Prevalence and determinants of antibiotic exposure in infants: a population-derived Australian birth cohort study

Original Article

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All authors had full access to all data (including statistical reports and tables) in the study.

Figure 1.

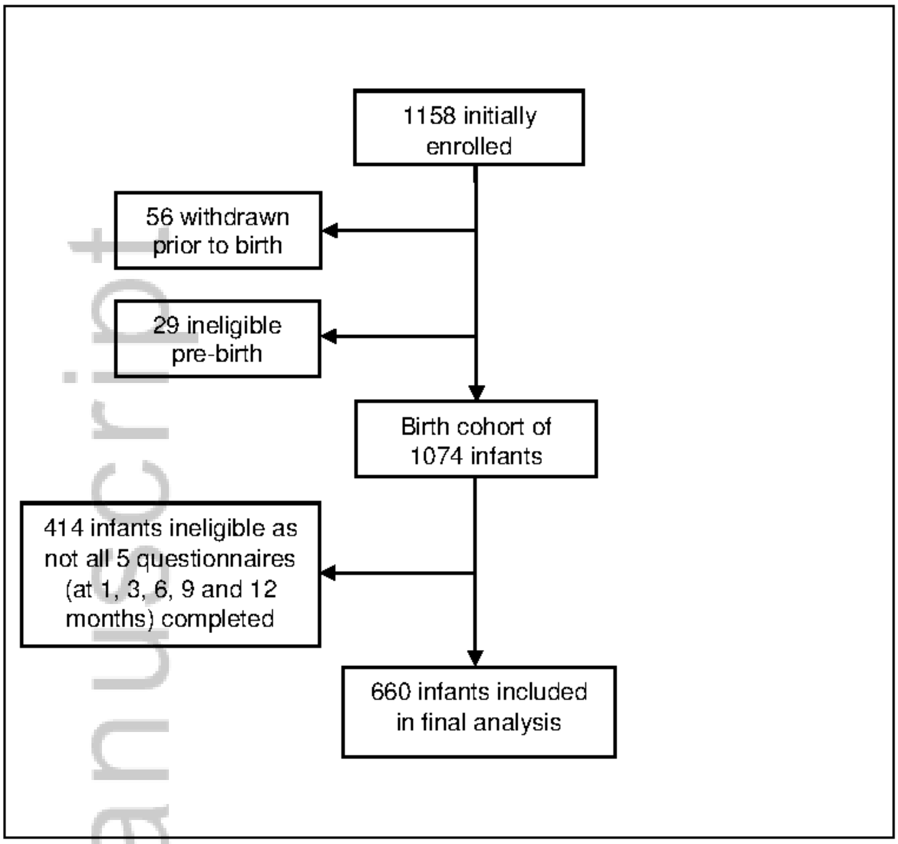

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Figure 2.

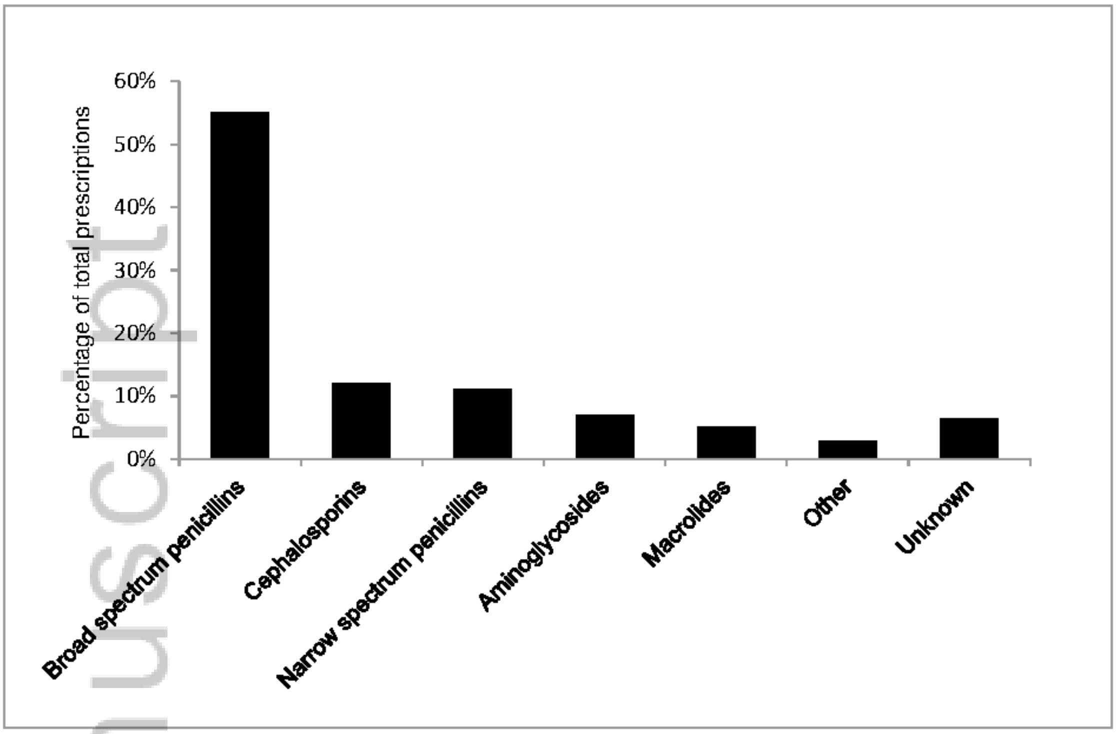

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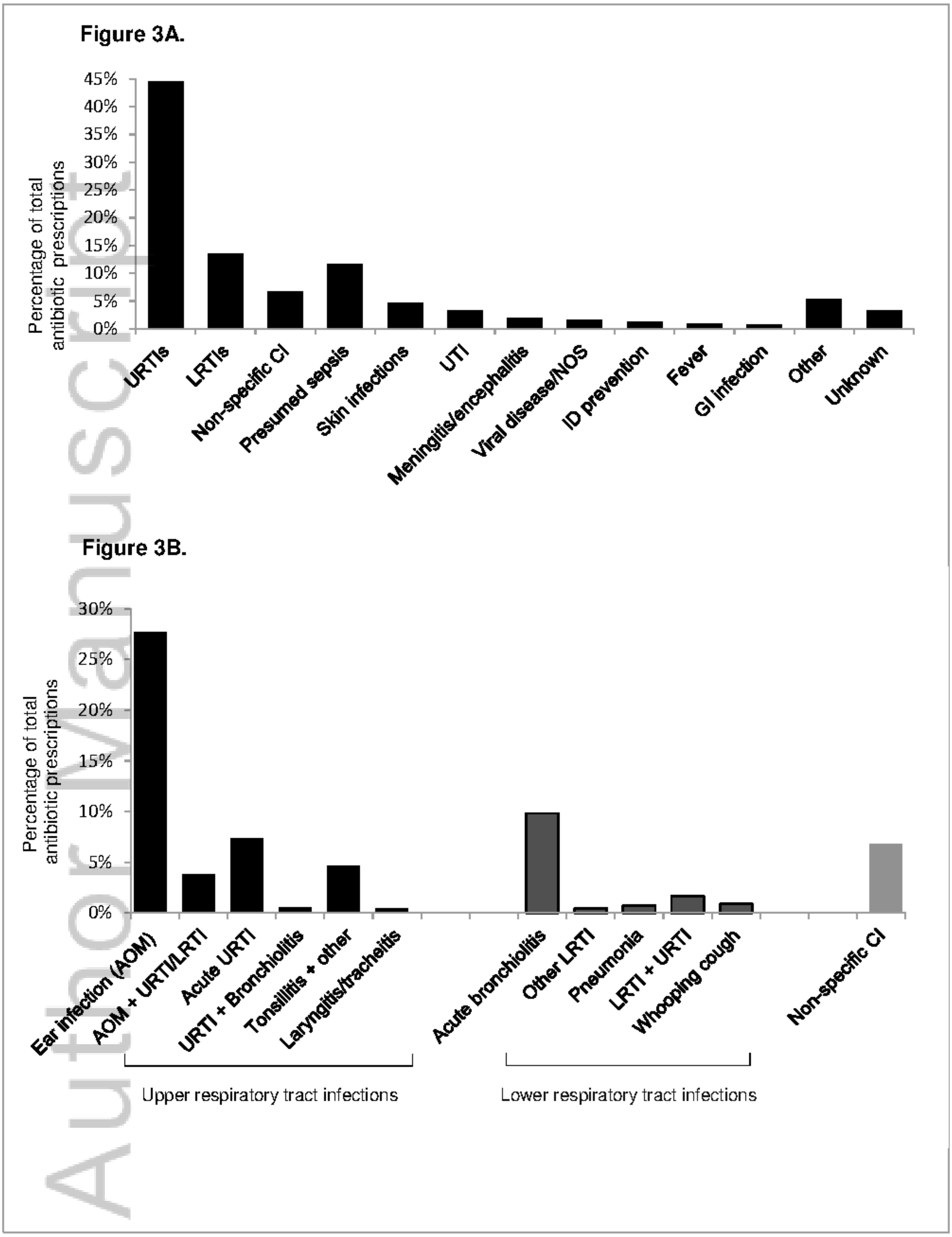
Figure 3



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Abstract

Aim: To describe antibiotic exposure in Australian infants during the first year of life, focusing on antibiotic class, indication, risk factors associated with exposure, and comparison with international counterparts.

Methods: The Barwon Infant Study is a birth cohort study (n=1074) with an unselected antenatal sampling frame from a large regional centre in Victoria, Australia. Longitudinal data on infection and medication were collected at 1, 3, 6, 9 and 12 months by parental questionnaire, and from general practitioner and hospital records. Predictors of questionnaire non-completion were identified. 660 infants with complete serial data were comprehensively examined. Antibiotic exposure was calculated in (i) antibiotic prescriptions and (ii) antibiotic days-exposed per person-year.

Results: Mean antibiotic prescription rate was 0.92 prescriptions (95% CI, 0.83-1.02) per person-year, with highest rates in those aged <1 month (1.50 [95% CI, 1.09-1.91] per person-year). 50.0% of infants were exposed to at least one antibiotic in their first year of life. Increasing number of siblings was associated with increased antibiotic exposure. Penicillins with extended spectrum (365 of 661 antibiotic prescriptions, 52.6%) and cephalosporins (12.0%) were the most frequently prescribed antibiotics. One fifth of antibiotics were prescribed for respiratory tract infections and bronchiolitis.

Conclusions: Australian infants in this large population-based study are exposed to considerably more antibiotics than the majority of their international counterparts. Interventions aimed at addressing avoidable prescribing by medical practitioners and modifiable risk factors associated with antibiotic exposure may reduce antibiotic use.

Keywords: antibacterial agents; infant; drug resistance, infection; prescription; cephalosporins; siblings; unemployment.

Introduction

Antibacterial resistance is a global health emergency.[1] In Australia, antibiotic resistance in both children and adults is increasing rapidly in hospitals and the community.[2] A major contributor is excessive antibiotic exposure.[2] Understanding the extent and risk factors associated with antibiotic exposure may inform strategies to reduce inappropriate prescribing, especially in populations with the highest prescription rates.

Population-level data, largely from high-income settings, show that exposure to antibiotics is greatest in infancy and early childhood.[3, 4] Childhood infections are predominantly viral in origin or, if bacterial, may not necessitate antibiotics (e.g. uncomplicated acute otitis media (AOM)).[5] Therefore, antibiotic use in early childhood may often be unnecessary. Furthermore, antibiotic use in infancy may alter the microbiome, which may increase the risk of chronic, non-infectious diseases.[6]

International studies have focused either on primary care, or hospital-based prescribing, but rarely both contemporaneously. There are few studies of antibiotic use and associated factors in Australian infants.

We describe antibiotic exposure from hospital and primary care in a population-derived cohort of Australian infants during the first 12 months of life, focusing on antibiotic class, indication, and factors associated with exposure.

Materials and Methods

Population

The Barwon Infant Study (BIS) is a population-derived birth cohort study established to examine the relationship between early life microbial exposures, immune development in the first year of life and later development of non-communicable diseases (n = 1,074).[7] From 2010-2013 a cohort of 1,158 women were recruited antenatally (33% recruitment rate) from two major hospitals in the Barwon region, Victoria, Australia. Exclusion criteria included mothers unable to complete the questionnaire without interpreter assistance, and those aged less than 18 years at 28 weeks gestation. Infants were excluded if they were < 32 weeks gestational age, or if they had a serious illness, genetic disease, or major congenital malformation.

The study was approved by the Barwon Health Human Research and Ethics Committee (HREC 10/24).

Data sources

Information regarding antibiotic exposure (number and length of prescriptions), clinical indication, and patient demographics were obtained from parental questionnaires administered at 1, 3, 6, 9 and 12 months postnatal age. Only participants with all five completed questionnaires were included. We excluded data on topical antibiotics (available without prescription; data therefore unverifiable), isoniazid for tuberculosis prevention, and on antifungals and antivirals.

All systemic (oral, intravenous and intramuscular) antibiotic prescriptions were included. Antibiotics were coded using the Anatomical Therapeutic Chemical (ATC) classification system (J: Anti-infectives for systemic use).[8]

The clinical indications for antibiotic prescription were coded using the International Classification of Primary Care, Second Edition (ICPC-2).[9] For the broad ICPC-2 categories ‘ear infection’ and ‘chest infection’, we tried to clarify the clinical indications from general practitioner records where available. Indications not readily categorised using ICPC-2 were grouped as ‘sepsis/presumed sepsis’, ‘prevention following infectious disease exposure’, and ‘post-operative prophylaxis’.

For all missing or ambiguous data, general practitioner and hospital records were examined, excluding interstate or overseas encounters. Where general practitioner or hospital records were inconsistent with parental reported data, the latter were used.

Data verification

Questionnaire data from 15 randomly selected participants who received antibiotics from primary care were compared with general practitioner records to assess reliability of parental reporting. Hospital prescription data were verified against available hospital records.

Statistical analysis

The main outcomes were (i) *antibiotic prescription rate* (antibiotic prescriptions per person-year) and (ii) *antibiotic exposure rate* (antibiotic days-exposed per person-year). Participants who received prolonged (≥45 days) antibiotic prophylaxis (n=2) were excluded to prevent inflated mean exposure rates. Person-years were used to account for the specific person-time contributed by each child, as most children were slightly over 1 year of age at the 12-month interview. Multivariate Poisson regression was used to determine the relationships between the outcome measures and variables of interest with estimated incidence rates ratios (IRR) and corresponding 95% confidence intervals (CI). Robust (information sandwich) standard errors were used for the parameter estimates to account for the higher variance (over-dispersion) observed in the data than would be expected under the assumptions of the Poisson model. The covariates investigated included mode of birth, birthweight z score, maternal and paternal age, index of relative social disadvantage (IRSD) score, paternal unemployment, maternal education level, maternal ante- and postpartum smoking status, season of birth, and birth order. In sensitivity analyses, population-weighted models were fitted to determine whether there was any loss to non-participation bias.[10] Prevalence estimates were also reweighted. The weight for each subject was the inverse of the probability of cohort entry, among those approached, given the mother's age, socioeconomic status by postcode, and parental history of asthma and eczema. Analyses were performed using Stata IC 13 Data Analysis and Statistical Software (StataCorp LP, College Station, TX, USA).

Results

Cohort characteristics

Of the BIS cohort, 660 infants had data from all 5 time points (Figure 1). Factors associated with incomplete records included younger parents, maternal smoking, large families, lower socio-economic status (IRSD score), not breastfeeding at 4 weeks, and non-university educated mothers (Table 1). The study infants contributed a total of 716.9 person-years, with an average of 1.1 years (SD 0.07 years) per child.

Prescription rates, exposure rates and prevalence

Table 2 shows prescription rates and proportion of total antibiotics prescribed for each age stratum. The average prescription rate for the cohort was 0.92/person-year (95% CI, 0.83-1.02). The highest prescription rate was in those aged <1 month (1.50/person-year; 95% CI, 1.09-1.91) and the lowest in those aged 1-3 months (0.36/person-year; 95% CI, 0.18-0.55). On average infants received 1.79 times more prescriptions in the second 6 months of life than in the first 6 months. The average antibiotic exposure rate overall was 5.07 days/person-year (95% CI, 4.50-5.64.) 330/660 (50.0%) of infants received at least one antibiotic prescription by 12 months of age and 85/660 (12.9%) of infants at least three.

Patient and family demographics associated with antibiotic prescription and exposure

Infants with siblings had 1.20 (95% CI, 1.04-1.38) times higher prescription rates with each additional sibling, compared to only children (Table 3). Infants with unemployed fathers had rates 1.61 (95% CI, 0.97-2.68) times higher than infants with employed fathers. Infants received 0.98 (95% CI, 0.95-1.00) times fewer antibiotic prescriptions with each increasing year of paternal age. Infants breastfed at 4 weeks received 0.81 (95% CI, 0.59-1.10) times fewer prescriptions than non-breast fed infants.

Similar trends were seen with antibiotic exposure rates (Table 3). In addition, winter and autumn-born infants received 0.86 (95% CI, 0.68-1.10) times fewer antibiotic days than summer or spring-born infants.

Antibiotic class

A total of 661 antibiotic prescriptions were recorded from 13 different classes (Figure 2). The most common class was penicillins with extended spectrum (365/661, 52.6% of all prescriptions), followed by cephalosporins (79/661, 12%). Age-stratified analysis showed that penicillins with extended spectrum were most commonly prescribed in all age strata, except for 0-1 months, when aminoglycosides (41/110, 37.3%) and beta-lactamase sensitive penicillins (37/110, 33.6%) predominated.

Clinical indication

Fifty-three distinct clinical diagnoses were classified into 13 broad categories (Figure 3). Neonatal sepsis, AOM and URTI were the most common. The leading indication for antibiotics was ear infection (209/661, 31.5% of all diagnoses). Based on verification against general practitioner records, approximately 201/209 (96%) of ear infections included AOM. Ear infection was the commonest indication from 3-12 months, and sepsis/presumed sepsis the commonest indication in 0-1 months of age (77/110, 70.0% of diagnoses). URTI and bronchiolitis together accounted for 117/661 (17.8%) of prescriptions. Clarification of parental reporting for ‘ear infections’ and ‘chest infections’ against general practitioner and hospital records suggested that the documented proportion was slightly higher (136/661, 21%).

Data clarification and verification

Ambiguous data included ‘ear infection’, ‘chest infection’ and other non-specific terms used for antibiotic name and/or indication. There were 119 ambiguous observations identified for antibiotic name, of which 58 (51.3%) could be clarified. 494 ambiguous observations for antibiotic indication were identified, of which 260 (47.4%) could be clarified. Of the 189 diagnoses recorded by parents as ‘ear infections’, 61 (32.3%) were clarified. Most (57/61, 93.4%) included AOM. Of the 75 recorded ‘chest infections’, 30 (40.0%) were clarified. 11/30 (3.7%) included bronchiolitis/URTI only, 14/30 (46.7%) included a lower respiratory tract infection (LRTI), and 5/30 (1.7%) included AOM.

Questionnaire data correlated well with data from general practitioner and hospital records (Supplementary Table 1). Records of 15 participants (18 total observations) who had received primary care prescriptions were verified against GP clinical records. Records of 24 participants (51 total observations) who had received hospital-based prescriptions were verified against hospital records. Parental recollection was excellent (80.4-98.0% accurate) for antibiotic name and indication, good (67.5%) for exact duration (only verified from hospital records); 92.3% of parents recalled the duration to within 2 days.

Population-weighted analyses

Prevalence estimates and rate ratios were not substantially altered after inverse probability weighting. For example, the prevalence of having at least one antibiotic during the first postnatal year changed from 50.0% (95% 46.1-53.9%) to 52.3% (95% 52.1-56.9%) after weighting.

Discussion

Infants in this large Australian population-representative study had a high antibiotic prescription rate and cumulative proportion of antibiotic exposure in the first year of life compared to data from other high-income countries.[4, 11] Half of all infants were exposed to at least one antibiotic before 12 months of age and almost half of all antibiotics were prescribed to infants aged 9-12 months. Increasing number of siblings was associated with increased antibiotic exposure. Associations were also observed between antibiotic exposure and paternal unemployment, younger parents, maternal postnatal smoking, not breastfeeding at 4 weeks, and being summer or spring-born. Two-thirds of antibiotics prescribed were broad-spectrum penicillins and cephalosporins. Viral respiratory tract infections were the stated indication for a fifth of prescriptions. The high rate of antibiotic exposure is of concern given increasing antimicrobial resistance and the putative association with chronic diseases, including asthma and childhood obesity.[6]

Prescription rate and prevalence

The overall infant antibiotic prescription rate is higher than almost all other high-income countries, apart from Italy (Table 4).[11] Indeed the rate is almost one-and-a-half times higher than the UK,[4] and almost five times higher than Switzerland.[11] The annual cumulative exposure is also markedly higher than other high-income countries (Table 4).[11]

Antibiotic prescription rates peaked at 0-1 and 9-12 months of age. The former largely represents hospital-based postnatal antibiotics given empirically for possible neonatal sepsis. The 9-12 month peak was predominantly due to general practitioner prescriptions for AOM and URTI, which have high incidence at this age.

Clinical indication and prescriber characteristics

Overall URTI and LRTI were the most common stated indications for antibiotic prescription, followed by sepsis/presumed sepsis. Within these infection groups, AOM was most common, followed by bronchiolitis and URTI. Three-quarters of Australian children with diagnosed AOM receive oral antibiotics.[12] Some guidelines recommend antibiotics as first-line management for AOM in infants <12 months of age, but the evidence base is relatively weak.[13] A Cochrane review suggests that antibiotics are most beneficial in patients under 2 years of age with bilateral AOM, or AOM and otorrhoea.[5] A policy of initial 'observation' (with no antibiotics) is encouraged for the majority.[14] In addition, a substantial proportion of infants diagnosed with AOM may not meet strict diagnostic criteria, particularly an acute onset, the presence of middle ear fluid, and suggestive signs and/or symptoms.[14]

The overall incidence of AOM in Australasia is similar to other high-income countries, indicating a higher infectious burden is unlikely.[15] However, Australian Aboriginal children have among the highest rates of severe AOM complications in the world, including development of chronic suppurative otitis media and tympanic membrane perforation.[12] This may result in Australian doctors prescribing antibiotics at a higher rate for Indigenous children, however a national study in 2007 concluded that management was very similar regardless of indigenous status.[12]

Bronchiolitis and URTI have viral aetiologies and do not warrant antibiotics in the absence of a secondary bacterial infection, which is relatively unusual.[16] The high rate of antibiotic prescription for these conditions suggests that some Australian prescribers may not be following best practice guidelines.

Various factors may contribute to prescribing practice, including parental pressure, which may drive inappropriate prescribing.[16] Recent National Institute for Health and Care Excellence guidelines on antimicrobial stewardship acknowledges these pressures and encourages strategies such as 'watchful waiting' to reduce unwarranted antibiotics.[17] Notably, education campaigns in Australia, for parents and health care professionals, have reduced antibiotic prescriptions for some viral infections, at least in the short term.[3]

Patient and family factors influencing exposure

Increased number of older siblings was associated with higher antibiotic exposure, possibly due to sibling-derived pathogen sharing.[18] No other factors were strongly associated with antibiotic exposure, although some plausible trends were observed. Paternal unemployment was associated with increased antibiotic exposure. Unemployment has previously been associated with increased rates of respiratory tract infections.[19] Socioeconomic status (SES) is negatively associated with childhood infection burden, possibly due to increased exposure to pathogens and greater susceptibility.[20] We adjusted for other SES-related cofounders and the relationship with parental employment remained. Other trends observed were less plausible, such as the association between maternal smoking during pregnancy and reduced antibiotic exposure. In contrast, postnatal maternal smoking corresponded with increased antibiotic exposure. Maternal smoking is associated with increased rates of respiratory tract infection, gastroenteritis and other childhood infections.[20] It is possible that our study was insufficiently powered to detect a concomitant association with antibiotic use. Other SES markers such as maternal education or IRSD score were not associated with antibiotic exposure.

In addition, infants with older fathers received fewer antibiotics. The greater child-rearing experience may result in less parental anxiety and pressure to prescribe antibiotics. There was no association between mode of delivery, infant birthweight, sex, or maternal age and antibiotic exposure.

Breastfeeding for at least 4 weeks was associated with fewer total antibiotic days, in keeping with the protective effects of breastfeeding on early life infection.[21] Infants born in summer and spring had higher antibiotic exposure, reflecting seasonal variation of infections.[22] These infants encounter their first winter season when transplacental antibodies have largely disappeared and breastfeeding may have ceased.

Antibiotic class

Broad-spectrum penicillins were the most commonly prescribed antibiotic. Amoxycillin is currently recommended in Australia as first-line treatment for common childhood bacterial infections, including some AOM, sinusitis and pneumonia.[23] Cephalosporins accounted for 12% of all antibiotics, higher than several other high-income countries (e.g. UK and Denmark), but lower than Italy.[24] Between 1990 and 2003, cephalosporin prescriptions in Australia doubled.[25] This is contrary to current recommendations for common childhood infections that favour penicillins with extended spectrum over cephalosporins.[23] Preferential prescription of broad-spectrum second-line antibiotics is a major concern for the development of antimicrobial resistance.

Strengths

To our knowledge, this is the first population-based study of antibiotic exposure in hospital and primary care settings in Australian infants. Most studies investigate general practitioner, hospital-based prescribing, or parental reporting but rarely data from all three sources, likely underestimating total exposure. Our study used a population-derived cohort[7] and the sensitivity analyses indicated little influence of non-participation at recruitment. Further, two factors used for reweighting, lower maternal age and lower SES, were also related to record incompleteness, thus this was partly accounted for. The findings, which warrant replication, are likely to be relevant to the general Australian infant population. A unique feature was the description of antibiotic exposure by prescription rates per person-year, and number of antibiotic days exposed per person-year, a better estimate of the total exposure as it incorporates duration. We were also able to comment on actual antibiotic consumption rather than prescriptions dispensed, and in a subgroup validate parent reporting against medical records.

Limitations

We excluded parents unable to complete the questionnaires without an interpreter, potentially limiting our ability to accurately investigate the effect of ethnicity on prescription rates. Parent recall was used for antibiotic prescriptions and indications, with inherent limitations, however questionnaires were administered approximately every 2-3 months and parents were encouraged to keep an infant health diary. Verification of general practitioner and hospital prescriptions showed that recall was excellent for antibiotic name and indication, and good for duration. Ideally we would have linked to PBS data, but this was beyond the scope of this study. Approximately half the ambiguous/missing data from families could be clarified against medical records. This was in part due to lack of response from general practitioner practices and also inaccurate parental recall of prescriber details. We were therefore unable to investigate prescriber characteristics, a key aspect of understanding antibiotic use and directing stewardship programs.

In summary, antibiotic exposure rates in Australian infants from this large population-based study cohort rank amongst the highest in the world. Cephalosporins are preferentially prescribed and many antibiotics appear to be given for viral childhood infections, indicating that best practice guidelines are likely not being followed. Several potentially modifiable factors associated with higher rates of antibiotic exposure were identified. Reducing antibiotic exposures in early life is key to reduce antimicrobial resistance and may have beneficial effects on non-communicable diseases.

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Figures

Figure 1. Flow chart of infants in the longitudinal antibiotic project

Figure 2. Antibiotic prescriptions by antibiotic class

Broad-spectrum penicillins include: J01CA – Penicillins with extended spectrum (Amoxicillin, Ampicillin), J01CR – Combinations of penicillins, incl. beta-lactamase inhibitors (Amoxicillin/Clavulanate)
Cephalosporins include: J01DB – First generation cephalosporins (Cefalexin), J01DD – Third generation cephalosporins (Cefotaxime, Ceftriaxone), J01DC – Second generation cephalosporins (Cefaclor, Cefuroxime)
Narrow-spectrum penicillins include: J01CE – Beta-lactamase sensitive penicillins (Benzylpenicillin, Phenoxymethylpenicillin), J01CF – Beta-lactamase resistant penicillins (Flucloxacillin)
Aminoglycosides include: J01GB – Other aminoglycosides (Gentamicin)
Macrolides include: J01FA – Macrolides (Erythromycin, Azithromycin, Clarithromycin, Roxithromycin)
Other: Trimethoprim/Sulfamethoxazole, Metronidazole, Trimethoprim, Ciprofloxacin, Isoniazid

Figure 3. Clinical indications for antibiotic prescription

Figure 3A. General indications†

Figure 3B. Respiratory indications†

Footnote to Figure 3:
Non-specific CI = Non-specific chest infection - likely represents bronchiolitis/URTI only (36.7%), lower respiratory tract infection (46.7%), and AOM (16.7%)
URTI = Upper respiratory tract infection – includes diagnoses reported as: URTI, cold, tonsillitis, laryngitis, tracheitis, AOM, respiratory tract infections with wheeze, and/or chest examination findings, and/or symptoms including rhinorrhoea, nasal congestion and red throat.
LRTI = Lower respiratory tract infection – includes diagnoses reported as: pneumonia, bronchiolitis, whooping cough and respiratory tract infections with wheeze, cough, or specific chest examination findings.
Resp. infection other = Respiratory infection other – cough and/or non-specific signs of respiratory distress without other signs of a LRTI.
UTI = Urinary tract infection
NOS = Not otherwise specified
†clinical categories derived from ICPC-2

What is already known on this topic:

1. Antimicrobial resistance is rising rapidly, in Australia and globally. A major driver is profligate antibiotic use.
2. Australia has one of the highest antibiotic exposures worldwide and prescription rates have increased by 230% in the last decade.
3. Children have the highest antibiotic exposures globally, yet there are very few studies of antibiotic exposure in Australian children.

What this paper adds:

1. Australian infants in this large population-based study are exposed to considerably more antibiotics than the majority of their international counterparts.
2. A significant proportion of antibiotics are prescribed for viral infections suggesting many antibiotics may be given inappropriately. Interventions aimed at addressing avoidable prescribing by medical practitioners may reduce antibiotic use.