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Title: Burden of Infection in Australian Infants

Type of manuscript: Original Article

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Acknowledgements

We thank all the parents and children who participated in BIS and the BIS staff for help with data collection and analysis. We also gratefully acknowledge the assistance of all participating general practitioner practices in the Barwon region and Geelong Hospital (Geelong) for providing participant health records.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the **Version of Record**. Please cite this article as doi: [10.1111/jpc.15174](https://doi.org/10.1111/jpc.15174)

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Conflicts of interest

None declared

Abstract

Aim

To determine the incidence, risk factors and health service utilisation for infection in the first 12 months of life in a population-derived Australian pre-birth cohort.

Methods

The Barwon Infant Study is a population-derived pre-birth cohort with antenatal recruitment (n=1074) based in Geelong, Victoria, Australia. Infection data were collected by parent report and general practitioner and hospital records at 1, 3, 6, 9 and 12 months of age. We calculated the incidence of infection, attendance at a health service with infection and used multiple negative binomial regression to investigate the effects of a range of exposures on incidence of infection.

Results

In the first 12 months of life, infections of the upper and lower respiratory tract (henceforth 'respiratory infections'), conjunctivitis and gastroenteritis occurred at a rate of 0.35, 0.04 and 0.04 episodes per child-month, respectively. 482 (72.4%) infants attended a general practitioner with an

infection and 69 (10.4%) infants attended the emergency department. Maternal antibiotic exposure in pregnancy and having older siblings were associated with respiratory infection. Childcare attendance by 12 months of age was associated with respiratory infections and gastroenteritis. Breastfeeding, even if less than 4 weeks in total, was associated with reduced respiratory infection.

Conclusions

Infection, especially of the respiratory tract, is a common cause of morbidity in Australian infants. Several potentially modifiable risk factors were identified, particularly for respiratory infections. Most infections were managed by general practitioners and 1 in 10 infants attended an emergency department with infection in the first year of life.

Key words: Respiratory tract infection, gastroenteritis, incidence, disease burden, health resources

Brief Points

What is already known on this topic?

- Globally, infection is responsible for almost 5 million deaths worldwide in pre-school children
- Up to 30% of Australian children are admitted to hospital with infection before their second birthday
- Hospitalisation with infection in infancy has been associated with maternal antibiotic use in pregnancy, smoking in pregnancy, lower socioeconomic status, infant sex, prematurity, low birthweight, no breastfeeding, passive smoke exposure, having siblings and childcare attendance

What this paper adds

- Infection is very common in Australian infants, with an incidence rate of 0.43 episodes of infection per child-month in the first year of life
- Health service utilisation amongst infants with infection is high, with almost three quarters of infants attending a GP, and 1 in 10 presenting to ED
- Maternal antibiotic exposure in pregnancy, older siblings, childcare attendance, and a lack of breastfeeding are associated with infection in infancy

Introduction

Infection causes a significant burden of disease among children, and is responsible for 2.5 million deaths worldwide in preschool children¹. In high income countries, infection remains a major cause of childhood morbidity². Up to 18% of Australian children are admitted to hospital with infection before their second birthday², and recent evidence suggests an increase in paediatric hospital presentations in Victoria³. However, findings are inconsistent⁴ and there are little data on less severe infections, as most studies have used general practitioner (GP) or hospital records^{2,5,6}, rather than parent-reported data⁴. Few recent studies have addressed incidence, risk factors and health service utilisation of infection in Australian infants. These data could inform public health prevention strategies, health systems planning and resource allocation.

We aimed to describe the incidence, predictors and health service utilisation of childhood infections among children in the first 12 months of life participating in a longitudinal cohort, by combining parent-reported data with that from GP and hospital medical records.

Materials and Methods

Study cohort

We used the Barwon Infant Study cohort, a population-derived pre-birth cohort study with antenatal recruitment (n=1074 infants born to 1064 mothers), based in Geelong, Victoria, Australia. Further details regarding the Barwon Infant Study have been published previously⁷. Briefly, between 2010 and 2013, 1158 pregnant women residing in the Barwon region of Victoria were recruited from local antenatal clinics. Infants were excluded if they were born before 32 weeks' gestation, had a serious illness identified in the first few days of life, major congenital malformation or genetically determined disease⁷. The study was approved by the Barwon Health Human Research and Ethics Committee (HREC 10/24).

Data collection

Research staff administered questionnaires in person and by telephone to parents in trimesters 1 or 2 and 3 of pregnancy and at 1, 3, 6, 9 and 12 months postnatally. We included delayed but completed 12 month reviews, up to 17 months of age. Questionnaire data included the number and type of

childhood infections, health service utilisation, reason for visiting a health service, and participant demographics.

Case definition

Parent-reported infections

We defined parent-reported respiratory tract infection (RTI) as the total number of episodes of parent-reported 'cold', acute otitis media (parent-reported 'ear infection') and throat infection (parent-reported 'throat infection involving redness or pus on the throat and swollen neck glands'). Parent-reported cold was classified as the highest reported number of episodes of 'cold with fever', 'cold longer than three days' or 'cold with cough' recorded in questionnaires. It was not possible to differentiate between upper and lower RTI based on the questionnaire data, so these data were analysed as a single category (RTI). We defined gastroenteritis as parent report of diarrhoea ('runny poo spilling out of the nappy, more frequent and smelly than usual, & lasting 24 hours or more') or vomiting lasting more than 24 hours. Conjunctivitis was defined as parent-reported eye infection, including redness of sclera and eye discharge. Genitourinary tract infection was defined as parent-reported urinary tract infection.

Parent-reported health care utilisation

We classified health service utilisation as GP, emergency department (ED) attendance or postnatal hospital admission. Parents reported when they attended a health service, what type of health service and for what reason. Reason for accessing a health service was available from two sources: parent recorded free text reasons for attending a health service and doctor diagnosis of the condition causing the presentation. If parent-reported reason for attendance was different from parent-reported doctor diagnosis, the latter was used, an approach used previously in this cohort⁸. We classified symptoms according to the International Classification of Primary Care, second edition (ICPC-2)⁹, which has been used in previous similar studies^{5,8,10}. Conditions not readily classified by ICPC-2 include neonatal sepsis and croup. Due to ambiguous symptom descriptions, 2.7% (77/2851) records could not be classified by ICPC-2 and were excluded. We classified each discrete onset of infection after 7 symptom-free days, such that if a child presented more than once in 7 days with infection, we considered it to be the same illness, an approach used in other population-based studies of childhood infection^{11,12}.

Statistical analysis

Our primary outcome was the incidence of infection in the first 12 months of life. We also investigated the effect of different exposures on incidence of infection, and proportion of infants attending a health service. Multiple negative binomial regression with robust error was used to quantify the effects of different exposures on incidence of infection, using incidence rate ratios and 95% confidence intervals (95% CI). Regression analyses were adjusted for socioeconomic status (measured by Socio-Economic Indexes for Areas, SEIFA), infant age at 12-month questionnaire completion, infant sex, parental smoking, and breastfeeding, which are all associated with differential risk of childhood infection. Breastfeeding was defined as parent reported age at cessation of breastfeeding; it includes exclusive and non-exclusive breastfeeding. Childcare attendance was defined as parent-reported age in weeks did the infant start receiving regular centre-based childcare, and parent reported cessation of regular childcare. We did not adjust for season as each child was followed for a complete year. We used inverse probability weighting to account for selection bias, as in previous studies of this cohort^{8,13}. Regression models were reweighted to account for potential differential distribution of exposures between the inception cohort and non-enrolled mothers. The weight for each participant was the inverse of the probability a mother would participate in the study, given her age, parental history of asthma, socioeconomic status, postcode and household size. Incidence rates amongst those with incomplete and complete data were compared to account for selection bias. Data cleaning and analysis was performed using Stata IC 15 Data Analysis and Statistical Software (StataCorp LP, College Station, TX, USA).

Validation

Validation of classification of infection using ICPC-2

Of 2851 records of parent-reported reason for health service attendance and parent-reported doctor diagnosis, 390 were independently classified by an additional clinical researcher (ZS), using ICPC-2. The percentage agreement, using kappa, for classification of upper RTI, acute otitis media, croup, bronchiolitis, pneumonia, viral disease not otherwise specified, gastroenteritis, urinary tract infection, infection not otherwise specified, and conjunctivitis was 96.0-100%.

Validation of parent-reported GP and ED attendance

We validated 17 parent-reported GP attendances with infection. The percentage agreement between parent-reported reason for attending GP and diagnosis from GP records was 64.5% ($\kappa = 0.48$, 95% CI [0.19, 0.77]). We validated 139 episodes of parent-reported ED attendance using a database of ED attendances among the Barwon Infant Study cohort with respiratory conditions. The percentage agreement between parent-report and hospital records for ED attendance with RTI was 88.5% ($\kappa = 0.69$, 95% CI [0.54, 0.85]).

Results

Cohort characteristics

Of the total cohort of 1074 participants, 62% (666/1074) had complete data (Figure 1). The distribution of exposures was similar amongst the inception cohort and those with complete data (Table S1, Supporting Information).

Incidence of infection in the first 12 months of life

Overall, we recorded 3772 episodes of infection in the first year of life among the cohort with complete data ($n=666$), giving an incidence rate of 0.43 (95% CI [0.42, 0.45]) episodes of infection per infant-month (Figure 2). In the first year of life, RTIs were the most common infection, with an incidence of 0.35 (95% CI [0.34, 0.36]) episodes per infant-month. Genitourinary infections were the least common, with an incidence of 0.002 (95% CI [0.001, 0.003]) episodes per infant-month (Table S2, Supporting Information). Infants experienced a 1.80 times higher incidence of infection in the second 6 months of life compared with the first 6 months. Incidence rates amongst infants with complete and incomplete data were not substantially different.

Health service utilisation in infants with infection

Table 1 shows the percentage of the cohort who attended a health service at least once with infection in the first 12 months of life. 72.4% (482/666) of infants attended their GP at least once with an infection in the first 12 months of life. RTIs were the most common reason for attending a health service in the cohort, where 56.3% (375/666) of infants and 25.1% (167/666) of infants attended their GP at least once with an URTI and LRTI, respectively.

10.4% (69/666) of infants in the first 12 months of life attended the ED with infection at least once, where RTIs represent the most common cause. 5.2% (35/666) of infants attended the ED at least once with a LRTI, while 3.8% (25/666) of infants attended the ED at least once with an URTI.

Factors associated with parent-reported infection in the first 12 months of life

Infection incidence rate ratios were adjusted for socioeconomic status, infant sex, breastfeeding, parental smoking in infancy and age at completion of the 12-month questionnaire (Table 2).

Maternal antibiotic exposure in pregnancy

Infants of women who received antibiotics in pregnancy had a higher rate of overall infection (adjusted incidence rate ratio (aIRR) 1.19, 95% CI [1.05, 1.35]); RTIs (aIRR 1.17, 95% CI [1.03, 1.35]); and gastroenteritis (aIRR 1.34, 95% CI [1.02, 1.78]).

Perinatal factors

There was some evidence of associations between higher birthweight z-score and overall infections (aIRR 1.05, 95% CI [1.01, 1.10]) and conjunctivitis (aIRR 1.12, 95% CI [1.01, 1.26]). We did not find evidence of an association between moderate to late preterm birth and incidence of infection.

Breastfeeding

On average, infants who were breastfed for up to 4 weeks experienced approximately 30% less overall infections than non-breastfed infants (aIRR 0.70, 95% CI [0.55, 0.90]), and RTIs (aIRR 0.68, 95% CI [0.49, 0.94]). Infants who were breastfed for more than 12 months experienced 28% less overall infection (aIRR 0.72, 95% CI [0.58, 0.89]) and 29% less RTIs (aIRR 0.71, 95% CI [0.53, 0.95]) compared to those who were not. We did not find evidence of an association between infants breastfed for 1 to 6 months, or for 6 to 12 months, compared with no breastfeeding, and incidence of infection.

Childcare attendance and siblings

There was evidence of associations between attending childcare for 1 to 20 weeks and each of overall infection (aIRR 1.29, 95% CI [1.17, 1.42]), RTIs (aIRR 1.28, 95% CI [1.16, 1.43]) and gastroenteritis (aIRR 1.41, 95% CI [1.08, 1.83]). There was also evidence of associations between childcare

attendance for 20 to 40 weeks and overall infection (aIRR 1.42, 95% CI [1.26, 1.60]) and RTIs (aIRR 1.46, 95% CI [1.29, 1.67]). We did not find an association between childcare attendance for more than 40 weeks and infection.

On average, infants with siblings aged 2 to 6 years at birth had more overall infections (aIRR 1.24, 95% CI [1.14, 1.36]) and RTIs (aIRR 1.29, 95% CI [1.17, 1.42]); those with siblings aged 10 to 21 years had increased risk of gastroenteritis (aIRR 1.62, 95% CI [1.11, 2.35]).

Demographic factors, exposure to smoking and hygiene

We did not find evidence of associations between any infection and SEIFA disadvantage tertile, maternal age, paternal age, maternal smoking during pregnancy, mode of delivery, parental postnatal smoking or ALSPAC hygiene score (Table 2). Male infants had a higher rate of gastroenteritis (aIRR 1.35, 95% CI [1.08, 1.68]). Incidence rate ratios were not substantially altered after inverse probability weighting.

Discussion

Infection in infants aged 0 to 12 months was commonly reported by parents and predominantly occurred in the second 6 months of life. The observed incidence (0.43, 95% CI [0.42, 0.45] infections per infant-month) is consistent with findings from a Danish population-representative birth cohort study (0.36 infections per infant-month)⁴. Our incidence rate was lower than findings from a recent Australian birth cohort study (0.56 RTIs per infant-month)¹⁴, which likely reflects differences in methodology.

Factors associated with infection in the Barwon Infant Study, though small in effect size, were consistent with past work, including maternal antibiotic exposure in pregnancy¹², male sex⁴, having siblings⁴ and childcare attendance for up to 40 weeks¹⁴. An elevated risk of infection was evident the longer infants attended childcare. We found that breastfeeding was associated with a decrease in respiratory infections, in contrast to a recent Australian study¹⁴; these discrepant findings may reflect differences in protection afforded by exclusive and non-exclusive breastfeeding. The association between maternal antibiotic exposure in pregnancy and infection in offspring has previously been reported with hospitalisation with infection as the sole outcome¹²; however this is the first study to

demonstrate this for less severe infections. The association between maternal antibiotic exposure and offspring infection may represent a genetic predisposition to infection, shared environmental factors or a causal relationship between antibiotic exposure and childhood infection, possibly via the maternal microbiome¹². The evidence of a modest association between increasing birthweight z-score and increased incidence of infection contrasts with many large studies that describe an association between low birthweight z-score and infection^{6,11,15}.

A number of previously observed associations with infection were not apparent our study, including lower socioeconomic status⁶, younger maternal age⁶, maternal smoking in pregnancy¹⁵, prematurity¹⁵, birth by caesarean section^{16,17} and parental smoking in infancy^{16,18}. Despite a high caesarean section rate, we did not find any association between birth by elective caesarean section and infection. This may suggest that birth by caesarean section does not increase the incidence of infection but does increase the severity of infection, measured by hospitalisation. Very few infants in our cohort were exposed to tobacco smoke in the home¹³, and this homogeneity likely explains why we did not observe an association between passive smoke exposure and infection. We also did not find any evidence suggesting ALSPAC hygiene score¹⁹, measured at 12 months of life, was associated with incidence of infection. Considerable evidence highlights the importance of hand hygiene reducing the spread of infection in the community²⁰, suggesting the hygiene score may not accurately reflect hygiene or that hygiene may be less relevant in non-outbreak prevention.

In the first 12 months of life, almost three quarters of infants attended a GP at least once with infection. Although direct comparison with other Australian data is difficult¹⁴, this represents a significant burden on primary care. Overall, 1 in 10 infants in our cohort presented to the ED at least once with infection. The rates of ED presentation in our study were much lower than other Australian data² and contrasts with recent evidence of marked increase in per capita presentations among children in the Barwon region³. These discrepancies may be due to higher health literacy and access to primary health care in the Barwon Infant Study cohort.

Strengths and limitations

The strengths of this study include use of an unselected antenatal sampling frame, relatively large sample size for a prospective population-representative cohort, detailed data on childcare attendance and sibling age, heterogeneity amongst the cohort and repeated questionnaires administered in

pregnancy and during the first year of life. Inverse probability weighting demonstrated that non-participation had little influence on our results.

There are a number of limitations. Our study relied heavily on parent-reported data, which may be affected by recall error, despite the frequency of questionnaires²¹. Validation of parent-reported health service attendances with infection using GP records demonstrated moderate parent recall accuracy, while hospital records demonstrated high recall accuracy. The discrepancy between accuracy of recall of GP and hospital visits with infection may be due to poor parental recall, especially of less severe presentations to the GP with infection, which may be compounded by the non-specific symptoms of many infections in early childhood. In addition, several factors are likely to be associated with parent-reported infection, but it is impossible to ascertain whether these factors were associated with infection per se or with parents who were more likely to report illnesses.

Our case definitions were constrained by the use of an extensive, multi-purpose questionnaire and were less specific for infection than those used by other studies^{10,14}, particularly with a specific focus on infection^{10,14}. Therefore, it is possible that we have misclassified the number of cases, leading to an underestimated incidence of infection. We were also unable to differentiate between upper and lower RTI based on questionnaire items. Parent reported data may also be limited by differential misclassification of exposures and outcomes, hence our results should be interpreted with caution.

Conclusion

Infection, especially RTI, is extremely common in infancy and has a large impact on primary care and ED utilisation. Other children – siblings and those at childcare – appear to be an important source of infection. Promoting appropriate antibiotic use in pregnancy²² and breastfeeding may reduce the early life burden of infection. Our data provide insight into the community burden of infection and complement previous Australian data linkage studies based in ED and hospitalised cohorts. Further studies in larger cohorts, using detailed questionnaires and data linkage of both GP and hospital attendances would provide more detailed and accurate information to guide infection prevention strategies and allocation of resources.

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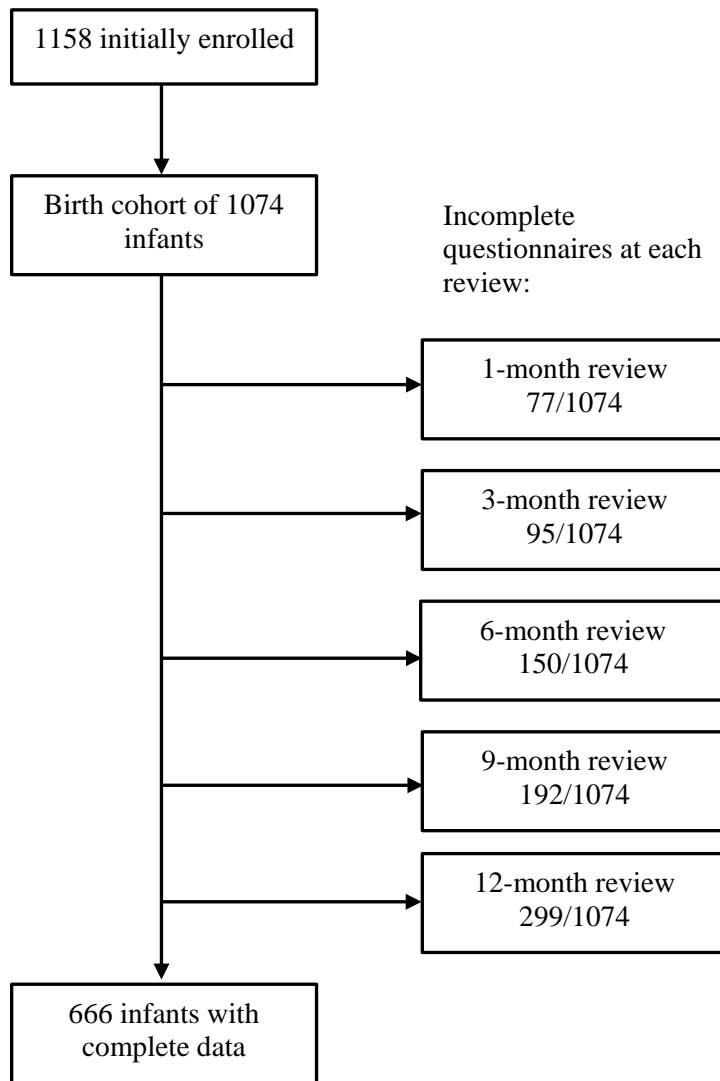


Figure 1: Barwon Infant Study questionnaire completion at each review

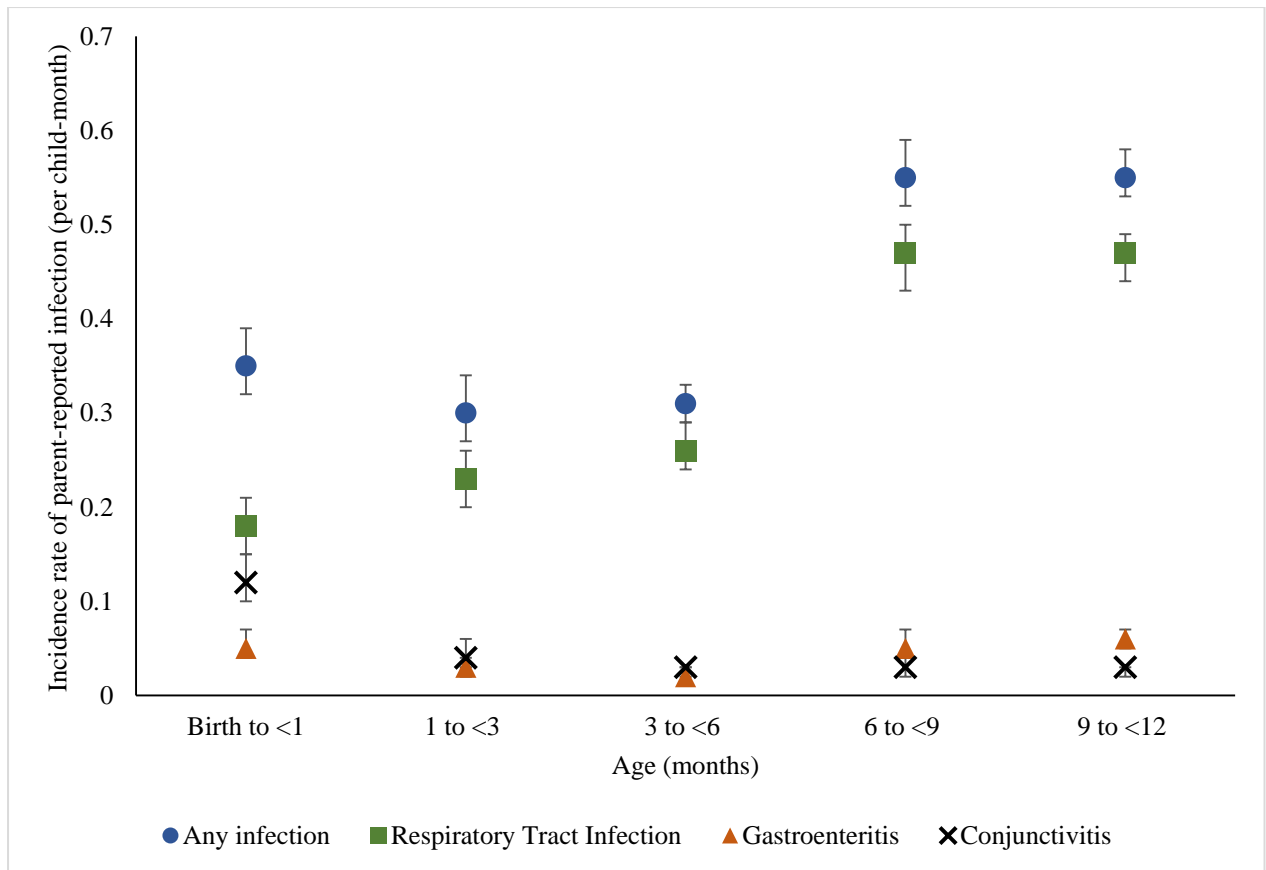


Figure 2: Incidence of parent-reported infection in the first 12 months of life. Incidence rate in child-months and 95% confidence interval (error bars) of any infection, respiratory tract infection, gastroenteritis and conjunctivitis.

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Perpetual Trustees. In-kind support was provided by the Cotton On Foundation and CreativeForce. The study sponsors were not involved in the collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication. Research at Murdoch Children's Research Institute is supported by the Victorian Government's Operational Infrastructure Support Program.

Conflicts of interest

None declared

Table 1: Percentage of cohort attending a health service at least once with infection in the first 12 months of life

Health service attended with infection †	Percentage of cohort attending a health service at least once in first 12 months of life (%)
GP	
Any infection	72.4
URTI	56.3
LRTI	25.1
GE	9.9
UTI	1.1
Viral	18.3
ED	
Any infection	10.4
URTI	3.8
LRTI	5.2
GE	1.8
UTI	0.8
Viral	2.0

GP, general practitioner; ED, emergency department; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; GE, gastroenteritis; UTI, urinary tract infection; Viral, viral diseases not otherwise specified. † Conditions classified according to International Classification of Primary Care, second edition.

Table 2: Association between participant characteristics and incidence rate ratio of parent-reported infection in the first year of life

	Any infection		Respiratory tract infection		Gastroenteritis		Conjunctivitis	
	Unadjusted IRR	Adjusted IRR	Unadjusted IRR	Adjusted IRR	Unadjusted IRR	Adjusted IRR	Unadjusted IRR	Adjusted IRR
	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]
SEIFA disadvantage tertile								
High	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Medium	0.93 [0.84, 1.04]	0.93 [0.84, 1.03] [†]	0.93 [0.83, 1.04]	0.91 [0.81, 1.02] [†]	0.89 [0.69, 1.15]	0.86 [0.66, 1.12] [†]	1.01 [0.76, 1.32]	1.02 [0.77, 1.34] [†]
Low	0.92 [0.82, 1.02]	0.90 [0.81, 1.00] [†]	0.92 [0.82, 1.04]	0.92 [0.81, 1.02] [†]	0.82 [0.62, 1.08]	0.78 [0.60, 1.02] [†]	0.94 [0.73, 1.24]	0.94 [0.71, 1.23] [†]
Maternal age (years)	1.01 [1.00, 1.02]	1.01 [1.00, 1.02] [‡]	1.01 [1.00, 1.02]	1.01 [1.00, 1.02] [‡]	1.02 [0.99, 1.04]	1.01 [0.99, 1.04] [‡]	1.01 [0.98, 1.03]	1.01 [0.97, 1.03] [‡]
Paternal age (years)	1.00 [0.99, 1.01]	1.00 [0.99, 1.01] [‡]	1.00 [0.99, 1.01]	1.00 [0.99, 1.01] [‡]	1.00 [0.98, 1.02]	1.01 [0.99, 1.03] [‡]	1.00 [0.98, 1.02]	1.00 [0.98, 1.02] [‡]
Antibiotic exposure in pregnancy								
None	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
At least one	1.16 [1.03, 1.32]	1.19 [1.05, 1.35] [‡]	1.14 [1.01, 1.31]	1.17 [1.03, 1.35] [‡]	1.31 [0.99, 1.72]	1.34 [1.02, 1.78] [‡]	1.12 [0.81, 1.54]	1.12 [0.81, 1.54] [‡]
Smoking during pregnancy								
None	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Any	0.90 [0.78, 1.04]	0.91 [0.78, 1.06] [‡]	0.86 [0.74, 1.01]	0.88 [0.75, 1.04] [‡]	1.07 [0.80, 1.44]	1.00 [0.71, 1.41] [‡]	1.10 [0.78, 1.57]	1.04 [0.70, 1.55] [‡]
Sex								
Female	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Male	1.05 [0.97, 1.15]	1.07 [0.98, 1.17] [§]	1.05 [0.95, 1.15]	1.07 [0.97, 1.17] [§]	1.30 [1.04, 1.62]	1.35 [1.08, 1.68] [§]	0.93 [0.74, 1.16]	0.92 [0.73, 1.16] [§]
Mode of delivery								
Vaginal	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Elective caesarean	1.06 [0.94, 1.20]	1.05 [0.93, 1.19] [‡]	1.05 [0.92, 1.20]	1.04 [0.91, 1.19] [‡]	0.97 [0.71, 1.31]	0.94 [0.70, 1.27] [‡]	1.37 [1.02, 1.82]	1.37 [1.03, 1.82] [‡]
Emergency caesarean	0.93 [0.82, 1.06]	0.95 [0.84, 1.09] [‡]	0.88 [0.77, 1.01]	0.90 [0.78, 1.03] [‡]	1.17 [0.87, 1.58]	1.19 [0.88, 1.61] [‡]	1.27 [0.96, 1.68]	1.29 [0.98, 1.73] [‡]
Gestational age (weeks)								
Term (37 - <42)	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Moderate to late preterm (32 - <37)	0.86 [0.68, 1.08]	0.88 [0.71, 1.11] [‡]	0.87 [0.69, 1.11]	0.91 [0.72, 1.16] [‡]	0.58 [0.31, 1.09]	0.60 [0.31, 1.11] [‡]	1.06 [0.54, 2.05]	1.01 [0.53, 1.91] [‡]
Birthweight Z-score	1.06 [1.01, 1.11]	1.05 [1.01, 1.10] [‡]	1.05 [1.00, 1.10]	1.05 [1.00, 1.10] [‡]	1.00 [0.90, 1.12]	1.02 [0.91, 1.14] [‡]	1.13 [1.01, 1.26]	1.12 [1.01, 1.26] [‡]
Duration of breastfeeding (months)								
No breastfeeding	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
<1	0.70 [0.55, 0.90]	0.70 [0.55, 0.90] [¶]	0.67 [0.48, 0.93]	0.68 [0.49, 0.94] [¶]	0.95 [0.38, 2.37]	0.92 [0.37, 2.27] [¶]	1.03 [0.41, 2.59]	1.02 [0.41, 2.53] [¶]
1 - <6	0.81 [0.65, 1.01]	0.83 [0.66, 1.03] [¶]	0.77 [0.57, 1.05]	0.80 [0.59, 1.07] [¶]	1.16 [0.49, 2.78]	1.12 [0.47, 2.64] [¶]	1.20 [0.50, 2.90]	1.17 [0.49, 2.79] [¶]

6 - 12	0.86 [0.69, 1.07]	0.86 [0.69, 1.07] [¶]	0.82 [0.61, 1.11]	0.84 [0.62, 1.12] [¶]	1.09 [0.46, 2.62]	1.06 [0.45, 1.48] [¶]	1.23 [0.51, 2.96]	1.19 [0.50, 2.84] [¶]
>12	0.72 [0.58, 0.89]	0.72 [0.58, 0.89] [¶]	0.71 [0.52, 0.95]	0.71 [0.53, 0.95] [¶]	0.86 [0.36, 2.04]	0.82 [0.35, 1.91] [¶]	1.03 [0.43, 2.46]	1.00 [0.42, 2.37] [¶]
Parental smoking in the first 12 months of life								
No	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Any	0.97 [0.86, 1.09]	0.96 [0.85, 1.09] ^{††}	0.92 [0.81, 1.05]	0.93 [0.81, 1.06] ^{††}	1.18 [0.90, 1.55]	1.12 [0.83, 1.52] ^{††}	1.15 [0.86, 1.53]	1.14 [0.84, 1.54] ^{††}
ALSPAC Hygiene score ¹⁹ quartile (most hygienic to least)								
4	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
3	1.19 [0.99, 1.45]	1.18 [0.98, 1.43] [‡]	1.21 [0.99, 1.49]	1.20 [0.98, 1.46] [‡]	1.03 [0.65, 1.64]	0.99 [0.62, 1.59] [‡]	1.24 [0.72, 2.12]	1.29 [0.74, 2.23] [‡]
2	1.20 [1.00, 1.45]	1.20 [1.00, 1.44] [‡]	1.19 [0.97, 1.44]	1.18 [0.97, 1.43] [‡]	1.11 [0.71, 1.74]	1.09 [0.69, 1.72] [‡]	1.53 [0.91, 2.60]	1.51 [0.89, 2.60] [‡]
1	1.19 [0.99, 1.43]	1.20 [0.99, 1.42] [‡]	1.17 [0.96, 1.42]	1.17 [0.97, 1.42] [‡]	1.02 [0.65, 1.59]	1.00 [0.64, 1.57] [‡]	1.70 [1.01, 2.85]	1.71 [1.00, 2.90] [‡]
Duration of childcare attendance at 12 months (weeks)								
None	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1 - <20	1.31 [1.19, 1.44]	1.29 [1.17, 1.42] [‡]	1.31 [1.18, 1.45]	1.28 [1.16, 1.43] [‡]	1.46 [1.13, 1.88]	1.41 [1.08, 1.83] [‡]	1.26 [0.95, 1.67]	1.26 [0.95, 1.68] [‡]
20 - <40	1.46 [1.30, 1.64]	1.42 [1.26, 1.60] [‡]	1.49 [1.32, 1.69]	1.46 [1.29, 1.67] [‡]	1.54 [1.15, 2.07]	1.35 [1.00, 1.83] [‡]	1.20 [0.87, 1.63]	1.22 [0.89, 1.67] [‡]
>40	1.29 [1.01, 1.64]	1.25 [0.95, 1.66] [‡]	1.34 [1.02, 1.75]	1.30 [0.96, 1.76] [‡]	1.67 [0.91, 3.04]	1.51 [0.78, 2.93] [‡]	0.62 [0.29, 1.32]	0.65 [0.31, 1.37] [‡]
Any siblings at birth (age in years)								
0 - <2	1.13 [0.98, 1.32]	1.15 [0.99, 1.33] [‡]	1.13 [0.96, 1.33]	1.14 [0.97, 1.35] [‡]	1.06 [0.76, 1.49]	1.10 [0.79, 1.53] [‡]	1.25 [0.90, 1.73]	1.25 [0.89, 1.74] [‡]
2 - <6	1.25 [1.14, 1.36]	1.24 [1.14, 1.36] [‡]	1.30 [1.18, 1.43]	1.29 [1.17, 1.42] [‡]	0.98 [0.78, 1.22]	0.96 [0.76, 1.21] [‡]	1.13 [0.89, 1.42]	1.15 [0.90, 1.46] [‡]
6 - <10	0.89 [0.76, 1.05]	0.91 [0.78, 1.07] [‡]	0.86 [0.72, 1.03]	0.88 [0.74, 1.05] [‡]	0.89 [0.59, 1.34]	0.93 [0.61, 1.40] [‡]	1.20 [0.79, 1.82]	1.21 [0.79, 1.86] [‡]
10 - <21	1.03 [0.80, 1.31]	1.06 [0.83, 1.34] [‡]	0.93 [0.72, 1.18]	0.96 [0.75, 1.22] [‡]	1.58 [1.07, 2.33]	1.62 [1.11, 2.35] [‡]	1.15 [0.67, 1.98]	1.16 [0.69, 1.97] [‡]
Age at 12-month questionnaire (years)	0.94 [0.50, 1.75]	0.99 [0.54, 1.83] ^{††}	0.88 [0.45, 1.76]	0.99 [0.50, 1.95] ^{††}	2.22 [0.50, 9.81]	2.30 [0.52, 10.29] ^{††}	0.72 [0.17, 3.07]	0.53 [0.13, 2.26] ^{††}

Analysis completed using multiple negative binomial regression with robust error. Analysis was completed on participants with complete data (n=666). Any infection is a combined measure of number of parent-reported episodes of respiratory tract infections, gastroenteritis and conjunctivitis. Respiratory tract infection is a measure of upper and lower respiratory tract infections, throat infections and acute otitis media

We were unable to differentiate between parent-reported upper respiratory tract infection and lower respiratory tract infection based on the questionnaire. The ALSPAC hygiene score was derived by Sherriff and Golding¹⁹.

[†]Adjusted for infant sex, duration of breastfeeding, parental smoking and age at 12-month questionnaire completion. [‡]Adjusted for SEIFA disadvantage tertile, infant sex, duration of breastfeeding, parental smoking and age at 12-month questionnaire completion. [§]Adjusted for SEIFA disadvantage tertile, duration of breastfeeding, parental smoking and age at 12-month questionnaire completion. [¶]Adjusted for SEIFA disadvantage tertile, infant sex, parental smoking and age at 12-month questionnaire completion. ^{††}Adjusted for SEIFA disadvantage tertile, infant sex, duration of breastfeeding and age at 12-month questionnaire completion. ^{‡‡}Adjusted for SEIFA disadvantage tertile, infant sex, duration of breastfeeding and parental smoking. IRR, incidence rate ratio; 95% CI, 95% confidence interval; SEIFA, socioeconomic indexes for area.

