreased from 100% in 1973–1977 to 57% in 1977–1978 while in the West Midlands only 10% of isolates were serotype 2 from 1978–1982, increasing to 70% in 1982–1983. Even different regions of the same country may show differing prevalences during the same epidemic season. While short electropherotypes were virtually absent in Glasgow in 1982–1983, they predominated in London and the West Midlands during the same epidemic year.

A three year survey in Brussels found simultaneous occurrence of various subgroups of virus in constant proportions even during the annual winter peak of gastroenteritis. In contrast, Japanese investigators reported a single dominant electropherotype during the first two months of an epidemic with various types found later on. Their hypothesis of antigenic drift was supported by the emergence of variants of the predominant electropherotypes during the Glasgow 1981–82 epidemic. This phenomenon is reminiscent of the behaviour of influenza strains, which also possess a segmented RNA genome.

Recovery of rotavirus from faeces can not be taken alone as diagnostically significant. A prospective series from a Paris hospital showed that 48% of their stool isolations represented asymptomatic rotavirus shedding with positive correlation between diarrhoea and virus shedding only in those cases of diarrhoea associated with fever and vomiting. Increasing age led to a decreasing proportion of carriers (positive stool EM and blocking ELISA, negative serology) and an increasing proportion of true infections (positive stool and sera with diarrhoea). This raised the aetiological issue of evolving intestinal maturity, further supported by finding six infants with initially low IgM and high IgG who had a late increase in IgM accompanied by diarrhoea as their IgG titre was declining. This was most compatible with infection acquired in hospital presumably as maternal immunity was waning.

Animal studies have consistently indicated that antibody in the lumen of the small intestine was of major importance in resistance to rotavirus disease. This pivotal role for local intestinal IgA antibody has been reinforced by studies in adult human volunteers. It was therefore postulated that maternal secretory IgA transmitted through breast milk might be protective. However, a prospective study of rotavirus gastroenteritis in Rochester showed no difference in age of infection, duration of diarrhoea or severity of diarrhoea between breast-fed and bottle-fed infants.

Public health and hospital microbiology laboratories in England and Wales send reports of rotavirus isolations to the PHLS Communicable Disease Surveillance Centre. Four-weekly summaries appear in the Communicable Disease Report (PHLS CDSC unpublished). Quarterly statistics also appear in the OPCS Monitor on Infectious Diseases. Although the volume of reports has increased (from 4413 in 1981–1982 to 6401 in 1984–1985) there have been only minor variations in the distribution by age, region or season.

Review of CDSC data confirms that rotavirus is primarily a disease of infancy and early childhood, with 42% of notifications in the first year and 83% under the age of 5 (PHLS CDSC unpublished). Month-by-month analyses are not available to confirm the 9–12 month peak in the age distribution observed in other industrialised countries.

Each year the number of rotavirus reports to CDSC begins to rise during weeks 37–40 and reaches its peak in the first quarter of the new year (figure). Examination of the CDSC reports by region shows that similar seasonal time trends occur in all areas of the country. In the last three epidemic years the initial excess isolations have come from Yorkshire and the North Western region, usually in weeks 41–44 (PHLS-CDSC unpublished). Comparing observed cases in each region with those expected based on population, there was a statistically significant (p < 0.05) excess of isolations for Yorkshire, North West Thames, the West Midlands and North Western regions during the 1983–1984 epidemic year. This could not be explained by differences in age distribution as the proportion under age 5 shows little variation between the regions (6–6.7%). Adjusting the expected figures for reporting bias (using the proportion of total viral notifications coming from each region) still showed higher than

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**Four-weekly summaries of rotavirus notification, England and Wales, 1982–5 (PHLS–CDSC, unpublished data).**
expected isolations from Yorkshire, North West Thames, and the West Midlands. The overall increase in isolations in the past two years has not led to significant changes in ranking of O/E ratios.

A live attenuated rotavirus vaccine containing subgroup 1 virus was initially tested in 20 seronegative Finnish adults, with no virus excretion or clinical symptoms. It was further tested on seronegative and seropositive Finnish 2 year olds with similarly favourable results and seroconversion rate of 70%.21 A subsequent randomised double-blind placebo-controlled trial in 178 infants aged 8–11 months during an epidemic of subgroup 2 virus in Tampere showed 88% efficacy against natural challenge by wild rotavirus.22 The same investigators then showed that seroconversion could be increased to 88% by simple milk feeding vaccination.23

Although the results from Finland are promising and show that the vaccine is safe and appears to be effective,24 rotavirus vaccine trials in this country must address the efficacy in our population. The aim would be a small-scale field trial to evaluate efficacy in the target population: children between the ages of 9 months and 2 years. Knowing the seasonal pattern of rotavirus isolations in this country it would be possible to time the trials to coincide with the beginning of the epidemic season (weeks 37–40) to provide optimum challenge from wild virus.

In the last epidemic year in England and Wales at least 5800 infants and children under the age of 5 were affected by the diarrhoea, dehydration and discomfort of rotaviruses. Although precise data on numbers of hospitalisations are not available, extrapolating from prospective series in other countries suggests that the burden upon the health service would have been significant. Rotavirus vaccine presents an exciting prospect for reducing this morbidity. What is known about the epidemiology of rotaviruses, coupled with the results of the current vaccine trials, can be used to (1) predict the effect introduction of vaccine might have on the pattern of disease in our population, (2) construct a balance sheet for evaluating the vaccine, and if appropriate (3) guide the planning of a sensible vaccine programme.

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