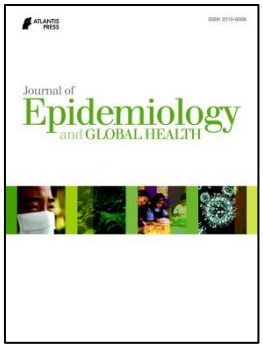

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Gastrointestinal pathogen distribution in symptomatic children in Sydney, Australia

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Abstract There is limited information on the causes of paediatric diarrhoea in Sydney. This cross-sectional study used clinical and microbiological data to describe the clinical features and pathogens associated with gastrointestinal illnesses for children presenting to two major public hospitals in Sydney with diarrhoea, for the period January 2007—December 2010.

Of 825 children who tested positive for an enteric pathogen, 430 medical records were reviewed. Adenovirus, norovirus and rotavirus were identified in 20.8%, 20.3% and 21.6% of reviewed cases, respectively. Younger children were more likely to have adenovirus and norovirus compared with rotavirus ($P = 0.001$). More viruses were detected in winter than in the other three seasons ($P = 0.001$). Rotavirus presented a distinct seasonal pattern with the lowest rates occurring in the warm months and peaking in the cooler months. Adenovirus showed a less consistent monthly trend, and norovirus detection increased in the cooler months ($P = 0.008$). A decline in the number of rotavirus cases was observed after mid-2008.

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The majority of childhood diarrhoeal illnesses leading to hospital presentations in Sydney are caused by enteric viruses with most infections following clear seasonal patterns. However, a sustained decrease in the incidence of rotavirus infections has been observed over the study period.

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1. Introduction

Acute diarrhoeal illnesses continue to be an important cause of morbidity in children, affecting both developed and developing countries [1]. Enteric viruses, especially rotavirus, have been recognised as the leading cause of childhood diarrhoea worldwide [1,2]. Several studies reveal that rotavirus, norovirus, adenovirus and astrovirus are the main viral causes of acute childhood diarrhoea [3]. Reports from the United Kingdom have shown viral agents responsible for up to 50% of all community-acquired and health-care associated gastroenteritis [4]. Australian data for all ages reveal that enteric viruses, mainly norovirus and rotavirus, are common causes of gastroenteritis, accounting for about 15—18% of all gastroenteritis cases [5].

Nearly all children worldwide become infected with rotavirus by their fifth birthday; with those aged between 6 months and 2 years more susceptible to severe disease resulting in hospitalisations [6]. The burden of rotaviral diarrhoea worldwide has resulted in the World Health Organization (WHO) placing priority on the development and distribution of rotavirus vaccines globally [7]. Norovirus infections, on the other hand, are recognised as a leading cause of epidemic gastroenteritis affecting all age groups, with sporadic cases occurring all year round with increased incidence observed in colder months [8]. In contrast to rotavirus, norovirus is the principal cause of healthcare-associated viral diarrhoea [9]. Enteric adenovirus types 40 and 41 and astrovirus are less frequently implicated, but are also important causes of acute diarrhoeal illnesses in sporadic and outbreak settings [9].

Over the last 15 years, great progress has been made towards the development and introduction of rotavirus vaccines, despite the withdrawal of an early vaccine due to safety concerns [10]. Vaccination programmes are estimated to prevent approximately 85—100% of hospitalisations due to rotavirus at least 1 year following vaccination [11]. The introduction of the rotavirus vaccine in the United States of America (USA) in 2006 and in Australia in 2007 has led to a dramatic reduction in the incidence and number of hospitalisations for acute gastroenteritis [12,13]. An American report projected that the administration of the rotavirus vaccine at ages 2, 4 and 6 months would result in an estimated 255,000 fewer physician visits; 137,000 fewer Emergency room visits; 44,000 fewer hospitalisations; and 13 fewer deaths per year in children aged <5 years [10].

The rotavirus vaccination programme was implemented in the Australian National Immunisation programme in the year 2007 [6]. Immunisation against rotavirus using Rotarix® at 2 and 4 months of age started in the Northern Territory from October 2006, while universally funded immunisation against rotavirus at 2 and 4 months of age (Rotarix®) or at 2, 4 and 6 months of age (Rotateq®) began from July 2007 in other States [6]. Immunisation or catch-up programmes for older children and adults is not recommended in Australia [14].

Little is known about the risk factors of paediatric gastrointestinal illnesses for children presenting to hospital with diarrhoea in Sydney. Knowledge of the actual causes and their prevalence is important to inform prompt diagnosis and treatment and evaluate the impact of the rotavirus vaccination programme. This retrospective study utilises the review of laboratory and hospital databases to describe the prevalence of diarrhoeal pathogens and associated clinical features in children presenting to hospital in urban Sydney up to 3 years after widespread vaccine uptake.

2. Methods

2.1. 2.1.1. Study setting

Two large hospitals serving the paediatric population of Sydney were included in the study; a major general public hospital in South Western Sydney (Hospital A) and a tertiary/quaternary paediatric centre in the Sydney children's hospital network (Hospital B). Ethical approval was granted by the Human Research Ethics Committees of both Hospitals and the University of Technology, Sydney.

2.1.2. Microbiology methods

Both laboratories routinely test for enteric pathogens in patients presenting with gastrointestinal symptoms. Both laboratories use the standard

methods for the identification and isolation of enteric pathogens as described below.

2.1.3. Virology

Both laboratories conducted testing for adenovirus and rotavirus routinely in all children $\leqslant$5 years of age unless otherwise indicated or requested by the clinician. However, Hospital A tested for norovirus on request or where outbreaks were suspected. Hospital A tested for rotavirus, adenovirus serotypes 40 and 41 and norovirus using the enzyme immunoassay (EIA) method for each species, respectively. Hospital B used the RIDA Quick Rotavirus/Adenovirus Combi immunochromatographic test (ICT) and the RIDASCREEN norovirus test (EIA). All tests were conducted following the manufacturer's recommendations. The adenovirus test used at Hospital B detects all adenovirus serotypes, and not just the enteric serotypes 40 and 41.

2.1.4. Bacteriology

Bacterial identification was done routinely in all laboratories using standard culture methods. Selective media (Xylose, Lysine Deoxycholate agar [XLD]), *Salmonella* selective broth, *Campylobacter* selective agar, and *Yersinia* selective agar were inoculated for the detection of *Salmonella* spp., *Shigella* spp., *Campylobacter* spp. and *Yersinia enterocolitica*. Detection of *Aeromonas, Plesiomonas* and *Vibrio* spp. was attempted only on special request, or where relevant clinical notes such as overseas travel or seafood consumption were provided. *Clostridium difficile* testing was performed using the EIA for diarrhoea greater than 3 days after hospital admission, on special request, or where relevant clinical notes were provided (e.g. history of antibiotic use, chemotherapy or immuno-suppressed). In Hospital A, *C. difficile* toxin testing was performed on one semi-formed/loose sample if requested.

2.1.5. Parasitology

At both sites, direct microscopy was routinely performed on all stool specimens for the detection of ova, cysts, and parasites. However, concentration techniques were performed only on special request or when indicated by certain circumstances; e.g. history of overseas travel or prolonged diarrhoeal illness. At Hospital A, stool specimens are routinely collected in sodium acetate acetic acid formalin (SAF) fixative (Oxoid Australia), and direct wet preparation microscopy was routinely performed on all stool specimens. In the instances where no clinical information was received and the patient was an adult or age $\leqslant$10 years old, or the specimen was not received in SAF, then a *Giardia/Cryptosporidium* screen enzyme immunoassay (EIA) (ProSpecT™ Giardia/Cryptosporidium Microplate Assay) was performed. A 10% suspension of stool samples was prepared in 10% formalin (for *Giardia intestinalis* and *Cryptosporidium*) and the EIA was performed in accordance with the manufacturer's instructions and without modification. A full COP test was done on all positive microscopy and EIA results using an Iron haematoxylin stain with modified acid fast stain. A similar procedure was employed for all stool specimens received at Hospital B, and samples positive by direct microscopy are placed into SAF fixative followed by confirmation by iron haematoxylin staining.

2.2. Medical record review

2.2.1. Selection criteria

The primary selection criteria were all children aged 0—5 years seen in each hospital and/or its affiliated clinics that had gastrointestinal symptoms and had a stool specimen testing positive for an enteric organism. Patients presenting with gastrointestinal symptoms including diarrhoea (defined as the passing of three or more unformed [loose, liquid, watery] stools within a 24-h period), with or without fever, abdominal/colicky pain, vomiting and nausea were included in the sample.

2.2.2. Sampling

Paediatric cases are a sub-group of a larger study involving adults and adolescents/children. Children with diarrhoea were identified from the microbiology results based on date of birth and/or age 5 years or younger at the date when the sample was tested. Laboratory data were then stratified based on two seasons (Spring/Summer and Autumn/Winter) in each year. Attempts were made to review 100% (154/154) of medical records at Hospital A and 50% (335/671) of records at Hospital B, owing to a larger number of children being seen. These proportions were chosen based on cost and time constraints. Samples were randomly selected using a random number generator.[2] The medical record charts were obtained for each case using their unique medical record number (MRN), and matched by date of visit/service date. Clinical summaries were reviewed for signs and symptoms, risk factors, diagnosis and treatment data.

2.3. Statistical methods

Analysis included the median, mean and standard deviation (SD) for distribution of demographic

[2] Available at http://stattrek.com/Tables/Random.aspx.

characteristics, clinical symptoms, proportion of pathogens isolated amongst all positive cases, association between clinical symptoms, season and viral pathogens using Pearson's Chi-square test. Odds Ratios (OR) and 95% confidence intervals (95% CI) for the association between age and viral agents detected were calculated using the binary logistic regression model where the dependent variable was each virus (rotavirus, adenovirus, norovirus) coded as 1 = No, 2 = Yes, and age groups being the independent variable, using the Enter method. Statistical analyses were performed using PASW Statistics Release version 18.0 [15].

3. Results

3.1. Demographics

A total of 825 children aged 0—5 years (154 at Hospital A and 671 at Hospital B) who presented to the hospitals had a stool specimen testing positive for an enteric organism over the period January 2007—December 2010. From Hospital A, only 78% (132/154) of cases were reviewed because the remaining medical records were either not available, or the age of the subject could not be determined. Of the 335 (50%) cases selected from Hospital B, only 89% (298/335) were reviewed due to either unavailability of records or legal/ethical reasons. The medical records for a total of 430 children were reviewed from the two hospitals (see Table 1). The median (LQ, UQ) age of children was 1.4 (0.8, 2.0) years [mean 1.6 years, SD 1.2]. There were slightly more males (56%) than females.

3.2. Clinical profile

Of the children reviewed, 89% (382/430) had symptoms prior to admission for 1—4 days with a median of 3 days and requiring admission for a median of 1 day. A total of 28% (120/430) of the children required admission to the emergency department for two or more nights. Just over half (58%) of all cases presented with elevated body temperature [mean ± SD: 37.8 ± 1.2 °C], ranging from 35.0 to —41.0 °C. The majority of children, 68% (264/430), presented with explosive or watery stools, 21% (90/430) had blood/mucous in their stools, and 3% (11/430) experienced persistent diarrhoea lasting for $\geqslant$14 days. Vomiting was frequently experienced (68%, 293/430), followed by dehydration (31%, 132/430) and abdominal cramping/pain (19%, 80/430). Other major signs and symptoms included: anorexia (31%, 134/430), lethargy 38% (165/430), and respiratory symptoms (25%, 106/430) (Table 2).

According to discharge coding, 79% (338/430) of the children were classified on presentation with an infectious gastrointestinal illness, 76% (323/430) of cases had a principal diagnosis and 70% (301/430) had an additional diagnosis of infectious gastrointestinal illness. Co-morbidities were noted in a few cases, including recent surgery 2% (10/429), complications related to neonatal period 4% (16/430) and cancer/lymphomas 3% (11/430). About 20% (82/430) of cases had a family member or close contact with gastrointestinal symptoms around the same time of their illness that included up to a week before or after onset. Prolonged antibiotic-therapy or chemotherapy was reported by 12% (53/429), but neither *C. difficile* antigens nor toxins were detected in any of these cases. Only 6% (27/430) of cases developed diarrhoea 48 h or more after hospitalisation, and significantly more were infected with norovirus (56%, 15/27) compared with rotavirus (33%, 9/27) and adenovirus (11%, 3/27) ($P = 0.022$).

3.3. Pathogen distribution

There was near equal distribution of each viral agent isolated as a percentage of the total pathogens isolated (Table 3). Overall, rotavirus was identified as a single pathogen in 22%, adenovirus in 21% and norovirus in 20% of cases reviewed. However, Table 4a shows that when laboratory results were considered, there was slightly more rotavirus (33.8% and 17.1%) isolated from cases at both hospitals than adenovirus and norovirus. *Campylobacter* spp. (11.0% and 27.1%) and non-typhoid *Salmonella* spp. (14.9% and 22.2%) were the most common bacteria isolated in both Hospitals A and B, respectively. *Giardia intestinalis* was the most common protozoa found in 3.2% and 3.7% of cases in each hospital, respectively. Non-typhoid *Salmonella* spp. and adenovirus were frequently found as a second pathogen in a few cases (Table 4b). Infection with adenovirus and norovirus decreased with increasing age ($P = 0.001$), but the opposite was true for rotavirus (Fig. 1). The lowest rate of rotavirus (12%) was observed in children under 1 year old, and approximately half of the adenovirus (52%) and norovirus (46%) cases were in children under one year old ($P = 0.001$). The relationship between age and the three viral agents was examined using a logistic regression model and adjusted for seasonal variations. Children under 1 year old age group were five to seven times more likely to have adenovirus and norovirus, than rotavirus, *Campylobacter* and *Salmonella* spp., isolated from their stools. Children in the 1—2 years age group had an increased risk of infection with norovirus (OR