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Patients with Enteric Adenovirus Gastroenteritis Admitted to an Australian Pediatric Teaching Hospital from 1981 to 1992

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During the period 1981 to 1992, 4,473 fecal specimens collected from children hospitalized with acute gastroenteritis at the Royal Children's Hospital, Melbourne, Australia, were examined by electron microscopy. A monoclonal antibody enzyme immunoassay for enteric adenovirus (EAd) types 40 (Ad40) and 41 (Ad41) was used when adenoviruses were visualized. Fecal samples were positive for adenovirus by both electron microscopy and enzyme immunoassay in 138 patients (3.1%). Ad40 was identified in 19 children (14%), and Ad41 was identified in 119 children (86%). These EAd were identified during each of the 12 years surveyed. EAd were present year-round, but the annual number of hospitalizations was not constant. Yearly prevalence varied from 0.7% (1981) to 6.5% (1985). This was associated with monthly fluctuations in Ad41 activity, with overall peak monthly prevalence in May (late autumn). By contrast, Ad40 numbers remained low and constant year-round. The frequency of Ad41 relative to Ad40 increased from 25% in 1981 to exceed 75% after 1983. Children admitted with EAd infection were more likely to have diarrhea for more than 5 days ($P < 0.001$) but less likely to be febrile or dehydrated ($P < 0.05$) than children with rotavirus infection. EAd are responsible for enteric symptoms of only a fraction of hospitalized children with infectious diarrhea but result in a more-protracted illness than rotavirus. Their relationship to persistent diarrhea requires further investigation.

Many of the 47 human adenovirus serotypes currently recognized can be shed in stools, often for prolonged periods, without being associated with diarrhea (31). There is strong epidemiologic and serologic evidence that infection with adenovirus 40 (Ad40) and adenovirus 41 (Ad41) can result in severe acute diarrhea in young children (31). These two serotypes form the F subgroup of the adenovirus genus, exhibit cross-reactivity in viral neutralization assays, and are colloquially referred to as enteric adenoviruses (EAd). The members of this subgroup are difficult to grow in cell culture, and this has delayed the development of specific diagnostic tests.

Following the introduction of monoclonal-antibody-based enzyme immunoabsorbent assays (EIA), epidemiologic studies have been conducted on their role as etiologic agents of severe acute infectious diarrhea (12). These studies have shown that Ad40 and Ad41 have a worldwide distribution and are of comparable prevalence in developed and developing countries and in urban and rural communities (3, 4, 7, 13, 26). EAd have also been implicated in nosocomial infections and day care center outbreaks (15, 29).

Etiologic surveys of fecal specimens collected over 2 to 9 years from children admitted to hospital with gastroenteritis show nonseasonal patterns of infection by EAd in different communities (3, 4, 22, 33). Although early surveys observed approximately equal prevalence of Ad40 and Ad41, recent reports indicate that these serotypes may occur within communities at different rates. Ad41 may undergo antigenic drift, raising the possibility of repeated community outbreaks due to this serotype (6, 22). Even though EAd and rotaviruses both produce as symptoms fever, vomiting, and watery diarrhea, there are conflicting reports as to whether EAd infection results in a milder but more prolonged illness than rotavirus (7, 13). The aims of this retrospective study of acute infective diarrhea in children admitted to a large pediatric teaching hospital were (i) to determine the rate of EAd gastroenteritis in children admitted during a prolonged period (12 years), (ii) to describe the annual and seasonal distribution of Ad40 and Ad41 gastroenteritis, and (iii) to compare the clinical features of infections due to Ad40 and those due to Ad41 and the clinical features of EAd and rotavirus gastroenteritis in patients hospitalized during the study period.

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MATERIALS AND METHODS

Study population and sample collection. All children admitted to the Royal Children's Hospital (RCH) in Melbourne, Australia, with acute diarrhea are nursed in the infectious diseases ward. During a 12-year period, from 1981 to 1992 inclusive, stool specimens were collected from 4,473 patients within 48 h of admission. Feces were prepared as 10% homogenates in phosphate-buffered saline (PBS; pH 7.4), clarified by low-speed centrifugation at 600 × *g* for 10 min, and concentrated approximately 10-fold by polyacrylamide hydrogel (Lyphogel; Gelman Sciences, Inc.) before negative staining with ammonium molybdate (pH 7.0) (32). Grids were stored for 1 to 2 weeks before examination by electron microscopy (EM). Adenovirus particles were identified by their characteristic morphology. Stool specimens containing adenovirus particles were stored at −70°C until further tested by EIA.

EIA detection of adenovirus group antigen, Ad40, and Ad41. Mouse ascites fluid containing antiadenovirus monoclonal antibodies MA 1-3 (group antigen specific), MA 5-8 (specific for Ad40), and MA 5-15 (specific for Ad41) were used in a double-sandwich EIA modified after Jarecki-Khan et al. (13). The monoclonal antibodies had been donated by J. C. de Jong of Rijksinstituut Voor Volksgezondheid en Milieuhygiene, Bilthoven, The Netherlands.

Hyperimmune rabbit antihexon antiserum was produced in rabbits (27) and used to coat microtiter plates (Nunc-Maxisorp, Roskilde, Denmark) at a dilution of 1/2,000 in carbonate buffer (pH 9.6). One hundred microliters was added to each well and bound overnight at 4°C. Test samples comprising 100 μl of 10% (wt/vol) fecal homogenates in PBS (pH 7.2) were added to each well and incubated at 37°C for 1 h. One hundred microliters of mouse monoclonal antibody diluted 1/1,000 in PBS (pH 7.1) containing 20% fetal calf serum and 2% Tween 20 (PBST) was added and incubated at 37°C for a further 1 h. Reactions were detected with sheep anti-mouse immunoglobulin G–horseradish peroxidase conjugate (Silenus, Melbourne, Australia), diluted 1/200 in PBST, followed by substrate containing *o*-phenylenediamine hydrochloride (Sigma, St. Louis, Mo.). This reaction proceeded at room temperature in the dark for 15 min before being stopped by addition of 25 μl of 4 N HCl to all wells. The optical density at 490 nm (OD_{490}) for each well was read with a Titertek EIA reader. Each fecal

TABLE 1. Scoring for severity of acute gastroenteritis

Symptom	Score with symptoms of indicated degree[a]		
	1	2	3
Diarrhea			
Maximum no. of stools/day	<5	5–8	>8
Duration (days)	<5	5–7	>7
Vomiting			
Maximum no. of vomits/day	<4	4–6	>6
Duration (days)	<3	3–5	>5
Dehydration (% body weight loss)	<5	5–9	>9
Fever (°C)	<38.5	38.5–38.9	>38.9
Acidosis		7.34–7.30	<7.30
Electrolyte abnormality			Present

[a] After Rieppenhoff-Talty et al. (20).

specimen was tested in triplicate against each of the three monoclonal detector antibodies (i.e., nine tests per specimen). After each step, plates were washed four times in PBS containing 0.1% Tween 20. The sensitivity and specificity of the EIA were monitored by the addition of prototype strains Ad40 (Dugan) and Ad41 (Tak) and of pooled nonenteric adenoviruses and a known negative sample to each plate. Samples were considered to contain either Ad40 or Ad41 if the OD_{490} for the respective wells was at least twice that of the negative control well and greater than 0.2 OD units. Samples which reacted only with MA 1-3 were considered to contain only nonenteric adenoviruses.

Clinical data and assessment. Hospital records of children with EAd infection were reviewed by K. Grimwood while blinded to the EIA results (Ad40 and Ad41). Clinical observations had been recorded by resident medical officers and nursing staff during the period of each child's admission to hospital. The preadmission clinical histories were obtained from parents or guardians. Resident medical officers determined dehydration by clinical signs. Serum electrolytes and pH were measured at the discretion of the admitting doctor.

A severity score devised by Riepenhoff-Talty et al. (20) and described in Table 1 was assigned to each patient. The maximum number of stools or vomits reported prior to admission or in hospital was recorded. Where documentation was not precise (29 of 138 patients), a score of 1 was assigned for the category infrequent or occasional, a score of 2 was assigned for frequent, and a score of 3 was assigned for profuse or persistent (2). Duration of diarrhea and vomiting was counted from the symptom onset until the last vomit or fluid stool passed during recovery. The maximum temperature read prior to or during admission was recorded.

Differences in clinical data and severity scores between children infected with Ad40 (11) and those infected with Ad41 (77) were compared in a total of 88 children. All had community-acquired EAd gastroenteritis and no concurrent enteric infection or underlying illness. Additional comparisons were made between 62 of these patients with EAd infection, who fell into the same age range of 6 to 30 months, and 108 previously reported rotavirus-infected children (2). These latter subjects were between 6 and 30 months of age, were admitted to the RCH infectious diseases ward during the same study period, and had undergone an identical chart review.

Statistics. Minitab computer software (16) provided descriptive statistics and comparisons of ordinal variables by the nonpaired t test or the Mann-Whitney test. Comparisons of nominal variables by the χ^2 test or Fisher's exact test, risk ratios, and 95th-percentile confidence intervals were performed with the Epi Info statistics program (8). Children who scored ≥2 for each individual sign or symptom for the clinical score (i.e., moderate or severe) were compared between EAd serotypes and with rotavirus.

RESULTS

During the 12-year stool collection period, 4,473 children were admitted to the infectious diseases ward at RCH with acute gastroenteritis. Adenovirus particles, observed by EM and later confirmed as positive for the hexon group antigen by EIA, were present in the stools of 154 children (3.4%). Of these 154 adenovirus-positive specimens, 138 (3.1%) belonged to Ad40 or Ad41 serotypes. Rotaviruses were detected in the stools of 1,553 children (34.7%) admitted to hospital with acute gastroenteritis during the same period.

The annual distribution of EAd gastroenteritis admissions to the RCH between 1981 and 1992 is shown in Fig. 1. Nineteen children had Ad40 (14%), and 119 (86%) had Ad41, in their stools. During the study period, the percentage of Ad41 increased from 25% in 1981 to 93% in 1984, after which it remained greater than 75% each year and was 100% in 1989 and 1992. The number of EAd gastroenteritis admissions was not constant over the 12 years. This was principally due to fluctuations in Ad41 prevalence dating back to 1983.

The annual rates of children hospitalized because of EAd gastroenteritis, as a proportion of the total number of children admitted to the infectious diarrhea ward, is shown in Fig. 2. There was a significant variation in rates of EAd gastroenteritis admissions over time ($P < 0.001$), and when adjusted for rotavirus admissions this remained highly statistically significant ($P < 0.001$). Annual rates fluctuated from 0.7% in 1981, when Ad40 was dominant, to peaks of 6.5 and 6.3% in 1985 and 1992, respectively, following the increased prevalence of Ad41. The monthly distribution of EAd gastroenteritis admis-

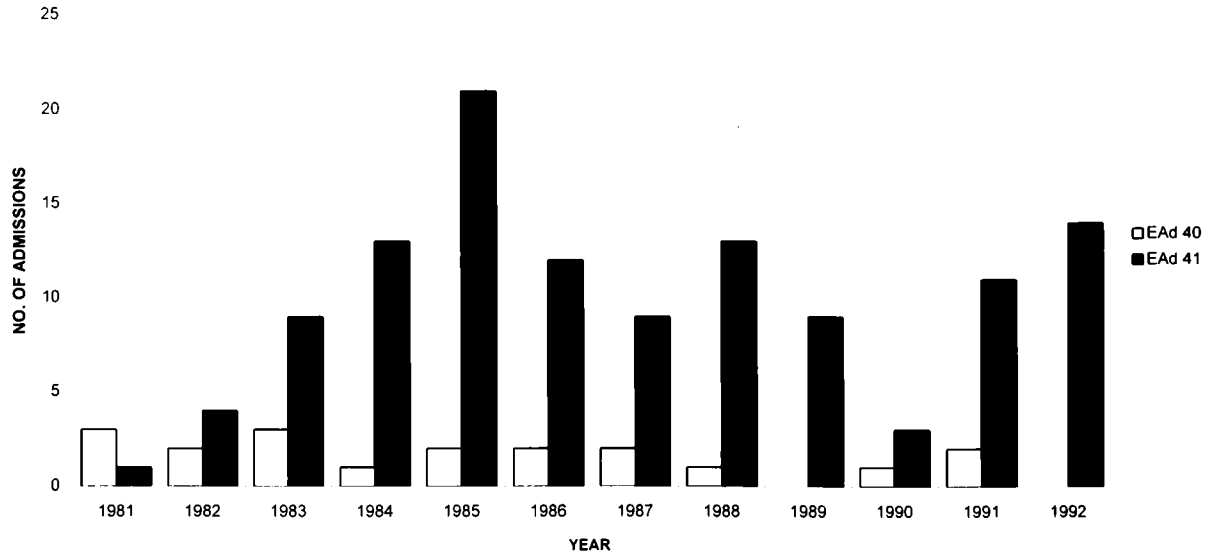

FIG. 1. Annual numbers of children with EAd gastroenteritis admitted to the RCH, 1981 to 1992.

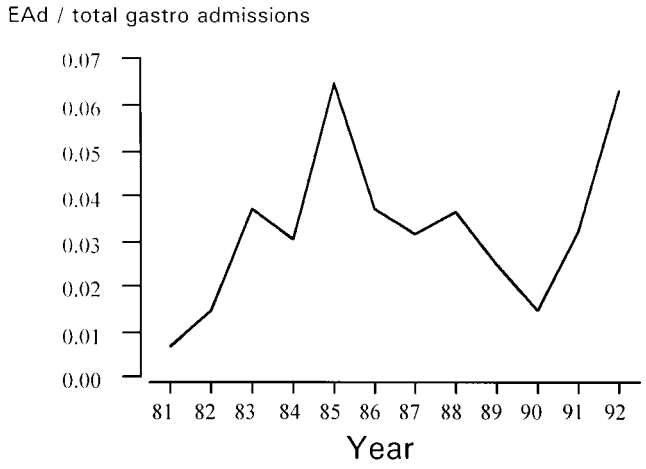

FIG. 2. Annual rate of children with EAd gastroenteritis per total number of gastroenteritis admissions to the RCH, 1981 to 1992.

TABLE 2. EAd gastroenteritis at the RCH, 1981 to 1992

Characteristic	Value for virus of indicated serotype	
	Ad40	Ad41
No. of patients[a]	19	119
Sex (no. of males/no. of females)	7/12	69/50
Age (months)[b]	7.0 (1–41)	9.0 (1–61)
Diarrhea		
Maximum no. of stools/day[b]	5.0 (2–20)	7.0 (2–25)
Days of diarrhea[b]	7.0 (2–25)	7.0 (1–60)
Mucus in stools (%)	11	25
Vomits[b]		
Maximum no. of vomits/day	5.0 (2–10)	4.0 (0–20)
Days of vomiting	4.0 (1–9)	3.0 (0–15)
No. of patients (%) with:		
Respiratory symptoms	7 (37)	36 (30)
≥5% dehydration	5 (26)	40 (34)
Sugar intolerance	1 (5)	15 (13)
Copathogens	3 (16)	21 (18)
Concomitant disease	6 (32)	32 (27)
No. of days in hospital[b]	4.0 (2–25)	4.0 (1–34)

[a] $P < 0.001$ ($P > 0.05$ for all other comparisons).
[b] Results are expressed as median (range).

sions is outlined in Fig. 3. Although there was no association between Ad40 or Ad41 and season, the total number of EAd admissions was not constant throughout the year, and a peak in May was observed during 6 of the 12 years of the study ($P = 0.002$). This observation was also true for the monthly rates of EAd infection calculated as a proportion of total gastroenteritis admissions ($P = 0.002$). Although constant for 10 months of the year with values of between 2 and 4%, rates fell below 2% in July and rose to 7.2% in May to account for much of the variance.

The clinical features of the 138 children with Ad40 and Ad41 gastroenteritis are shown in Table 2. There were no significant differences regarding composition or clinical symptoms between the two groups of children. The sex ratio was 1.2:1 in favor of males, and 90% of patients were younger than 2 years. During the first year of life there were approximately equal numbers of children younger or older than 6 months (25 versus 29, respectively). The principal symptoms were vomiting (89%) and diarrhea (100%). The children had been unwell with vomiting or diarrhea for a mean period of 4.8 days prior to hospitalization. The diarrhea was prolonged and ranged from 1 to 60 days with a mean and median duration of 9 and 7 days, respectively. Although 23% of patients had mucous stools, frank blood was not reported. High fevers or rashes were uncommon, but respiratory symptoms such as cough or coryza were present in 32% of cases. The illness was complicated by dehydration in 33% of the children, and lactose intolerance was detected in 12% of the children. Overall, 24 patients (17%) had mixed infections. Enteric copathogens were identified in 14 patients (10%). Exclusion of these 14 patients from analysis did not alter our results. This may have been due to small patient numbers and to equal division between those with a brief rotavirus illness ($n = 7$) and those experiencing prolonged symptoms associated with *Salmonella* ($n = 4$), *Campylobacter* ($n = 3$), and *Cryptosporidium* ($n = 1$) infections. Thirty-eight patients (28%) had other illnesses, such as bron-

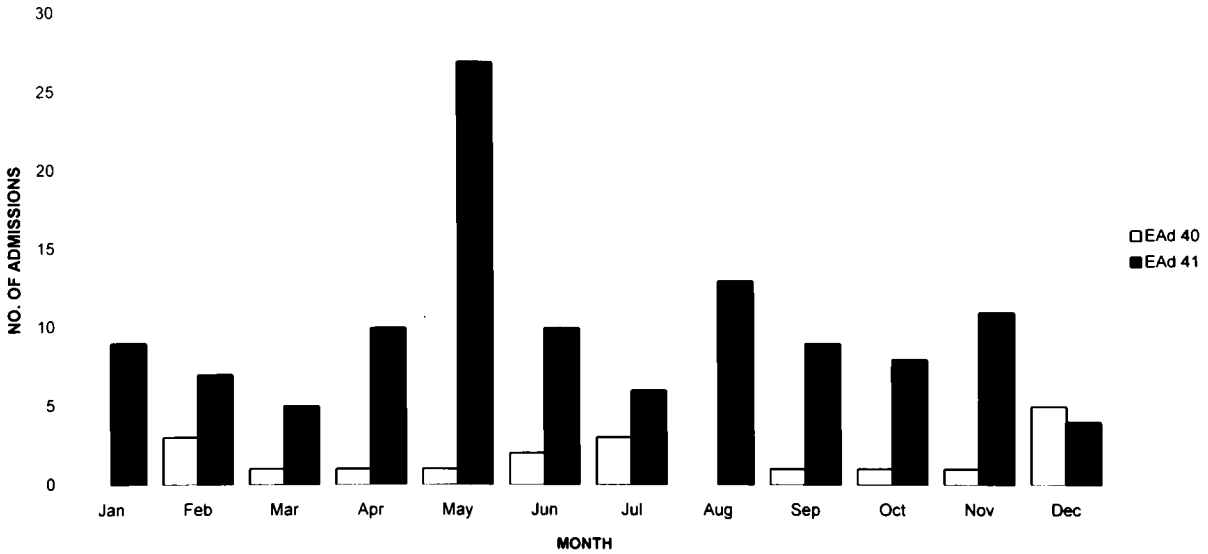

FIG. 3. Monthly numbers of children with EAd gastroenteritis admitted to the RCH, 1981 to 1992.

TABLE 3. Severity of clinical symptoms associated with infection by EAd or rotaviruses in hospitalized children aged 6 to 30 months

Characteristic	Value with indicated virus		Risk ratio[a]	*P*
	EAd	Rotavirus		
No. of patients	62	108		
Age (months)[b]	12.6 (5.7)	14.0 (5.6)		0.06
Sex (no. of males/no. of females)	37/25	67/41		0.76
Score[b]	10.8 (2.9)	10.3 (3.1)		0.28
% of patients with indicated symptom(s)				
≥5 stools/day	79	76	1.0 (0.9,1.2)	0.64
≥5 days of diarrhea	81	32	2.5 (1.9,3.4)	<0.001
≥4 vomits/day	63	71	0.9 (0.7,1.1)	0.26
≥3 days of vomiting	63	39	1.6 (1.2,2.2)	0.004
≥5% dehydration	30	46	0.6 (0.4,1.0)	0.03
Temp ≥38.5°C	6	42	0.15 (0.06,0.33)	<0.001

[a] The 95th percentile confidence interval is shown in parentheses.
[b] Mean (standard deviation).

chiolitis ($n = 5$) or chronic cardiorespiratory disorders ($n = 16$), which influenced their admission criteria and length of hospital stay.

A comparison of disease severity between EAd and rotavirus gastroenteritis is outlined in Table 3. Although no differences in clinical scores were observed, patients hospitalized with EAd infection were less likely to have high fever or dehydration ($P < 0.05$) but their symptoms of vomiting and diarrhea were more protracted than those observed for children with rotavirus gastroenteritis ($P < 0.005$). When these comparisons were made between 11 children with Ad40 and 77 children with Ad41 infection, no differences in either clinical scores or severity of symptoms were detected.

DISCUSSION

This study has shown that over a 12-year period, 3.1% of children admitted with gastroenteritis to a major Australian pediatric hospital had EAd detected in their feces. EAd were identified in a proportion of children in each of the 12 years. Rates of admission each year varied from 0.7% (1981) to 6.5% (1985) of children with gastroenteritis. This is in general agreement with studies from other developed countries, where the frequency of EAd infection in hospitalized populations has been reported to be 1.1 to 7.9% (9, 22, 31, 34). EAd are also common causes of gastroenteritis in developing countries. The rates of infection in children from these countries vary widely. Studies from Thailand and Bangladesh have reported EAd gastroenteritis in less than 3% of outpatients, compared with 26% in children from the highlands of Papua New Guinea and 31% in hospitalized rural Guatemalan children (7, 11, 13, 25). This wide variation in detection rates amongst developing countries remains unexplained, but studies have been cross-sectional and the results may reflect fluctuations of EAd infection in these regions. Seroprevalence studies from many countries have shown that almost all children experience an EAd infection by 4 years of age (14, 23).

This study did not attempt to define hospital-acquired infection. Other hospital-based series indicate that nosocomially acquired EAd infections form a major proportion of cases (15, 31). Rates obtained from outpatient settings or family studies have shown a similar range of 2 to 5.4% for EAd gastroenteritis (17, 21). An earlier survey from Melbourne reported that 8.9% of children who presented to a primary care facility and 7.4% of children admitted to hospital with acute diarrhea had EAd identified from fecal specimens (19). However, this study was conducted during a 7-month period and the diagnosis of an EAd infection was made by the visualization of adenovirus particles in feces by EM and their failure to grow, or to be passaged, in routine cell culture used for viral diagnosis. The short period of observation and the use of less-specific diagnostic techniques could have led to an overestimate of EAd infection. Our results indicate that approximately 90% of adenoviruses visualized by EM can be identified as EAd by use of monoclonal antibodies specific for Ad40 and Ad41 in an EIA system.

An unexpected observation was the overall predominance of Ad41 as the agent of EAd gastroenteritis. The literature has generally reported equal frequencies for Ad40 and Ad41 (10, 13). However, recent longitudinal studies from England (3, 33), Canada (6), Japan (22), and The Netherlands (9) have recorded substantial annual decreases in numbers of Ad40-positive fecal specimens. The shifts in EAd serotype were first detected during the mid-1980s, and only one study reported a subsequent increase in Ad40 isolation rates (3). Our results show fairly constant, but minimal, numbers of Ad40 infections for 10 of the 12 years surveyed.

An important finding was the significant fluctuations in annual rates for EAd gastroenteritis that were related to fluctuations in Ad41 activity. Annual prevalence of EAd in relation to all other gastroenteritis admissions (Fig. 2) suggests that the two peaks of EAd infections (1985 and 1992) may represent two sustained epidemics perhaps caused by antigenic changes in Ad41. It is possible that epidemics of EAd gastroenteritis elsewhere have gone undetected in other longitudinal studies of short duration. Determination of DNA restriction endonuclease digestion patterns provides evidence that EAd is highly heterogeneous (1, 31). At least six different genome types of Ad40 were identified in fecal specimens from South Africa, Canada, and Europe. Canadian and European strains of Ad41 were identical, but four different genomic types were identified among South African strains (31). Difficulties experienced in adapting EAd to growth in cell culture have inhibited epidemiologic studies of genomic variation among field strains of subgenus F adenoviruses. The recent promising development of specific monoclonal antibodies directed against antigenic determinants in the hexon region has been tempered by this genomic variation (9, 18). Changes in genomic restriction patterns and in monoclonal subtypes of Ad41 have been described as coinciding with increased fecal isolation rates of this serotype in children admitted to hospital and with outbreaks in day care centers but not with an overall increase in the rate of EAd disease within the community (9, 28). Serial alterations of Ad41 antigenic determinants resemble the antigenic drift of the influenza virus (30). As a result, it has been suggested that each alteration in Ad41 antigens may be followed by an increase in EAd gastroenteritis as the proportion of susceptible individuals within the community is increased. Until now, no study has shown significant fluctuations in EAd rates suggestive of such a relationship. Because vaccine development needs to consider changes within neutralization epitopes, additional studies examining the genomic and antigenic variations of the EAd serotypes are required.

Our results confirm that EAd infection occurs year-round (9) and indicate that EAd infections were particularly prevalent during the month of May, which is late autumn in the Southern Hemisphere. Earlier studies have failed to detect regular seasonal variations, although a recent study from

Bangladesh described a seasonal increase in EAd infections during the dry winter period (13).

Admission to hospital preselects children with severe disease, so it was no surprise that there were few differences in severity scores between patients with EAd infection and those with rotavirus gastroenteritis. However, there were significant differences in clinical characteristics between the two groups. Children admitted to hospital with EAd were more likely to have been unwell for several days with symptoms of vomiting and diarrhea but less likely to have been highly febrile or dehydrated. By contrast, young children with rotavirus infection were hospitalized with an acute history of fever, vomiting, diarrhea, and dehydration. Our results support the contention that patients suffering from EAd infection are likely to have a protracted illness (31). Persistent gastrointestinal symptoms may increase the risk of malnutrition in children from developing countries. Why children with an EAd infection should have a longer illness is unclear. Neither an increased rate of secondary lactose intolerance nor prolonged excretion of EAd in the stools has been reported in children with EAd gastroenteritis (29). The children suffering from EAd tended to be younger than those of the rotavirus comparison group, but unlike some previous researchers (4, 9) we did not find a preponderance in the first 6 months of life. However, even when the analysis was repeated and included children younger than 6 months with EAd, such that the difference in age groups with rotavirus became highly significant (9.6 versus 14.0 months, respectively; $P < 0.001$), disease characteristics and risk ratios remained unchanged. Thus, age difference does not adequately explain the different clinical courses for both viruses.

No differences in disease severity between young patients admitted to hospital with Ad40 gastroenteritis and those with Ad41 gastroenteritis were detected. As this was a hospital-based study, it is possible that overrepresentation of Ad41 in our sample population reflects severe disease caused by this particular serotype. However, no such sample bias was observed in day care centers, where outbreaks followed increased Ad41 activity (28). The small numbers of children with an Ad40 infection greatly reduced the power of the study to detect even large differences between the two patient groups. Other studies with small numbers and multiple subgroup analyses have given conflicting results as to which serotype gives more-severe symptoms (24, 31). A community-based study with greater numbers of Ad40-infected subjects is required to answer this question.

It is possible that we underestimated the true number of EAd infections. Our approach to diagnosis, screening of fecal samples by EM and confirmation by EIA, may be less sensitive than use of a monoclonal-based EIA for initial diagnosis. All samples containing adenovirus particles identified by EM reacted in the EIA system. However, 10% reacted solely with the group antigen-specific monoclonal antibody and were likely to be cultivable adenoviruses of other serotypes. This is consistent with observations made by others (5). It has been shown that EM detects $\geq 10^6$ particles per ml and that specimens containing adenoviruses below the detection threshold for EM would be recorded as negative.

Although less than 5% of Melbourne children hospitalized with acute gastroenteritis had EAd present in their feces, this pathogen was the second-most-common enteric virus detected and was comparable to *Salmonella* and *Campylobacter* species as a cause of infectious diarrhea within this community (19). Infants and young children hospitalized because of an EAd infection were more likely to have persistent symptoms and to be admitted later in the course of their illness than those suffering from the more common rotavirus infection, in which the onset is acute and associated with dehydration. As previously observed in the Northern Hemisphere, Ad40 was replaced by Ad41 as the dominant serotype, and a new finding was the annual fluctuation of EAd gastroenteritis during the 12-year study period. Whether increased activity was associated with genomic or antigenic variation in the circulating Ad41 strains is unknown but is worthy of further study should vaccine development be planned in the future.

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