Title: The community-level burden of acute diarrhoeal illness in the first 2 years of life in Brisbane, Australia: a birth cohort study

Type of manuscript: original article

Author full names: Gabor Mihala^{1,2}, Keith Grimwood^{1,2,3}, Stephen Bernard Lambert⁴, Robert Stuart Ware^{1,2}

Addresses of the institutions at which the work was carried out:

1. Griffith University, School of Medicine, Nathan, QLD, Australia
2. Griffith University, Menzies Health Institute Queensland, Nathan, QLD, Australia
3. Departments of Infectious Diseases and Paediatrics, Gold Coast Hospital and Health Service, Southport, QLD, Australia
4. Child Health Research Centre, Faculty of Medicine, The University of Queensland, South Brisbane, QLD, Australia

Address of corresponding author: Gabor Mihala, Griffith University, School of Medicine, N78 2.34, Nathan, QLD 4111, Australia. Phone: +61737359129, email: g.mihala@griffith.edu.au, ORCID: orcid.org/0000-0001-6654-405X

Acknowledgements: The authors acknowledge generosity of the families who participated in the Observational Research in Childhood Infectious Diseases study. GM is a recipient of a Higher Degree Research Scholarship from the Australian Government Research Training Program. The Observational Research in Childhood Infectious Diseases study was supported by an Australian National Health and Medical Research Council project grant (GNT615700) and a programme grant from the Children's Health Foundation Queensland (5006). No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Conflicts of interest: KG participated in a rotavirus strain outbreak advisory board for GlaxoSmithKline, Rixensart, Belgium. The remaining authors did not declare a conflict of interest.

Data accessibility statement: data collected during the ORChID study will not be made available publicly.

Title: The community-level burden of acute diarrhoeal illness in the first 2 years of life in Brisbane, Australia: a birth cohort study

ABSTRACT

Aim

This study sought to describe the burden of acute diarrhoeal illness (ADI) in an Australian subtropical urban setting following rotavirus vaccine introduction and to investigate the associations between child/family characteristics and ADI.

Methods

Parents of 154 children from the Observational Research in Childhood Infectious Diseases birth cohort provided daily symptom and healthcare data until the age of 2 years.

Results

The incidence rate of ADI was 1.07 per child-year (95% confidence interval 0.94–1.21). The median length of episode duration was 3 days (25th–75th percentiles 1–6). The incidence rate was significantly higher in the first month of life and between 6–17 months of age compared with 18–23 months, also for children with siblings and in formal childcare. Overall, 49% of ADI episodes led to healthcare visits.

Conclusions

Despite a successful rotavirus vaccine program, ADI still results in a substantial disease burden affecting young Australian children and their families.

KEY WORDS

child; incidence; infections; diarrhoea; gastroenteritis;

BRIEF POINTS

What is already known on this topic:

- acute diarrhoea is a major cause of child morbidity and mortality globally,
- despite the introduction of rotavirus vaccines, acute diarrhoea in young children remains an important public health problem in Australia,
- the burden of acute diarrhoea managed at the community-level is not well understood.

What this paper adds:

- the incidence rate of acute diarrhoeal illness (ADI) in Australian child in the first 2 years of life was 1.07 episodes per child-year (95% confidence interval 0.94–1.21),
- approximately half the ADI episodes resulted in a visit to a healthcare practitioner, and 8% to a hospital emergency department,
- incidence of ADI peaked around 12 months of age and was higher for children with siblings and in formal childcare.

INTRODUCTION

Acute diarrhoeal illness (ADI) is a major cause of child morbidity and mortality globally.¹ While rotavirus remains the most important aetiological agent of severe paediatric ADI, especially in the first 2 years of life, countries that have introduced rotavirus vaccines have witnessed a dramatic decline in both rotavirus and all-cause ADI hospitalisations and emergency department (ED) visits.^{2,3} In Australia, rotavirus vaccines were introduced into the national immunisation program in 2007 and a rapid reduction in hospital presentation for ADI in children under 5 years of age followed.⁴ Over the next 5 years the vaccine program was estimated to have resulted in a decrease in gastroenteritis or rotavirus-coded hospitalisations by 55%, ED presentations by 10%, and general practitioner (GP) consultations by 18%.⁵

Despite the success of rotavirus vaccines, ADI remains an important public health problem in Australia where children under 5 years of age still have the highest rates of illness and healthcare utilisation for their symptoms.⁶ The burden of ADI managed solely within the community is challenging to quantify,⁷ and is typically estimated or inferred from surveys such as the Australian National Gastroenteritis Survey (NGS), most recently conducted in 2008.⁶ The NGS reported 1.58 acute gastroenteritis episodes per child under 5 years of age per year.⁶ However, cross-sectional and retrospective surveys, such as the NGS that have a 4 week recall period, are vulnerable to recall error.⁸ Accurate evaluation of future public health interventions for infectious causes of ADI, such as novel vaccines or additional infection control strategies in high-risk settings, require better community-level disease estimates.

The aim of this study was to describe the incidence and burden of ADI at the Australian community-level in this high-risk age group in the rotavirus vaccine era using data from a prospective community-based Australian birth cohort, the Observational Research in Childhood Infectious Diseases (ORChID) study. Secondly, we investigated the associations between child/family characteristics and ADI, and between ADI and healthcare use.

METHODS

The ORChID study was a prospective birth cohort study of healthy children born at term and conducted in subtropical Brisbane, Queensland, Australia, between September 2010 and October 2014. ORChID focussed on respiratory and gastrointestinal illness episodes in the first 2 years of life.⁹ Researchers recruited women antenatally in 2 metropolitan hospitals and followed the children from birth until their second birthday. The Children's Health Queensland

(HREC/10/QRCH/16), the Royal Brisbane and Women's Hospital (HREC/10/QRBW/125) and The University of Queensland (2010000820/HREC/10/QRCH/16) Human Research Ethics Committees approved the study, which was registered on clinicaltrials.gov (NCT01304914). Ethical clearance was granted by Griffith University (2020/197) for this study.

Parents recorded the number of loose stools in a daily symptom diary. A separate impact diary was completed for each ADI. Written instructions provided to parents defined episodes as beginning on the first day there were 3 or more loose stools and finishing when stools returned to their usual consistency. Parents recorded the number of consultations with their GP and ED/hospital visits for each illness episode, the time spent on seeking healthcare for the child's illness, and the total time spent caring for their ill child during the episode. Data from symptom diaries and impact diaries were linked using participant identifier and date. Symptom diary entries without a linked impact diary record were excluded from the analysis of healthcare use.

The definition of ADI was based on an adaptation of the World Health Organization (WHO) definition for diarrhoea. An ADI episode required 3 or more loose (liquid or looser than normal) stools within a 24-hour period and included a refractory period of 3 days with no loose stools.

Child and family characteristics were collected at baseline; breastfeeding, childcare arrangements, and presence of other children in the household were collected progressively. Childcare was categorised as formal (defined as regulated care outside the child's home) or informal (non-regulated care provided by family or friends). The child was considered as exclusively breastfed from birth until the introduction of milk formula or solid food. Vaccination information was extracted from the national, population-based Australian Immunisation Register at study completion.

Child/family characteristics and symptom-diary data were presented descriptively. Time to first, second, and third ADI episodes were calculated using life tables. The incidence rate of ADI was calculated using Poisson regression, with exposure time including the first day of each ADI episode but excluding all other episode-days and the refractory period. The associations between child/family characteristics and ADI incidence rate were assessed using univariable and multivariable Poisson regression models (with the model offset by the natural logarithm of exposure time). Age, childcare, presence of other child in household, and season of observation were treated as time-varying variables. All multivariable models were adjusted

for the same set of variables, which were identified by stepwise backward elimination of covariables at $p \geq 0.05$, and interactions explored if the change in effect exceeded 10%. Identified variables (age group, presence of other child in household, and childcare arrangement) were confirmed using forward-selection. Effect estimates were reported as incidence rate ratios with 95% confidence intervals (CIs). Differences in episode duration by child/family characteristics were explored with Wilcoxon rank-sum tests. Stata statistical software v16 (Stata Corporation, College Station, TX, USA) was used for all analyses. P-values at <0.05 were considered statistically significant.

RESULTS

There were 87,641 daily observations returned by the parents of the participating 154 singleton children from the day of birth until the second birthdays (78% of possible days; Supplementary Figure 1). Three-quarters ($n=117$) of the children were followed for at least 12 months, and 61% ($n=94$) returned symptom diaries until the end of the study period (Supplementary Figure 2). In terms of their rotavirus vaccine status, of the 131 children remaining in the study at 8 months of age, 123 (94%) had received all 3 RotaTeq (Seqirus, Victoria) vaccine doses. The majority of participating families had above-median gross household incomes,¹⁰ and the mothers' level of highest educational attainment was generally higher than the 2010 Queensland levels.¹¹ Almost all children were introduced to food other than breastmilk by the age of 6 months, and almost half (44%) attended formal childcare by their first birthday (Supplementary Table 1).

The daily symptom diaries contained 2,080 (2.4%) reports of days with any loose stool, including 833 (1.0%) days with 3 or more loose stools (Table 1). The average daily number of loose stools was approximately twice as great in the first month of life than between the ages of 3 and 6 months, although the daily probability of any loose stool was similar throughout the first 6 months of life (Supplementary Figure 3). Overall, 96 children experienced 253 ADI episodes during the ORChID study, with 75% of children experiencing an ADI by their second birthday (Supplementary Table 2). The median age at first ADI episode was 10.9 months (Supplementary Table 2 and Supplementary Figure 4).

Table 1. Descriptive statistics of symptom diary records from the ORChID study (87,641 study-days, 253 ADI episodes)

		Days <i>n</i> (%)
Symptom diary records	Number of loose stools (per day, <i>N</i>= 87,641):	
	1	741 (0.8%)
	2	506 (0.6%)
	3 or more	836 (1.0%)
ADI episodes	Total number of days (<i>N</i>=87,641)[†]	1,431 (1.6%)
	Duration (<i>N</i>=252)^{†‡}:	
	1 day	64 (25.4%)
	2 days	43 (17.1%)
	3 days	27 (10.7%)
	4 to 5 days	49 (19.4%)
	6 to 7 days	30 (11.9%)
	8 to 14 days	24 (9.5%)
	15 days or longer	15 (6.0%)

categories of 'no' and 'none' omitted where applicable; ADI = acute diarrhoeal illness; ORChID = Observational Research in Childhood Infectious Diseases; † excluding the refractory periods; ‡ one missing duration value (symptom diary ended during an ADI episode);

The overall incidence rate of ADI was 1.07 episodes per child-year (95% CI: 0.94–1.21). The minimum rate was 0.41 episodes per child-year during the second month of life, before it rose to 1.89 episodes during the eleventh month, and then declined during the second year of life (Figure 1). When adjusted for the potentially confounding variables of age, presence of other child in household, and childcare arrangement, the incidence rate of ADI episodes was 2.2 (95% CI: 1.2–4.0) times higher in the first month of life, 1.8 (95% CI: 1.2–2.6) times higher between 6–11 months, and 1.6 (95% CI: 1.1–2.4) times higher between 12–17 months of age when compared to children between 18 to 23 months of age. The adjusted incidence rate was 1.3 (95% CI: 1.0–1.7) times higher with other children in the household (when compared to those without siblings) and 1.4 (1.0–1.9) times higher for children in formal childcare (when compared to children not in any childcare) (Table 2).

Figure 1. Incidence rates (including 95% confidence intervals) of acute diarrhoeal illness from birth to 2 years of age in the Observational Research in Childhood Infectious Diseases Study. One month equals 30.4 days.

Table 2. Associations between participant characteristics and ADI incidence in the ORChID study (87,641 study-days, 253 ADI episodes)

	No. of children[†]	Exposure (child-year)	Episodes (%)	IR per child-year (95% CI)	IRR (crude, 95% CI)	IRR (adj., 95% CI)
Age group:†						
<1 month	153	12.4	18 (7.1)	1.45 (0.91–2.30)	1.70 (0.92–3.00)	2.19 (1.18–4.03)
1 to <3 months	149	23.9	12 (4.7)	0.50 (0.29–0.88)	0.59 (0.28–1.13)	0.75 (0.38–1.51)
3 to <6 months	142	34.0	29 (11.4)	0.85 (0.59–1.23)	1.00 (0.60–1.63)	1.25 (0.74–2.12)
6 to <12 months	135	60.6	79 (31.2)	1.30 (1.05–1.62)	1.53 (1.04–2.26)	1.77 (1.20–2.62)
12 to <18 months	117	54.4	71 (28.1)	1.30 (1.03–1.65)	1.53 (1.03–2.28)	1.61 (1.10–2.35)
18 to ≤24 months	109	51.5	44 (17.4)	0.85 (0.64–1.15)	ref.	ref.
Sex of child:						
male	74	106.8	110 (43.5)	1.03 (0.85–1.24)	ref.	ref.
female	80	130.1	143 (56.5)	1.10 (0.93–1.29)	1.07 (0.83–1.38)	1.07 (0.84–1.38)
Delivery method:						
vaginal	105	159.1	179 (70.8)	1.12 (0.97–1.30)	ref.	ref.
caesarean	49	77.8	74 (29.2)	0.95 (0.76–1.20)	0.85 (0.64–1.12)	0.88 (0.67–1.16)
Other child in household[†]:						
no	102	153.7	151 (59.7)	0.98 (0.84–1.15)	ref.	ref.
yes	75	82.9	102 (40.3)	1.23 (1.01–1.49)	1.25 (0.96–1.62)	1.31 (1.02–1.69)
Season of birth:						

spring	43	65.7	56 (22.1)	0.85 (0.66–1.11)	0.77 (0.53–1.11)	0.76 (0.54–1.09)
summer	42	65.3	88 (34.8)	1.35 (1.09–1.66)	1.22 (0.88–1.69)	1.19 (0.87–1.63)
autumn	26	41.6	38 (15.0)	0.91 (0.67–1.26)	0.83 (0.54–1.25)	0.86 (0.58–1.28)
winter	43	64.4	71 (28.1)	1.10 (0.87–1.39)	ref.	ref.
Mother's education:						
no university degree	57	80.4	90 (35.6)	1.12 (0.91–1.38)	ref.	ref.
university degree	96	155.9	163 (64.4)	1.05 (0.90–1.22)	0.93 (0.72–1.22)	0.96 (0.74–1.24)
Exclusive breastfeeding[‡]:						
≥4 months	78	132.1	143 (58.8)	1.08 (0.92–1.28)	ref.	ref.
<4 months	59	98.1	100 (41.2)	1.02 (0.84–1.24)	0.94 (0.72–1.23)	0.94 (0.73–1.22)
Childcare arrangement^{†§}:						
none	153	121.6	115 (45.4)	0.95 (0.79–1.14)	ref.	ref.
informal	47	33.4	35 (13.8)	1.05 (0.75–1.46)	1.11 (0.74–1.63)	1.07 (0.71–1.61)
formal	90	81.6	103 (40.7)	1.26 (1.04–1.53)	1.33 (1.01–1.76)	1.39 (1.00–1.94)
Season of observation[†]:						
spring	143 [†]	59.6	69 (27.3)	1.16 (0.92–1.47)	ref.	ref.
summer	142 [†]	58.2	67 (26.5)	1.15 (0.91–1.46)	0.99 (0.70–1.41)	0.99 (0.70–1.38)
autumn	138 [†]	59.5	64 (25.3)	1.08 (0.84–1.38)	0.93 (0.65–1.32)	0.92 (0.66–1.30)
winter	139 [†]	59.7	53 (20.9)	0.89 (0.68–1.16)	0.77 (0.53–1.11)	0.74 (0.52–1.06)

*ADI = acute diarrhoeal illness; adj. = adjusted for age group, number of children at home, and childcare arrangement; CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; ORChID = Observational Research in Childhood Infectious Diseases; ref. = reference category; † the same child can appear in multiple categories when these are time varying (eg. a single child may contribute observations in multiple age, sibling, childcare and season categories); ‡ missing data from 17 subjects; § formal childcare = regulated care outside the child's home; informal childcare = non-regulated care provided by family or friends; **bold** indicates statistical significance (Poisson regression, Wald test); exposure-time was 86,466 days as it excluded all ADI days other than the first days of episodes; 1 month equals 30.4 days;*

Episodes had a median length of 3 days (25th–75th percentiles: 1–6). The median episode length was significantly longer (4.5 days) in the first month of life than between 18 and 23 months of age (3.0 days; $p=0.04$), and for children born in the Southern Hemisphere autumn season between March and May (5.0 days) compared to the summer months of December to February (3.0 days, $p=0.04$) (Supplementary Table 3 and Supplementary Figure 5).

Of the 253 ADI episodes reported in symptom diaries during ORChID, 89% ($n=226$) had a matching entry in the illness impact diary. Of ADI episodes with impact diaries, 49% resulted in formal healthcare use: 44% required at least one GP consultation, 8% resulted in an ED visit without hospital admission, and 3% led to a hospital admission (Table 3). The rate of formal healthcare use ranged from 0% in the second month of life (i.e. 1 month of age) to 67% in the eighth month of life (i.e. 7 months of age) (Supplementary Figure 6). Antibiotic medication was prescribed in 15% (31/211) of ADI episodes. When considering episode duration, healthcare use was lowest for episodes lasting 1 to 3 days and highest for episodes of 8 to 14 days duration, and carer-time was higher at longer episode durations (Table 3).

Table 3. Associations between ADI episode/duration and healthcare utilization in the ORChID study

	<i>N</i>	Utilisation[†]					Carer time (hours)[§]
		Any	GP	GP only	ED [‡]	H	
Episodes	226	110 (49)	100 (44)	84 (37)	19 (8)	7 (3)	10 (3.3–24)
Duration:							
1–3 days	120	48 (40)	42 (35)	36 (30)	9 (8)	3 (2)	7 (3–17)
4–7 days	75	42 (56)	39 (52)	34 (45)	5 (7)	3 (4)	12 (3–28)
8–14 days	21	14 (67)	13 (62)	10 (48)	4 (19)	0 (0)	24 (10–53)
≥15 days	10	6 (60)	6 (60)	4 (10)	1 (10)	1 (10)	38 (31–105)
Age[¶]:							
<1 month	9	5 (56)	4 (44)	2 (22)	1 (11)	2 (22)	9 (5–43)
1–2 months	8	2 (25)	2 (25)	2 (25)	0 (0)	0 (0)	8 (4–8)
3–5 months	23	8 (35)	7 (30)	6 (26)	2 (9)	0 (0)	3 (1–8)
6–11 months	75	43 (57)	39 (51)	28 (37)	11 (14)	4 (5)	15 (6–31)
12–17 months	68	34 (49)	31 (45)	29 (42)	4 (6)	1 (1)	6 (3–22)

18–23 months	41	18 (44)	17 (41)	17 (41)	1 (2)	0 (0)	16 (6–26)
--------------	----	---------	---------	---------	-------	-------	-----------

ADI = acute diarrhoeal illness; ED = emergency department; GP = general practitioner; H = hospital; ORChID = Observational Research in Childhood Infectious Diseases; frequency and row proportion (%) shown unless noted otherwise; † not mutually exclusive as participants could have more than one healthcare encounter in different settings; ‡ no associated hospitalisation (discharged home); § median (25th–75th percentiles) shown; ¶ 1 month equals 30.4 days;

DISCUSSION

Despite 94% of participants being fully vaccinated against rotavirus, this community-based birth cohort of healthy Australian children born between 2010 and 2012 still averaged more than one ADI episode per year, with symptoms present for a median of 3 days per episode. Incidence peaked in the first month and again in the eleventh month of life (i.e. 10 months of age). Almost half the ADI cases were seen by healthcare professionals, but only 3% led to hospitalisation.

ADI incidence was associated with having siblings and with formal childcare attendance, both of which are recognised risk factors.^{12, 13} The relative peak in ADI incidence rate and the longer median episode duration in the first month of life was unexpected since ADI is believed to be uncommon in healthy newborns.¹⁴ Our data show that this peak was driven by the relatively higher daily number of loose stools reported in the first month of life and did not result in above-average healthcare utilisation. Given that healthy, thriving breast-fed infants can produce a relatively high number of liquid stools in their first weeks of life,¹⁵ this peak appears to be from over-reporting of normal newborn stools leading to a misclassification of ADI episodes.¹⁶ This highlights the difficulties of defining ADI in this age group where frequent loose stools can have a low positive predictive value for an underlying disorder and may result from several different causes.¹⁷ Future analyses considering the alignment between ADI and pathogen detection are planned for this cohort to determine whether the peak in ADI episodes in the first month of life was associated with recognised enteric pathogens. Children born during the autumn months (March to May) had similar ADI incidence rates to those born during the winter months but had significantly longer disease episodes. This was also an unexpected finding as the season of observation was not associated with the incidence rate or duration

during ORChID (unlike evidence from temperate Australia where disease peaks occurred during winter and spring, and was attributed previously to rotavirus).⁴

For Australian children aged 0 to 4 years, the NGS 2001–2002, which was conducted in the pre-rotavirus vaccine era, found that 17% of diarrhoea cases were presented to a ‘medical person’.¹⁸ The proportion of healthcare-seeking was considerably higher during the ORChID study (49%), a difference most likely due to the younger age of ORChID children and the variability in data quality.¹⁹ Other studies conducted before the introduction of rotavirus vaccination in Australia and the United Kingdom found the ratio of ADI-related GP consultations to hospital admissions ranged from 6:1 to 15:1 in the <5 years age group;^{20, 21} this ratio was 12:1 during the ORChID study. The length of episode duration was positively correlated with healthcare use and is consistent with the results of the NGS 2001–2002²² and a more recent Australian cross-sectional survey.²³

Illness incidence rates depend on the disease definition used.⁶ When compared to five other published definitions applicable to small children, the WHO definition (with a refractory period of 1 day) provided a mid-range estimate of incidence when applied to the ORChID cohort.²⁴ The refractory period was increased to 3 days for this study (an arbitrary decision based on clinical judgement) and resulted in a somewhat lower incidence rate but did not influence the overall findings of the study.

Features of the ORChID study included progressive recruitment over a 2-year period and good retention and compliance rates with symptom and illness impact diaries, when one considers the intensive sampling undertaken on each child until their second birthday. The daily recording of symptoms prospectively reduced the potential impact of bias associated with retrospective or cross-sectional studies. However, the ORChID study was limited by the self-reported nature of the data collection and by using a daily symptom diary (which implies a period from midnight to midnight each day), where it was possible to distribute three or more loose stools that occurred over 24 hours over two consecutive days, resulting in a slight underestimation of ADI burden. Although the data were collected from 2010–2014, the epidemiology of ADI in this age group during the last decade has not changed significantly. The initial decline in rotavirus-associated diarrhoea after the vaccine was introduced into the Australian infant immunisation program in 2007 has been followed by biennial fluctuations in rotavirus notifications, with the vaccine maintaining its overall effectiveness in younger

children. Thus, the results are still likely to have good external validity.^{4, 5, 25} Other limitations were the aforementioned challenge of defining diarrhoea in the very young, and reduced generalisability for the more diverse Australian population when considering mother's education, household size, family income levels, and early use of formal childcare facilities.

The rotavirus vaccination program has been a success in Australia, as it has reduced ADI morbidity and the associated costs.^{4, 5, 25} However, other causes remain, and so ADI still results in a substantial disease burden affecting young Australian children and their families. Our estimates in the first 2 years of life of the diarrhoea-related burden in the rotavirus vaccine era will support further research into the other pathogens causing ADI in young children to identify where additional prevention strategies are needed.

REFERENCES

1. Troeger C, Blacker BF, Khalil IA, Rao PC, Cao SJ, Zimsen SRM, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infectious Diseases*. 2018;**18**(11):1211-28.
2. Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. *J Infect Dis*. 2017;**215**(11):1666-72.
3. Troeger C, Khalil IA, Rao PC, Cao S, Blacker BF, Ahmed T, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. *JAMA Pediatr*. 2018;**172**(10):958-65.
4. Buttery JP, Lambert SB, Grimwood K, Nissen MD, Field EJ, Macartney KK, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. *Pediatr Infect Dis J*. 2011;**30**(1 Suppl):S25-9.
5. Reyes JF, Wood JG, Beutels P, Macartney K, McIntyre P, Menzies R, et al. Beyond expectations: Post-implementation data shows rotavirus vaccination is likely cost-saving in Australia. *Vaccine*. 2017;**35**(2):345-52.
6. Barker SF, Zomer E, O'Toole J, Sinclair M, Gibney K, Liew D, et al. Cost of gastroenteritis in Australia: A healthcare perspective. *PLoS One*. 2018;**13**(4):e0195759.

7. Flint JA, Van Duynhoven YT, Angulo FJ, DeLong SM, Braun P, Kirk M, et al. Estimating the burden of acute gastroenteritis, foodborne disease, and pathogens commonly transmitted by food: An international review. *Clin Infect Dis*. 2005;**41**(5):698-704.
8. Jones MP, Walter S, Faresjo A, Grodzinsky E, Kjellstrom L, Viktorsson L, et al. Gastrointestinal recall questionnaires compare poorly with prospective patient diaries for gastrointestinal symptoms: data from population and primary health centre samples. *Eur J Gastroenterol Hepatol*. 2019;**31**(2):163-9.
9. Lambert SB, Ware RS, Cook AL, Maguire FA, Whiley DM, Bialasiewicz S, et al. Observational Research in Childhood Infectious Diseases (ORChID): A dynamic birth cohort study. *BMJ Open*. 2012;**2**(6):e002134.
10. Australian Bureau of Statistics. Household Income and Wealth. Summary of results, 2017–18 (65230DO001_201718). Canberra 2019.
11. Australian Bureau of Statistics. Education and Work. Level of highest educational attainment by state or territory of usual residence and sex, persons aged 15–64 years (62270DO001_201005). Canberra 2010.
12. Hullegie S, Bruijning-Verhagen P, Uiterwaal CS, van der Ent CK, Smit HA, de Hoog ML. First-year daycare and incidence of acute gastroenteritis. *Pediatrics*. 2016;**137**(5):e20153356.
13. King CL, Leask J. Parental disease prevention health beliefs and triggers for keeping children home from childcare-a qualitative study in Sydney, Australia. *Child Care Health Dev*. 2018;**44**(2):326-31.
14. Ciccarelli S, Stolfi I, Caramia G. Management strategies in the treatment of neonatal and pediatric gastroenteritis. *Infection and drug resistance*. 2013;**6**:133-61.
15. Lemoh JN, Brooke OG. Frequency and weight of normal stools in infancy. *Arch Dis Child*. 1979;**54**(9):719-20.
16. Breastfeeding and gastroenteritis. <https://www.breastfeeding.asn.au/bfinfo/breastfeeding-and-gastroenteritis> accessed 08 Nov 2019: Australian Breastfeeding Association; 2017 [updated Aug 2017].
17. Passariello A, Terrin G, Baldassarre ME, De Curtis M, Paludetto R, Berni Canani R. Diarrhea in neonatal intensive care unit. *World J Gastroenterol*. 2010;**16**(21):2664-8.
18. Scallan E, Majowicz SE, Hall G, Banerjee A, Bowman CL, Daly L, et al. Prevalence of diarrhoea in the community in Australia, Canada, Ireland, and the United States. *International journal of epidemiology*. 2005;**34**(2):454-60.

19. Hall G, Kirk MD, Becker N, Gregory JE, Unicomb L, Millard G, et al. Estimating foodborne gastroenteritis, Australia. *Emerg Infect Dis*. 2005;**11**(8):1257-64.
20. Galati JC, Harsley S, Richmond P, Carlin JB. The burden of rotavirus-related illness among young children on the Australian health care system. *Aust N Z J Public Health*. 2006;**30**(5):416-21.
21. Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. *Vaccine*. 2007;**25**(20):3962-70.
22. Hall G, OzfFoodNet Working Group. Results from the National Gastroenteritis Survey 2001–2002. <https://core.ac.uk/download/pdf/156615109.pdf> accessed 06 Feb 2020. Canberra: National Centre for Epidemiology & Population Health, The Australian National University, 2004 Contract No.: NCEPH Working Paper Number 50.
23. Chen Y, Ford L, Hall G, Dobbins T, Kirk M. Healthcare utilization and lost productivity due to infectious gastroenteritis, results from a national cross-sectional survey Australia 2008-2009. *Epidemiol Infect*. 2016;**144**(2):241-6.
24. Mihala G, Grimwood K, Morley C, Lambert SB, Ware RS. Effect of definitions of acute gastroenteritis episodes using symptom diaries in paediatric cohorts: A systematic review. *J Pediatr Gastroenterol Nutr*. 2020;**70**(3):e54-8.
25. Maguire JE, Glasgow K, Glass K, Roczo-Farkas S, Bines JE, Sheppeard V, et al. Rotavirus epidemiology and monovalent rotavirus vaccine effectiveness in Australia: 2010-2017. *Pediatrics*. 2019;**144**(4):e20191024.

Title: The community-level burden of acute diarrhoeal illness in the first 2 years of life in Brisbane, Australia: a birth cohort study

List of abbreviations: ADI: acute diarrhoeal illness. CI: confidence interval; ED: Emergency Department. NGS: Australian National Gastroenteritis Survey. ORChID: Observational Research in Childhood Infectious Diseases. WHO: World Health Organization.

Supplementary Figures

- Supplementary Figure 1. ORChID participant, symptom- and impact-diary data flowcharts.
- Supplementary Figure 2: Proportion of children contributing daily symptom observations over time in the ORChID study.
- Supplementary Figure 3. Daily loose stool observations in the first 6 months of life in the ORChID study. Values on horizontal axes represent age (in months) at the start of each month. One month equals 30.4 days.
- Supplementary Figure 4. The cumulative failure of the first, second and third ADI episodes over time during the ORChID study. Observation series with missing data for a consecutive period of ≤ 30 days were imputed assuming no acute diarrhoeal illness episode.
- Supplementary Figure 5. Box plot of ADI episode lengths by age during the ORChID study. Median and 25th–75th percentiles shown. Values on horizontal axis represent age (in months) at the start of each month. One month equals 30.4 days.
- Supplementary Figure 6. Proportion of ADI episodes with any healthcare utilisation by age during the ORChID study. Observed value and 95% binomial confidence intervals shown. Values on horizontal axis represent age (in months) at the start of each month. One month equals 30.4 days.

Supplementary Tables

- Supplementary Table 1. Characteristics of children and families enrolled in the ORChID study (N=154)
- Supplementary Table 2. Age at first/second/third ADI episodes, and percentage of children who had one/two/three ADI episodes at 6 monthly intervals, during the ORChID study
- Supplementary Table 3. ADI episode duration by personal/family characteristics during the ORChID study

Unit of analysis:
child

Unit of analysis:
symptom-diary

Unit of analysis:
impact-diary

Supplementary Figure 1. ORChID participant, symptom- and impact-diary data flowcharts. † day of birth is day zero, the first full day of life is day 1, and so on. Day 730 was study child's the last day in the study.

Supplementary Figure 2: Proportion of children contributing daily symptom observations over time in the ORChID study

Supplementary Figure 3. Daily loose stool observations in the first 6 months of life in the ORChID study. Values on horizontal axes represent age (in months) at the start of each month. One month equals 30.4 days

Supplementary Figure 4. The cumulative failure of the first, second and third ADI episodes over time during the ORChID study. Observation series with missing data for a consecutive period of ≤ 30 days were imputed assuming no acute diarrhoeal illness episode

Supplementary Figure 5. Box plot of ADI episode lengths (excluding refractory periods) by age during the ORChID study. Median and 25th–75th percentiles shown. Values on horizontal axis represent age (in months) at the start of each month. One month equals 30.4 days

Supplementary Figure 6. Proportion of ADI episodes with any healthcare utilisation by age during the ORChID study. Observed value and 95% binomial confidence intervals shown. Values on horizontal axis represent age (in months) at the start of each month. One month equals 30.4 days

Supplementary Table 1. Characteristics of children and families enrolled in the ORChID study
(*N*=154)

	<i>n</i> (%)
Sex of child: female	80 (52)
Gestation:	
36–38 weeks	35 (23)
39–42 weeks	119 (77)
Delivery: vaginal	105 (68)
First-born child	100 (65)
Season of birth:	
spring	43 (28)
summer	42 (27)
fall	26 (17)
winter	43 (28)
Rotavirus vaccination status (at 8 months of age; <i>n</i> =131 [†])	
not received	3 (2)
one dose received	2 (1)
two doses received	3 (2)
three doses received	123 (94)
Mother's education (<i>N</i> =153):	
secondary school	19 (12)
diploma or certificate	38 (25)
university degree	96 (63)
Household income (<i>N</i> =151):	
lowest to first quartile	0 (0)
first quartile to median	17 (11)
median to third quartile	51 (34)
third quartile to highest	83 (55)
Exclusive breastfeeding:	
at birth (<i>N</i> =154)	147 (95)
at 3 months of age (<i>N</i> =142)	97 (68)
at 6 months of age (<i>N</i> =133)	5 (4)

Childcare (formal[‡]):

at 6 months of age (N=133)	17 (13)
at 12 months of age (N=115)	51 (44)
at 18 months of age (N=108)	69 (64)
at 24 months of age (N=94)	63 (67)

[†] the pentavalent human-bovine reassortant vaccine (RotaTeq; Commonwealth Serum Laboratories/Merck and Co Inc) was Queensland's publicly funded rotavirus vaccine during ORChID and administered in a three-dose schedule at 6 weeks, 4 and 6 months of age, with the upper age limit for the third dose being 32 weeks; [‡] formal childcare = regulated care outside the child's home; parents were defined as all primary carers within the family unit;

Supplementary Table 2. Age at first/second/third ADI episodes, and percentage of children who had one/two/three ADI episodes at 6 monthly intervals, during the ORChID study

	Age (months) at ADI episodes					Percentage of ADI episodes			
	minimum	10 th percentile	25 th percentile	50 th percentile	75 th percentile	6 months	12 months	18 months	24 months
ADI episodes:									
first	0.0 [†]	1.9	6.6	10.9	22.8	25%	53%	69%	75%
second	0.2	7.7	11.7	-	-	8%	24%	38%	42%
third	0.5	11.6	21.4	-	-	4%	12%	20%	27%

ADI = acute diarrhoeal illness; [†] the first ADI was recorded on the first day of life;

Supplementary Table 3. ADI episode duration by personal/family characteristics during the ORChID study

	No. of ADI	ADI episode length (days)				<i>p</i> -value
		25 th pctl	50 th pctl	75 th pctl	95 th pctl	
Age group:						
<1 month	18	3.0	4.5	24.0	136.0	0.043
1–2 months	12	1.0	3.0	13.0	44.0	0.99
3–5 months	28	2.0	3.0	7.0	12.0	0.66
6–11 months	79	1.0	3.0	6.0	16.0	0.68
12–17 months	71	1.0	3.0	5.0	10.0	0.64
18–23 months	44	1.5	3.0	5.5	10.0	ref.
Gender:						
male	110	2.0	4.0	7.0	17.0	ref.
female	143	1.0	3.0	5.0	19.0	0.19
Delivery:						
vaginal	179	2.0	3.0	6.0	22.0	ref.
caesarean	74	1.0	3.0	7.0	11.0	0.61
Other child in household:						
no	151	1.0	3.0	6.0	19.0	ref.
yes	102	2.0	3.0	6.0	17.0	0.99
Season of birth:						
spring	56	2.0	3.0	5.5	24.0	0.65
summer	88	1.0	3.0	6.0	17.0	0.82
autumn	38	2.0	5.0	7.0	28.0	0.040
winter	71	1.0	3.0	5.0	12.0	ref.
Mother's education:						
secondary	18	1.0	2.0	3.0	24.0	ref.
TAFE certificate	72	1.0	3.0	5.5	44.0	
university	163	2.0	4.0	6.0	12.0	
Breastfed exclusive for ≤4 months:						
no	109	2.0	3.0	5.0	24.0	ref.
yes	143	1.0	3.0	6.0	17.0	0.68
Childcare:						
none	115	1.0	3.0	6.0	26.0	ref.
informal	35	1.0	2.0	6.0	9.0	0.53
formal	103	2.0	3.0	6.0	12.0	0.87
Season of observation:						
spring	70	1.0	3.0	6.0	24.0	0.70
summer	67	2.0	4.0	6.0	13.0	0.36
autumn	64	2.0	3.5	6.0	24.0	0.33
winter	52	1.0	3.0	5.0	12.0	ref.

pctl = percentile; 1 month equals 30.4 days; formal childcare = regulated care outside the child's home; ref. = reference category; ADI = acute diarrhoeal illness; **bold** indicates statistical significance (Wilcoxon rank-sum test);