

Antibiotic use, gastroenteritis and respiratory illness in South Australian children

A. TALBOT-SMITH AND J. HEYWORTH*

Department of Public Health, The University of Western Australia, Crawley, Western Australia

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SUMMARY

This study examines the incidence of antibiotic-associated diarrhoea (AAD) in children in the community setting. Parents of 965 children aged 4–6 years and resident in rural/semi-rural South Australia completed a questionnaire on socio-demographic factors, and a 6-week daily diary detailing symptoms of gastroenteritis, antibiotic use, respiratory illness, and contact with someone with gastroenteritis. The incidence of AAD was 32·3%, falling to 23·5% when episodes associated with a respiratory illness were excluded. Respiratory illness in the previous 3 days (OR 6·76, 95% CI 4·87, 9·38), and contact with someone with gastroenteritis in the previous 14 days (OR 1·8, 95% CI 1·48, 2·19), were both associated with gastroenteritis. After adjusting for these, only the first day of antibiotic use was associated with gastroenteritis (OR 3·8, 95% CI 1·8, 8·06). Potential confounding factors, in particular inter-current respiratory illness, need to be considered when examining AAD.

INTRODUCTION

Gastroenteritis is a major cause of morbidity in children, with incidences of 1·5–2·5 per child per year described in those under 5 years [1, 2]. In addition to the burden of disease in the community, it results in a substantial number of hospital admissions. In the United States, gastroenteritis accounts for 12% of hospital admissions in children aged 0–4 years [3]. Similarly, in South Australia in 1996, 15% of hospital admissions for children aged 0–5 years were for gastroenteritis.

Antibiotic-associated diarrhoea (AAD), or unexplained diarrhoea occurring with the administration of antibiotics, is a recognized and common complication of antibiotic treatment. The underlying mechanisms include disturbance of the composition and

function of the normal intestinal flora, overgrowth by pathogenic micro-organisms such as *Clostridium difficile*, allergic and toxic effects on the intestinal mucosa, and pharmacological effects on motility [4]. Nearly all antibiotics have been implicated although the rate varies, ranging from 5 to 39% depending upon the antibiotic [5, 6] and with the duration of antibiotic treatment and repeated courses of antibiotics cited as risk factors [7]. An incidence rate of 7·7 per 100 000 person-years was found by Hirschhorn et al. [8] in a study of community acquired *Clostridium difficile*-associated diarrhoea.

A wide spectrum of clinical presentations has been observed for AAD. Uncomplicated diarrhoea has the highest incidence, but vomiting, fever, and systemic illness with fulminant pseudomembranous colitis are also described [6, 7]. Symptoms can occur from within a few hours to up to 2 months after antibiotic intake [9], although for AAD due to *Clostridium difficile* symptoms 5–10 days after the start of therapy are quoted as classical [10].

* Author for correspondence: Department of Public Health, The University of Western Australia, 35 Stirling Highway, Crawley 6009, Western Australia.

Much of the work on AAD has focused on the hospital setting [7] and, in particular, on infectious causes such as *Clostridium difficile*. This is despite only 10–20% of all AAD cases being positive for toxigenic *Clostridium difficile* [11–13]. Although outpatient use of antibiotics is common in children, AAD in children and in community settings has been less extensively studied. More recent interest has developed with studies suggesting the ability of probiotics to reduce the incidence of AAD in children [14, 15].

One North American community-based randomized trial study found a 26% incidence of AAD among the placebo group of children receiving a single antimicrobial treatment [15]. Others have quoted the incidence in children as 20–40% of those receiving broad-spectrum antibiotics [16]. However, many children are prescribed antibiotics for pre-existing gastroenteritis or for other illnesses that can themselves cause diarrhoea. With between 27 and 44% of all enteric illnesses estimated to be due to respiratory illness [17], this needs to be accounted for when examining the incidence of AAD.

The aim of this study was to examine the incidence of AAD in South Australian children in the community setting, taking into account the effects of potential confounding factors including inter-current systemic illness.

METHODS

The study sample consisted of 965 children aged between 4 and 6 years, resident in Adelaide Hills (a semi-rural region of South Australia) and rural South Australia. These children were selected from a larger cross-sectional study which examined the prevalence of gastroenteritis in relation to drinking-water source among 9500 South Australian children attending a pre-school health check. A total of 3413 of these children were resident in rural or semi-rural areas, and the parents of 1960 (57%) of them indicated their willingness to participate in a further diary study. One hundred and six children were subsequently excluded due to either an ongoing illness or its treatment which resulted in symptoms of gastroenteritis, or because they were of Aboriginal or Torres Strait islander descent. The latter were excluded due to the difficulty of controlling for the poor environmental health conditions experienced by the majority of these children. A further 691 children were excluded as they did not drink tank rainwater and/or chlorinated

and filtered public mains water which was the main focus of the initial study. This left a final sample of 1163 children aged between 4 and 6 years whose parents were asked to participate in the second study on their child's behalf.

Parents were asked to complete a baseline survey and a daily diary for 6 weeks, which was followed up with telephone interviews at 3 and 6 weeks. All diaries were conducted during late summer/autumn (between February and early June 1999) with the diary periods arranged to avoid school holiday periods. The daily diary asked parents to record the presence of gastroenteritis symptoms in terms of stool consistency (normal, soft, liquid), the number of bowel movements per day, nausea, vomiting, and abdominal cramps. Also recorded was antibiotic use, the reason for starting antibiotics, known contact with someone with symptoms of gastroenteritis, and symptoms of respiratory illness (fever, earache or ear infection, sore throat, cold or influenza). The baseline survey provided data regarding sex, number of children in the home aged less than 15 years, drinking-water source and socio-economic status (as determined from the index of relative socio-economic disadvantage [18]).

An episode of gastroenteritis was defined using the criteria for 'Highly Credible Gastroenteritis Symptoms' (HCGI) [2], as one or more symptomatic days involving at least one of the following combinations: liquid bowel movements; soft stool plus abdominal cramps; vomiting; nausea plus abdominal cramps. A new episode of gastroenteritis was designated if there were 7 symptom-free days since the last day of symptoms.

When calculating the incidence of gastroenteritis and AAD children with gastroenteritis were considered 'not at risk' until 7 symptom-free days had elapsed from the last day of symptoms. For children with multiple episodes of gastroenteritis following antibiotic use, only the first episode was counted. For those taking multiple courses of antibiotics the first course was used as the index event.

An inter-current respiratory illness was defined as a child reporting earache or ear infection in conjunction with fever, or reporting sore throat or cold or influenza in conjunction with fever, that day or in the previous 3 days. Recent contact with a gastroenteritis sufferer was defined as known contact inside or outside the home during the previous 14 days. Drinking-water source was classified into three groups: public mains water only, any tank rainwater (generally an untreated water supply collected from

domestic roof catchments), and any spring/bottled water.

Data analysis was performed using STATA 6.0 for windows [19]. Logistic regression was used to examine the association between episodes of gastroenteritis and antibiotic use, estimating odds ratio (OR) and 95% confidence interval (CI) and using a random effects model to account for multiple records on each child. Various measures of antibiotic use were considered in univariate analysis: first day of antibiotic use; started antibiotic course in last 7 days; took antibiotics that day (regardless of day of course); took antibiotics at any preceding time in diary study; numbers of course of antibiotics; and duration of antibiotic use. Those significant at the 5% level were considered in multivariate analysis, each modelled with the potential confounding factors of sex, socio-economic group, number of children in the household under 15 years, drinking-water source, known contact with someone with gastroenteritis in the previous 14 days, and inter-current respiratory illness in the 3 days prior to gastroenteritis. These were removed by backwards elimination if they did not improve the fit of the model or substantially influence the effect of antibiotic use.

RESULTS

Of the 1163 parents approached, 965 completed the diary on their child's behalf, a response fraction of 83%. The duration of completed diaries ranged from 7–49 days (median 42 days), resulting in a total of 39949 observations on 965 children. Characteristics of these children are detailed in Table 1. The median age was 5 years (82.6%).

Reported episodes of gastroenteritis and antibiotic use are detailed in Table 2. There were 524 episodes of gastroenteritis reported by 414 children, giving an incidence of 5.01 episodes per child per year (95% CI 4.55–5.52). The duration of gastroenteritis episodes ranged from 1 to 11 days, with a median of 2 days. Thirty-three gastroenteritis episodes (6.3%) were preceded by antibiotic use during the at risk period. Fifty-five gastroenteritis episodes (10.5%) were associated with an inter-current respiratory illness, and 11 episodes (2.1%) with both antibiotic use and inter-current respiratory illness.

Ninety-nine children took a total of 111 courses of antibiotics. Duration of antibiotic use ranged from 1 to 33 days, with a median of 7 days and a cumulative

Table 1. *Characteristics of the 965 children aged 4–6 years and resident in Adelaide Hills or rural South Australia, whose parents completed the diary study*

	Number of children	(%)
Sex		
Male	521	(54.0)
Female	444	(46.0)
Socio-economic group		
Highest	153	(15.9)
Upper middle	212	(22.0)
Lower middle	367	(38.0)
Lowest	225	(23.3)
Unknown	8	(0.8)
Number of children under 15 years in household		
One	4	(0.4)
Two	83	(8.6)
Three	447	(46.3)
Four	278	(28.8)
Five	114	(11.9)
Six	29	(3.0)
Seven	9	(0.9)
Eight	1	(0.1)
Drinking-water source		
Rainwater only	417	(43.2)
Use of public mains	519	(53.8)
Use of spring or bottled water	29	(3.0)
Known contact with someone with gastroenteritis*	487	(50.4)
Inter-current respiratory illness†	180	(18.7)

* Known contact with someone with gastroenteritis, inside or outside the home during previous 14 days.

† Earache or ear infection in conjunction with fever, or, sore throat, cold, or influenza in conjunction with fever, in the previous 3 days.

number of 802 days of antibiotic use. Of the 99 antibiotic courses that were the first course taken by a child, 32 (32.3%) were followed by an episode of gastroenteritis. For none of these was gastroenteritis the reason for taking antibiotics. The time period between starting antibiotics and occurrence of symptoms ranged from 0 to 37 days with a median 8 days. Nine children (28%) commenced antibiotics and had gastroenteritis on the same day.

Of the 32 first antibiotic courses followed by gastroenteritis, 11 children had an inter-current respiratory illness when their symptoms of gastroenteritis commenced. When all children whose gastroenteritis was associated with an inter-current respiratory illness

Table 2. *Episodes of gastroenteritis and antibiotic use among the 965 children aged 4–6 years and resident in Adelaide Hills or rural South Australia, whose parents completed the diary study*

	<i>n</i>	(%)
Number of children reporting an episode of gastroenteritis	414	(42.9)
Number of gastroenteritis episodes per child		
None	551	(57.1)
One	317	(32.8)
Two	84	(8.7)
Three	13	(1.4)
Total number of reported gastroenteritis episodes	524	
Episodes of gastroenteritis		
With known contact with gastroenteritis sufferer*	177	(33.8)
With inter-current respiratory illness†	55	(10.5)
Preceded by antibiotic use during at risk period	33	(6.3)
With antibiotic use on the first day of symptoms	21	(4.0)
With both previous antibiotic use during at risk period and inter-current respiratory illness†	11	(2.1)
With both antibiotic use on the first day of symptoms and inter-current respiratory illness†	10	(1.7)
Without antibiotic use during at risk period but with inter-current respiratory illness†	44	(8.4)
Total number of antibiotic courses	111	
Number of children taking antibiotics	99	(10.2)
Number of antibiotic courses per child		
No course	866	(89.8)
One course	88	(9.1)
Two courses	10	(1.0)
Three courses	1	(0.1)
First antibiotic courses		
Followed by gastroenteritis	32	(32.3)
Followed by gastroenteritis and with inter-current respiratory illness† when started antibiotics	15	(15.2)
Followed by gastroenteritis and with inter-current respiratory illness† at time of gastroenteritis episode	11	(11.1)
Not followed by gastroenteritis	67	(67.7)

* Known contact with someone with gastroenteritis, inside or outside the home during previous 14 days.

† Earache or ear infection in conjunction with fever, or sore throat, cold, or influenza in conjunction with fever in the previous 3 days.

were excluded from the analysis (52 children and 55 episodes of gastroenteritis), 81 first courses of antibiotics were taken by the remaining 913 children. Nineteen (23.5%) of these were followed by an episode of gastroenteritis.

Results of univariate logistic regression are shown in Table 3. Starting a course of antibiotics that day (OR 8.75, 95% CI 4.38, 17.47), any antibiotic use that day (OR 2.49, 95% CI 1.55, 3.40), starting a course of antibiotics in the previous 7 days (OR 2.41, 95% CI 1.51, 3.85) and the number of antibiotic courses (OR 1.40, 95% CI 1.03, 1.90) were all significantly associated with an episode of gastroenteritis. Ever having previously taken antibiotics (during an at risk period) and the total duration of antibiotic usage per child were not.

Results of the multivariate analysis are shown in Table 4. Sex, socio-economic group, drinking-water

source, and the number of children under 15 years in the household were all dropped from the model. Inter-current respiratory illness and contact with someone with gastroenteritis were retained. After adjusting for these factors only the first day of antibiotic use was significantly associated with an episode of gastroenteritis (OR 3.8, 95% CI 1.8–8.06). Both inter-current respiratory illness (OR 6.76 95% CI 4.87, 9.38) and contact with someone with gastroenteritis (OR 1.80, 95% CI 1.48, 2.19) were associated with an increased risk of gastroenteritis. No effect modification was evident when interaction terms were entered into the multivariate model; interaction of inter-current respiratory illness and first day of antibiotic use (OR 1.0, 95% CI 0.22, 4.65), interaction of contact with someone with gastroenteritis and first day of antibiotic use (OR 0.23, 95% CI 0.04, 1.31).

Table 3. Odds ratio (OR) and 95% confidence interval (CI) estimates for episodes of gastroenteritis among the 965 children aged 4–6 years and resident in Adelaide Hills or rural South Australia whose parents completed the diary study, derived from univariate random effects logistic regression

Variable	OR	95% CI
First day of antibiotic course	8.75	4.38–17.47
Started antibiotic course in preceding 7 days	2.41	1.51–3.85
Took antibiotics that day	2.49	1.55–3.40
Took antibiotics in preceding diary days	1.36	0.95–1.95
Number of antibiotic courses per child	1.40	1.03–1.90
Total duration of antibiotic use per child	1.02	0.97–1.07

DISCUSSION

The incidence of AAD was 32.3% in our study, lying within the 20–40% incidence of AAD quoted for children given broad spectrum antibiotics [16]. However, it is higher than the 26% found for North American children receiving antibiotics as a placebo [15], suggesting that in our and in others [16] estimates undetermined causes and confounding factors may be playing a part.

No children in our study took antibiotics for pre-existing gastroenteritis. Furthermore an ongoing illness or its treatment resulting in symptoms of gastroenteritis at the start of the diary period was one of our exclusion criteria. We considered inter-current respiratory illness at the time of the gastroenteritis episode (i.e. within the preceding 3 days) as a potential confounding factor, and found it to be significantly associated with gastroenteritis. This association is likely to be complex, since respiratory illness can cause gastroenteritis in children, and antibiotics that can cause gastroenteritis are often prescribed for respiratory illness. In our study 10.5% of gastroenteritis episodes had a reported respiratory illness in the previous 3 days, somewhat lower than the 27–47% of enteric illness estimated to be related to respiratory illness in other studies [17]. Excluding children who reported these episodes from the analysis lowered our estimate of AAD to 23.5%, although we probably excluded a number of children whose inter-current respiratory illness was coincidental rather than causal.

Controlling for both inter-current respiratory illness (in the 3 days prior to gastroenteritis) and for previous contact with someone with gastroenteritis had a major effect on the association between antibiotic use and gastroenteritis. Only the association

with the first day of antibiotic use was significant at the 5% level, although the model implies this to have an important independent effect beyond those that may result from respiratory illness. Interestingly, we found no association of gastroenteritis with the duration of antibiotic treatment, or with the number of antibiotic courses, despite these being recognized as risk factors for AAD [7].

Rates of AAD are likely to vary to some extent with the definition of diarrhoea used. Diarrhoea is commonly defined based purely on stool characteristics, with increased frequency of bowel movements (3 or more per 24 h) and/or decreased stool consistency (mushy or watery stool), and/or increased stool weight (per day stool weight of >220) [19]. It has been suggested that AAD is clinically significant when there are three mushy or watery stools per day [11]. However, AAD is known to have varied presentations, including vomiting, fever and pseudomembranous colitis. The criteria of HCGI used to define gastroenteritis in our study is therefore more likely to capture a greater proportion of AAD. Our study had a number of other advantages when compared to other studies. It was community based, where antibiotic use is relatively common. Being prospective in nature and diary based, it was less subject to recall bias and ‘telescoping’ of symptoms into short periods. We asked about specific symptoms rather than the occurrence of ‘diarrhoea’, a term which may have different meanings to different people. Importantly, we were able to examine the effects of, and control for, potential confounding factors with multivariate logistic regression. The use of a random effects model also enabled us to account for multiple observations on each child, increasing the power of the analysis by including each day of diary data as a separate observation.

Table 4. *Adjusted* odds ratio (OR) and 95% confidence interval (CI) estimates for episodes of gastroenteritis among the 965 children aged 4–6 years and resident in Adelaide Hills or rural South Australia whose parents completed the diary study, derived from multivariate random effects logistic regression*

Variable	OR	95% CI
First day of antibiotic course	3.8	1.8–8.06
Started antibiotics in previous 7 days	1.16	0.69–1.94
Took antibiotics that day	1.25	0.75–2.08
Number of antibiotic courses per child	1.03	0.75–1.42

* All estimates adjusted for inter-current respiratory illness (in the previous 3 days) and contact with someone with gastroenteritis (in the previous 14 days).

Although we achieved an 83% response rate for completion of the daily diaries, our sample was not truly cross-sectional in nature for two reasons. First, eligible children were identified during the larger prevalence survey, and only 1960 parents of the 3413 identified (57%) were willing to participate. Second, a number of children (691) were excluded on the basis of their drinking-water source. However, the prevalence (as estimated from the incidence of gastroenteritis) was similar to that found in the larger prevalence study in 4-year-old South Australian children (J. Heyworth, unpublished observations). Interestingly, this was twofold greater than that reported in other studies [1, 2, 16], and may reflect regional differences and/or methodological differences discussed above.

We did not collect data regarding antibiotic use in the period immediately prior to the study, and may have misclassified some children's exposure to antibiotics. With calculations based prospectively on those known to have taken antibiotics this is unlikely to have affected our estimate of gastroenteritis associated with antibiotics incidence. Any effects on the estimates of risk are harder to determine, since the misclassification will have occurred both for children with, and without, episodes of gastroenteritis.

In summary, our study highlights the complex interaction of inter-current respiratory illness with AAD in children, and the need to consider this as a potential confounding factor when examining AAD in children.

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