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TITLE PAGE

Factors predicting amoxicillin prescribing in primary care among children: a cohort study

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ABSTRACT

Background: Antibiotic prescribing during childhood contributes to antimicrobial resistance, which is a major public health concern. Antibiotics are most commonly prescribed to children for respiratory tract infections (RTI).

Aim: To identify factors associated with amoxicillin prescribing and RTI consultation attendance in primary care in young children.

Design and Setting: Cohort study in Bradford with data from pregnancy to age 24-months collected between 2007-2013, linked to electronic primary care and air pollution data.

Methods: We calculated amoxicillin prescribing rates/1,000 child-years, and fitted mixed-effects logistic regression models, with general practice (GP) surgery as the random effect, to establish risk factors for amoxicillin prescribing and RTI consultation during the first two years.

Results: Among 2,493 children, the amoxicillin prescribing rate was 710/1,000 child-years during the first year (95% CI: 677-744) and 780/1,000 (745-816) during the second year. Odds of amoxicillin prescribing during year one were higher for infants who were male (adjusted OR 1.4 (1.1-1.6)), socio-economically deprived (1.4 (1.0-1.9)), and with a Pakistani ethnic background (1.4 (1.1-1.9)). Odds of amoxicillin prescribing during the second year were higher for infants with a Pakistani ethnic background (1.5 (1.1-2.0)/1.6 (1.2-2.0)) and pre-/early-term infants (1.2 (1.0-1.5)). Additional risk factors included caesarean delivery, congenital anomalies, household overcrowding, birth season, and formal childcare attendance. GP surgery-level variation explained 7-9% of variation in amoxicillin prescribing.

Conclusions: Socio-economic status and ethnic background are strongly associated with amoxicillin prescribing and RTI consultations during childhood. Interventions reducing RTI spread in household and childcare settings may reduce antibiotic prescribing in primary care.

KEYWORDS

Respiratory tract infections; Drug Resistance, Bacterial; Anti-Bacterial Agents; Drug prescriptions; Medical record linkage; Paediatrics

HOW THIS FITS IN

Prescribing of antibiotics during childhood contributes to antimicrobial resistance, which is a major public health concern. This study links rich cohort data to routinely collected primary care data to identify ethnic and socio-economic inequalities in childhood respiratory infections and amoxicillin prescribing. Our study highlights that population-level interventions, including reducing household overcrowding and supporting hygiene measures in childcare settings, are required to reduce the need for antibiotic prescribing in young children, thereby supporting antimicrobial stewardship efforts in primary care.

INTRODUCTION

Antimicrobial resistance is a public health emergency, to which prescribing of antibiotics contributes.[1] In the UK, most antibiotics are prescribed in primary care.[2,3] Several studies have found that patient-level factors, including gender, influenza vaccination status, obesity, smoking, previous antibiotic receipt and comorbidities, increase antibiotic prescribing among adults.[4,5] Prescribing rates also vary geographically according to area-level deprivation and the proportion of patients with comorbidities.[6,7]

Few studies have examined antibiotic use among children, despite one-third of children under five being prescribed at least one antibiotic annually.[3] Childhood antibiotic prescribing in the UK peaks between ages one and four years, and three-quarters of antibiotics prescribed to children in primary care are for respiratory tract infections (RTIs).[8,9] Furthermore, antibiotic prescribing in childhood is linked with adverse health outcomes in later childhood, including asthma and obesity.[10,11]

The severity of presenting illness determines the likelihood of being prescribed an antibiotic for common childhood infections.[9] Therefore, we expect antibiotic prescribing rates among children to differ according to the factors that increase the risk of contracting common infections, including overcrowding and having older siblings,[12,13] and factors that reduce the immune system's ability to fight infections if exposed, such as prematurity, exposure to air pollution, and lack of breastfeeding.[14-16] Furthermore, qualitative studies suggest parent-clinician communication may impact childhood antibiotic prescribing.[17] However, few studies have examined risk factors for antibiotic prescribing among children.

We aimed to establish child, family, and environmental factors that were associated with prescribing of amoxicillin to children aged less than two years, to inform antimicrobial

stewardship efforts among children. In order to examine the importance of individual and primary care level factors, we determined what proportion of total variation in amoxicillin prescribing is due to general practice (GP) surgery-level variation. We focused on amoxicillin because it is the most commonly prescribed antibiotic in UK primary care.[8,9] As amoxicillin is most commonly prescribed for RTI, we also examined the risk factors associated with primary care consultation rates for RTI.

METHODS

Data sources

We used data from the Allergy and Infection (ALL-IN) sub-study of the Born in Bradford (BiB) cohort. ALL-IN and BiB have been described in detail elsewhere.[18,19] Briefly, pregnant women attending the Bradford Royal Infirmary (BRI) for an oral glucose tolerance test (offered to all women booked for delivery at the BRI at 26-28 weeks of pregnancy) between March 2007-November 2010 were invited to participate in BiB. Parents completed baseline questionnaires, and details about the birth were extracted from hospital electronic maternity records. Details of congenital anomalies were obtained from a local register linked to the cohort.[20] Linkage to routinely collected electronic primary care data facilitated follow-up.[18]

Children born from March 2008 whose parents had completed the BiB baseline questionnaires were invited to participate in the ALL-IN sub-cohort when aged 11 months.[19] Families who agreed to participate in ALL-IN completed questionnaires at ages 12 and 24 months, completed February 2009-September 2013.

We used openly available data on annual average levels of fine particulate matter ($PM_{2.5}$) modelled at a 1x1 km grid across the UK using atmospheric transport models, from the

Department for Environment, Food and Rural Affairs (DEFRA). $PM_{2.5}$ levels were mapped to lower super output areas (LSOA, a small geographical area with an average population of 1,500 people) and linked to the cohort via the LSOA of the infant's home address.[21,22]

Outcome variables

Our primary outcome was the receipt of at least one amoxicillin prescription in primary care during the first and second year of life (Supplementary Table 1). Our secondary outcomes were at least one primary care consultation for upper respiratory tract infections (URTI) or lower respiratory tract infections (LRTI). Diagnostic information from electronic primary care records were recorded using Read codes version 3 (CTV3; Supplementary Table 2).[24-26]

Exposure variables

Table 1 summarises the source and characteristics of all outcome and exposure variables. Gestational age was coded as a binary variable for being born pre-/early-term (<39 weeks) or term (≥39 weeks). We initially used 37 weeks to define a variable for pre-term/term, however the number of infants born <37 weeks was low (n=36, 4.5%). The five-category variable defining socio-economic status had previously been derived from the BiB baseline questionnaire.[27] Information on whether the child had spent any time in formal childcare (e.g. with a nursery or childminder), or lived in a household with ≥6 people or with visible mould or damp, was collected via parental questionnaires.

We mapped the 1x1 km annual ambient $PM_{2.5}$ levels to the LSOA of the child's residence at birth and age one year. $PM_{2.5}$ exposure during pregnancy was calculated using the average $PM_{2.5}$ level in the calendar year(s) covering the gestation period, weighted by the number of days' gestation during each calendar year. $PM_{2.5}$ exposure during the first year of life was also

weighted by the number of days spanning each calendar year. We calculated annual quartiles of average $PM_{2.5}$ levels across the Bradford postcode area and derived two variables to indicate weighted $PM_{2.5}$ exposures at the child's LSOA, relative to the distribution of $PM_{2.5}$ exposures in the Bradford area, throughout gestation and the first year of life. As few children lived in lower pollution areas, we created a three-category variable to indicate $PM_{2.5}$ exposure during pregnancy and the first year of life: first/second quartile, third quartile, and fourth quartile of BD postcode area levels. Summary statistics for the absolute levels of $PM_{2.5}$ exposure corresponding to each group are displayed in the headings of Tables 2-3.

Statistical analyses

We calculated amoxicillin prescribing rates, and rates of consultations for URTI and LRTI per 1,000 child-years for the first and second years of life, overall and according to each exposure variable of interest. 95% confidence intervals (CI) were calculated to compare rates across exposures. We fitted crude and mutually adjusted mixed-effects logistic regression models ('`xtlogit`' function in Stata) to determine factors associated with receiving at least one amoxicillin prescription in the first and second years of life. GP surgery was included as the random intercept to determine surgery- and child-level variation in prescribing. For the small number of children who changed GP surgery during the year, we assigned them to the surgery they were registered for longer.

Based on a priori knowledge, all mutually adjusted models included ethnic background, socio-economic status, and sex as core confounders. Due to the exploratory nature of this study, additional exposure variables were selected for inclusion if they improved model fit, determined using likelihood ratio (LR)-tests (p-value <0.05). LR-tests were conducted until no further variables improved model fit. Variables were dropped from the final model if they no

longer improved fit in the fully adjusted model. Model fitting and selection procedures were repeated for having at least one URTI or LRTI consultation during the first and second years of life.

491 participants did not attend the ALL-IN 24-month follow-up; we therefore used multiple imputation using chained equations to impute data for the 24-month follow-up (MICE; '`mi`' function in Stata; 30 imputed datasets).[28] The MICE model included all variables in the substantive model (including outcome variables), variables from the 12-month questionnaires, additional variables predictive of missingness, and GP surgery. To avoid perfect prediction, in which categorical outcomes are predicted almost perfectly resulting in instability during estimation, we combined all GP surgeries with <10 participants into one group (2.7% of participants). Models for the second year of life were undertaken with and without MICE as a sensitivity analysis.

All analyses were undertaken in Stata version 16.1 (Stata Corp., College Station, TX).

RESULTS

The cohort included 2,493 singleton children. 2,002 (80%) attended the 24-month follow-up (Supplementary Figure 1). 49% of all mothers had a Pakistani ethnic background and 38% were from the two most deprived socio-economic groups (Table 2).

Amoxicillin prescribing

1,594 children (64%) received one or more amoxicillin prescriptions during the first two years of life; 43% during the first year and 47% during the second year. Prescribing rates were 710 (95% CI 677-744) per 1,000 child-years during their first year of life, and 780 (95% CI 745-816) during the second year (Table 2).

Table 3 displays the best-fitting model for amoxicillin prescribing during the first and second years of life. Compared with children of White British mothers, the odds of receiving at least one amoxicillin prescription during the first year of life were higher for children with mothers with a Pakistani ethnic background, regardless of their country of birth (adjusted odds ratio (aOR) 1.4 (95% CI 1.1-1.9)), and lower for those with 'other' ethnic backrounds (aOR 0.7 (95% CI 0.5-1.0)). Infants from the most deprived households had higher odds of being prescribed amoxicillin (aOR 1.4 (95% CI 1.0-1.9)) compared with the least deprived. Odds were also higher for infants who were male, had at least one congenital anomaly, born in April-June (compared with January-March), born via caesarean section, living in a household with ≥6 people, and attending formal childcare. Based on the intraclass correlation coefficient (ICC), GP surgery-level variation explained 9% (95% CI 6-15%) of the residual variation in amoxicillin prescribing during year one.

The odds of receiving at least one amoxicillin prescription during the second year of life were higher for children with mothers with a Pakistani ethnic background (regardless of whether mothers were born within (aOR 1.5 (95% CI 1.1-1.9) or outside of (aOR 1.6 (95% CI 1.2-2.0)) the UK) compared with children with White British mothers. Children born pre-/early-term, and those attending formal childcare also had higher odds of amoxicillin prescribing (aOR 1.2 (95% CI 1.0-1.5) and 1.5 (95% CI 1.1-1.9), respectively). GP surgery-level variation explained 7% (95% CI 4-11%) of the residual variation in amoxicillin prescribing during year two.

No significant associations were observed between amoxicillin prescribing and maternal smoking during pregnancy, breastfeeding duration, nor exposure to environmental $PM_{2.5}$, household mould or damp, or household gas cooking during either year. Model results based on complete cases were comparable (Supplementary Table 4).

GP consultations for RTIs

Rates of URTI consultations were 309 (95% CI 287-332) per 1,000 child-years during the first year of life and 263 (95% CI 243-284) during the second year. Rates of LRTI consultations were 458 (95% CI 432-486) per 1,000 child-years during the first year and 409 (95% CI 384-435) during the second year (Supplementary Table 5).

We found associations between the odds of having at least one URTI GP consultation and ethnic background and breastfeeding duration during years one and two (Supplementary Table 6). 13% (95% CI 8-20%) of the residual variation in URTI consultations was explained by GP surgery-level variation during year one, and 14% (95% CI 9-22%) during year two. For LRTI, significant associations were found between GP consultation attendance and sex, ethnicity, and socio-economic status during year one, and ethnicity, socio-economic status, congenital anomalies, delivery mode, and childcare attendance during year two (Supplementary Table 7). 11% of the residual variation in LRTI consultations (95% CI 7-18%) during year one, and 15% (95% CI 9-23%) during year two, was explained by GP surgery-level variation. No significant associations were observed between RTI consultations and maternal smoking, season of birth, gestational age at delivery, household overcrowding, nor exposure to ambient air pollution, household mould or damp, or household gas cooking.

DISCUSSION

Summary

43% of children were prescribed amoxicillin at least once during their first year of life and 47% during their second year. Having a mother with a Pakistani ethnic background, irrespective of their country of birth, was associated with amoxicillin prescribing across both years. Socio-

economic status, birth characteristics, childcare attendance, and household overcrowding were significantly associated with amoxicillin prescribing during the first year only, while prematurity was significantly associated with amoxicillin prescribing during the second year only. Less than 10% of the total variance was attributed to GP surgery-level variation in amoxicillin prescribing.

Ethnic background and childcare attendance were significantly associated with having at least one primary care consultation for URTI and LRTI. Breastfeeding status was associated with URTI consultation attendance only, while socio-economic status, congenital anomalies, and delivery mode were associated with LRTI consultation attendance only. 11-15% of the variation in the probability of attending at least one RTI consultation was attributed to GP surgery-level variation.

Strengths and limitations

A strength of our study is the comprehensive analysis of risk factors for amoxicillin prescribing, enabled by linking rich, longitudinal questionnaire data to routinely collected maternity and primary care records, and air pollution data. The ethnic diversity of the BiB cohort makes it particularly well-suited to study ethnic differences in child health outcomes.

However, the data include children growing up in Bradford, and a limitation is therefore that this may not be representative of all children in England. Additionally, some environmental exposures were collected by parental report and may be subject to recall bias. Third, we did not examine the indications for antibiotic prescribing, as these are inconsistently recorded in primary care.[29] Further, we focused on prescribing in primary care, excluding prescribing for more severe indications in hospitals.[2] Lastly, the prescribing data were collected between 2008-2013, before the development of the UK 5 year antimicrobial resistance strategy to

reduce the overprescribing of antibiotics.[30] Despite these limitations, our data are well suited to provide new insights on amoxicillin prescribing patterns among children in England.

Comparison with existing literature

Rates of amoxicillin prescribing in our study are considerably higher than previous estimates, which may reflect the characteristics of the BiB cohort (Supplementary Table 8).[3,6] Our findings of an increased likelihood of amoxicillin prescribing for more deprived children and children with mothers with a Pakistani ethnic background mirror findings in adults.[4,5,19] Ethnic differences in prescribing may reflect differences in the severity of presenting illness, which is a key determinant for antibiotic prescribing, or differences in population mixing, parental expectation, or clinician response.[31]

We observed an increased odds of amoxicillin prescribing during the first year of life for the most deprived children. Significant socio-economic differences were also observed in GP consultation attendance for LRTI, but not URTI, suggesting infection severity differs by socio-economic background. The socio-economic disparity may be more significant than our results suggest, as poorer BiB mothers are less likely to consult primary care once health status is taken into account.[32] We found that socio-economic differences were more profound for LRTI consultation compared with amoxicillin prescribing, which may indicate that antibiotic prescribing guidelines reduce socio-economic differences in prescribing, but not incidence of infection.[33,34]

Primary care physicians play a vital role in reducing antibiotic prescribing. We identified a modest but significant variation in amoxicillin prescribing between practices (7-9%). This is smaller than previous estimates, which range from 32-65%.[6,35,36] However, previous studies have included data from across England, whereas the GP surgeries in this study all reside within

the Bradford District and Craven clinical commissioning group. Residual variation in antibiotic prescribing may reflect differences in provider services and prescribing practices, or differences in health need. Our secondary analysis found higher variation in consultation attendance for RTI between GP surgeries, hinting that surgery-level variation in prescribing may be driven by differences in health need or individual access to services, rather than the GP surgery's prescribing practices. While previous studies suggest that targeting physician behaviour can reduce antibiotic prescribing,[37] our findings highlight the importance of interventions at the population level. Further research considering detailed individual-level characteristics and indicators of infection risk (including overcrowding and childcare attendance), would determine where population-level antimicrobial stewardship efforts are best targeted.

Surprisingly, we did not observe associations between maternal smoking or outdoor air pollution and RTI consultation attendance or amoxicillin prescribing. Regarding maternal smoking, this may be unique to the Bradford population due to the disparity between smoking habits observed between mothers of White British and Pakistani ethnic background. Furthermore, self-report of maternal smoking may not represent true behaviours; research has shown that mothers from less deprived areas are less likely to report their smoking during pregnancy.[38] $PM_{2.5}$ has previously been found to increase the risk of URTI and LRTI.[39,40] However, given that small effect sizes are expected, larger studies over broader geographical areas with greater variation in $PM_{2.5}$ exposure are required to address its role in RTI and antibiotic prescribing.[41] Linking datasets on environmental exposures to newly available national primary care dispensing data could aid in these studies.[42]

Implications for practice

Our findings highlight the need for policies addressing the population-level inequalities associated with RTIs when addressing antimicrobial stewardship efforts among children, particularly ethnic background and socioeconomic status. Primary Care Networks (PCNs), through which primary care practices link with other health and social care providers, provide an opportunity for GPs to promote hand-washing and improved ventilation in homes (particularly those which are overcrowded) and childcare settings to prevent the spread of infection. Partnerships with pharmacies and voluntary sector organisations, for example, could help facilitate these efforts. Furthermore, we found that children who were breastfed for less than one month were more likely to attend consultations for URTIs. There are useful published resources to aid GPs when providing breastfeeding support, including those published by the UK GP Infant Feeding Network.[43,44] PCNs could also play a role in linking primary care to local breastfeeding support groups. Larger, national studies investigating the effect of environmental exposures on childhood respiratory health and antibiotic prescribing are recommended.

List of abbreviations

ALL-IN	Allergy and Infection

aOR	Adjusted odds ratio
BD	Bradford postcode area
BiB	Born in Bradford
CI	Confidence interval
DEFRA	Department for Environment, Food and Rural Affairs
ICC	Intraclass correlation coefficient
LRTI	Lower respiratory tract infection
LSOA	Lower super output area
MICE	Multiple imputation using chained equations
NHS	National Health Service
GP	General practice
PM25	Particulate matter 2.5
RTI	Respiratory tract infection
URTI	Upper respiratory infection

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Ethical approval

Parents in BIB and ALL-IN gave informed consent for use of cohort data and electronic records for research studies. The ALL-IN study has been approved by the Bradford Research Ethics Committee, reference number 08/H1302/21.

Competing interests

The authors state no competing interests.

Availability of data

The data that support the findings of this study are available from several different sources, some of which are openly available, others which are available only upon request. Restrictions apply to the availability of data from the Born in Bradford and Allergy and infection cohorts, which are not publicly available and were used under license for the current study. Data are

however available from the authors upon reasonable request and with permission of Born in Bradford. PM2.5 data are freely available at https://uk-air.defra.gov.uk/data/pcm-data.

REFERENCES

1. World Health Organisation. Global Action Plan on Antimicrobial Resistance 2015. [Internet]. 2016 [Accessed 2021 Jun 1]. Available from: https://www.who.int/publications/i/item/9789241509763
2. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. [Internet]. 2013 [Accessed 2021 Jul 16]. Available from: https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018
3. Sun X, Gulliford MC. Reducing antibiotic prescribing in primary care in England from 2014 to 2017: population-based cohort study. BMJ Open. 2019;9(7):e023989.
4. Palin V, Molter A, Belmonte M, et al. Antibiotic prescribing for common infections in UK general practice: variability and drivers. J Antimicrob Chemother. 2019;74(8):2440-50.
5. Shallcross L, Beckley N, Rait G, Hayward A, Petersen I. Antibiotic prescribing frequency amongst patients in primary care: a cohort study using electronic health records. J Antimicrob Chemother. 2017;72(6):1818-24.
6. Pouwels KB, Dolk FCK, Smith DRM, Smieszek T, Robotham JV. Explaining variation in antibiotic prescribing between general practices in the UK. J Antimicrob Chemother. 2018;73(suppl_2):ii27-ii35.

7. Molter A, Belmonte M, Palin V, et al. Antibiotic prescribing patterns in general medical practices in England: Does area matter? Health Place. 2018;53:10-6.
8. Schneider-Lindner V, Quach C, Hanley JA, Suissa S. Secular trends of antibacterial prescribing in UK paediatric primary care. J Antimicrob Chemother.. 2010;66(2):424-33.
9. O'Brien K, Bellis TW, Kelson M, et al. Clinical predictors of antibiotic prescribing for acutely ill children in primary care: an observational study. Br J Gen Pract. 2015;65(638):e585-92.
10. Souza da Cunha S, Santorelli G, Pearce N, et al. Evidence for causal associations between prenatal and postnatal antibiotic exposure and asthma in children, England. Clin Exp Allergy. 2021;51(11):1438-1448.
11. Bailey LC, Forrest CB, Zhang P, et al. Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr. 2014;168(11):1063-9.
12. Hardelid P, Verfuerden M, McMenamin J, Smyth RL, Gilbert R. The contribution of child, family and health service factors to respiratory syncytial virus (RSV) hospital admissions in the first 3 years of life: birth cohort study in Scotland, 2009 to 2015. Euro Surveill. 2019;24(1).
13. Hardelid P, Verfuerden M, McMenamin J, Gilbert R. Risk factors for admission to hospital with laboratory-confirmed influenza in young children: birth cohort study. Eur Resp J. 2017;50(3).
14. West J, Kelly B, Collings PJ, et al. Is small size at birth associated with early childhood morbidity in white British and Pakistani origin UK children aged 0–3? Findings from the born in Bradford cohort study. BMC Pediatr. 2018;18(1):22.

15. MacIntyre EA, Gehring U, Molter A, et al. Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE Project. Environ. Health Perspect. 2014;122(1):107-13.

16. Di Mario S, Gagliotti C, Donatini A, et al. Formula feeding increases the risk of antibiotic prescriptions in children up to 2 years: results from a cohort study. Eur J Pediatr. 2019;178(12):1867-74.

17. Cabral C, Horwood J, Symonds J, et al. Understanding the influence of parent-clinician communication on antibiotic prescribing for children with respiratory tract infections in primary care: a qualitative observational study using a conversation analysis approach. BMC Fam. Pract. 2019;20(1):102.

18. Wright J, Small N, Raynor P, et al. Cohort Profile: the Born in Bradford multi-ethnic family cohort study. Int. J. Epidemiol. 2013;42(4):978-91.

19. Pembrey L, Waiblinger D, Griffiths P, at al. Cytomegalovirus, Epstein-Barr virus and varicella zoster virus infection in the first two years of life: a cohort study in Bradford, UK. BMC Infect. Dis. 2017;17(1):220.

20. Sheridan E, Wright J, Small N, et al. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. The Lancet. 2013;382(9901):1350-9.

21. Ricardo Energy & Environment. Technical report on UK supplementary assessment under The Air Quality Directive (2008/50/EC), The Air Quality Framework Directive (96/62/EC) and Fourth Daughter Directive (2004/107/EC) for 2014. [Internet]. 2019 [Accessed 2021 March 17]. Available from: https://uk-air.defra.gov.uk/assets/documents/reports/cat09/1903201606_AQ0650_2017_MAAQ_technical_report.pdf

22. Department for Environment FaRA. Modelled background pollution data. [Internet]. 2019 [Accessed 2021 March 1]. Available from: https://uk-air.defra.gov.uk/data/pcm-data

23. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010;60(572):e128-36.

24. Benson T. The history of the Read Codes: the inaugural James Read Memorial Lecture 2011. Inform. Prim. Care. 2011;19(3):173-82.

25. Davé, S and Petersen, I. Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiol. Drug Saf. 2009;18: 704-707.

26. Hardelid P, Rait G, Gilbert R, Petersen I. Recording of Influenza-Like Illness in UK Primary Care 1995-2013: Cohort Study. PLoS One. 2015;10(9):e0138659.

27. Fairley L, Cabieses B, Small N, et al. Using latent class analysis to develop a model of the relationship between socio-economic status and ethnicity: cross-sectional analyses from a multi-ethnic birth cohort study. BMC Public Health. 2014;14(1):835.

28. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J. Stat. Softw. 2011; 45(1): 1–67.

29. Thompson PL, Spyridis N, Sharland M, et al. Changes in clinical indications for community antibiotic prescribing for children in the UK from 1996 to 2006: will the new NICE prescribing guidance on upper respiratory tract infections just be ignored? Arch. Dis. Child. 2009;94(5):337-40.

30. Department of Health and the Department for Environment, Food and Rural Affairs. UK five year antimicrobial resistance strategy 2013 to 2018. Department of Health, London. [Internet] 2013. [Accessed June 18 2021]. Available from:

https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018

31. Kelly B. Ethnic mixing in Bradford: Local dynamics of diversity: evidence from the 2011 Census. Manchester: ESRC Centre on Dynamics of Ethnicity (CoDE); 2015.

32. Kelly B, Mason D, Petherick ES, et al. Maternal health inequalities and GP provision: investigating variation in consultation rates for women in the Born in Bradford cohort. J. Public Health. 2017;39(2):e48–e55.

33. Cook R, Davidson P, White A. Clinicians prescribe antibiotics for childhood respiratory tract infection based on assessment, rather than parental expectation. BMJ. 2020;368:l6768.

34. Willems S, De Maesschalck S, Deveugele M, et al. Socio-economic status of the patient and doctor-patient communication: does it make a difference? Patient Educ. Couns. 2005;56(2):139-46.

35. Hawker JI, Smith S, Smith GE, et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. J. Antimicrob. Chemother. 2014;69(12):3423-30.

36. Gulliford MC, Dregan A, Moore MV, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ Open. 2014;4(10):e006245.

37. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database Syst. Rev. 2007;(4):CD000409.

38. Shipton D, Tappin DM, Vadiveloo T, et al. Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. BMJ. 2009;339:b4347.

39. Brauer M, Hoek G, Van Vliet P, et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. Am. J. Respir. Crit. Care Med. 2002;166(8):1092-8.

40. Karr C, Lumley T, Schreuder A, et al. Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am. J. Epidemiol. 2007;165(5):553-60.

41. Wright J, Hayward A, West J, et al. ActEarly: a City Collaboratory approach to early promotion of good health and wellbeing. Wellcome Open Res. 2019;4:156.

42. NHS Digital. Medicines dispensed in Primary Care NHS Business Services Authority data 2021. [Internet]. 2021. [Accessed: 2021 Oct 16] Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/medicines-dispensed-in-primary-care-nhsbsa-data.

43. Marshall J, Ross S, Buchanan P, Gavine A. Providing effective evidence based support for breastfeeding women in primary care BMJ 2021;375:e065927.

44. The GP Infant Feeding Network (UK). Breastfeeding Support. [Internet] 2017. [Accessed March 9 2022]. Available from: https://gpifn.org.uk/breastfeeding-support/

FIGURES

Table 1. Source and characteristics of each variable included in our analysis.

Variable	Source	Type	Coding
Primary outcome			
GP amoxicillin prescribing	*Electronic primary care records*	*Binary*	*≥1 prescription each year: yes/no*
Secondary outcome			
GP consultation for URTI	*Electronic primary care records*	*Binary*	*≥1 consultation each year: yes/no*
GP consultation for LRTI	*Electronic primary care records*	*Binary*	*≥1 consultation each year: yes/no*
Exposure			
Sex of infant	*Maternity records*	*Binary*	*Male* *Female*
Delivery mode	*Maternity records*	*Binary*	*Vaginal* *Caesarean*
Quarter of birth	*Maternity records*	*Categorical*	*January-March* *April-June* *July-September* *October-December*
Gestational age	*Maternity records*	*Binary*	*<39 weeks* *≥39 weeks*
Congenital anomalies	*Congenital anomaly register at Bradford Royal Infirmary*	*Binary*	*0 congenital anomalies* *≥1 congenital anomaly*
Ethnic background	*BiB baseline questionnaire*	*Categorical*	*White British* *Pakistani, UK born* *Pakistan, non-UK born* *Other*
Socio-economic status	*BiB baseline questionnaire*	*Categorical*	*Least deprived and most educated* *Employed not materially deprived* *Employed with no access to money* *On benefits but coping* *Most deprived*
Maternal smoking during pregnancy	*BiB baseline questionnaire*	*Binary*	*Smoked during pregnancy: no/yes*
Breastfeeding duration	*ALL-IN 12m questionnaire*	*Categorical*	*<1 month* *1-6 months* *≥6 months*
Childcare	*ALL-IN 12m and 24m questionnaires*	*Binary*	*Child in formal childcare: no/yes*
Number of people in household	*ALL-IN 12m and 24m questionnaires*	*Binary*	*Child in overcrowded (≥6 people) dwelling: no/yes*
Household mould/damp	*ALL-IN 12m and 24m questionnaires*	*Binary*	*Child in dwelling with visible mould/damp: no/yes*
Gas cooking	*ALL-IN 12m and 24m questionnaires*	*Categorical*	*Gas cooking only* *Gas and electric cooking* *Electric cooking only*
Quartile of $PM_{2.5}$ in relation to Bradford level	*Department for Environment linked with LSOA from BiB baseline questionnaire and ALL-IN 12m questionnaire*	*Categorical*	*1st/2nd quartile* *3rd quartile* *4th quartile*

Table 1 legend: GP, general practice; URTI, upper respiratory infection; LRTI, lower respiratory tract infection; PM2.5, particulate matter 2.5; BiB, born in Bradford; ALL-IN, allergy and infection; LSOA, lower super output area

Table 2. Summary of cohort characteristics, and amoxicillin prescribing rates

Baseline characteristics	Total cohort *n* = 2,493	Amoxicillin prescribing rate/1,000 child-years *Rate (95% CI)* Year 1	Year 2
Total		*710 (677-744)*	*780 (745-816)*
Sex of infant			
Male	51%	*776 (728-827)*	*823 (774-875)*
Female	49%	*642 (597-689)*	*735 (688-786)*
Missing	0%		
Mother's ethnic background			
White British	37%	*529 (483-579)*	*638 (587-692)*
Pakistani, UK born	18%	*845 (760-936)*	*900 (813-994)*
Pakistani, not UK born	31%	*969 (901-1042)*	*935 (868-1006)*
Other	14%	*436 (369-512)*	*659 (576-751)*
Missing	0%		
Socio-economic status			
Least deprived and most educated	20%	*608 (541-680)*	*704 (632-782)*
Employed not materially deprived	18%	*505 (440-576)*	*711 (632-795)*
Employed no access to money	18%	*641 (568-720)*	*786 (705-874)*
Benefits but coping	29%	*872 (805-944)*	*881 (813-953)*
Most deprived	15%	*856 (763-956)*	*776 (688-872)*
Missing	0%		
Mother smoking during pregnancy			
No	86%	*724 (688-761)*	*796 (758-835)*
Yes	14%	*617 (536-706)*	*682 (596-777)*
Missing	0%		
Congenital anomalies			
No	97%	*702 (669-737)*	*763 (728-799)*
Yes	3%	*940 (743-1173)*	*1270 (1039-1537)*
Missing	0%		
Gestational age			
Term/late term	72%	*703 (665-744)*	*749 (710-791)*
Early/pre term	28%	*729 (666-796)*	*862 (793-935)*
Missing	0%		
Quarter of birth			
Jan-Mar	26%	*696 (632-764)*	*731 (665-801)*
Apr-Jun	24%	*833 (761-910)*	*775 (706-850)*
Jul-Sep	24%	*694 (629-765)*	*805 (735-880)*
Oct-Dec	26%	*624 (565-690)*	*810 (741-883)*
Missing	0%		
Delivery mode			
Vaginal	79%	*693 (656-731)*	*768 (729-808)*
Caesarean	21%	*778 (703-859)*	*829 (751-912)*

Missing		0%		
Breastfeeding duration				
Less than 1 month	44%		*774 (723-829)*	*841 (787-898)*
1 to 6 months	24%		*706 (639-777)*	*765 (696-839)*
6 months & above	32%		*622 (567-680)*	*714 (656-776)*
Missing		0%		
Characteristics collected at 12m and 24m	**Year 1** *n* = 2,493		**Year 2** *n* = 2,002	
Quartile of $PM_{2.5}$ in relation to Bradford level*				
1st/2nd quartile of $PM_{2.5}$ (10.0 (9.1-10.5))	36%		33%	*623 (573-678)* *802 (742-865)*
3rd quartile of $PM_{2.5}$ (11.2 (11.1-11.4))	44%		43%	*769(718-822)* *784 (731-840)*
4th quartile of $PM_{2.5}$ (12.1 (11.9-12.6))	20%		24%	*738 (662-821)* *750 (681-824)*
Missing		0%	0%	
Formal childcare attendance				
No	82%		78%	*746 (708-784)* *793 (748-839)*
Yes	18%		22%	*553 (485-627)* *852 (766-945)*
Missing		0%	22%	
Household mould/damp				
No mould or damp	77%		79%	*702 (665-741)* *808 (764-854)*
Mould or damp	23%		21%	*746 (676-822)* *803 (720-893)*
Missing		1%	20%	
Number of people in household				
2-5 people	69%		69%	*593 (557-631)* *705 (666-747)*
6 or more people	31%		31%	*977 (908-1050)* *948 (880-1020)*
Missing		0%	20%	
Cooking type				
Electric cooking only	13%		11%	*560 (480-651)* *635 (534-750)*
Electric and gas cooking	19%		18%	*569 (502-643)* *699 (614-791)*
Gas cooking only	69%		71%	*777 (735-821)* *862 (814-912)*
Missing		0%	20%	

Table 2 legend: Amoxicillin prescribing rates per 1,000 child-years during the first two years of life for the total cohort, and summarised according to exposure categories.

* $PM_{2.5}$ exposure for year 1 represents exposure in-utero and year 2 represents exposure during the first year. The median and interquartile range (IQR) for the absolute $PM_{2.5}$ levels corresponding to each quartile are displayed in the heading (median(IQR)), displayed in µg/m3.

CI, confidence interval; 12m, 12 months; 24m, 24 months; $PM_{2.5}$, particulate matter 2.5

Table 3. Associations between exposures and amoxicillin prescribing during the first two years of life

	OR for amoxicillin prescribing OR(95% confidence interval)			
	Year 1		Year 2*	
Total	**Crude**	**Mutually adjusted: n=2,450**	**Crude**	**Mutually adjusted: n=2,476**
Rate of amoxicillin prescribing/1,000 child-years	*710.1 (677.2-744.3)*		*780.1 (745.4-815.9)*	
Sex of infant				
Male	*1.33 (1.13-1.58)*	*1.36 (1.14-1.61)*	*1.13 (0.96-1.33)*	*1.14 (0.96-1.34)*
Female	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Mother's ethnic background				
White British	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Pakistani, UK born	*1.44 (1.09-1.89)*	*1.44 (1.06-1.94)*	*1.36 (1.04-1.77)*	*1.46 (1.10-1.94)*
Pakistani, not UK born	*1.48 (1.16-1.91)*	*1.42 (1.07-1.90)*	*1.40 (1.10-1.77)*	*1.56 (1.19-2.04)*
Other	*0.68 (0.51-0.90)*	*0.70 (0.52-0.96)*	*0.88 (0.67-1.15)*	*0.98 (0.74-1.31)*
Socio-economic status				
Least deprived and most educated	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Employed not materially deprived	*0.82 (0.62-1.09)*	*0.79 (0.59-1.06)*	*1.15 (0.88-1.50)*	*1.13 (0.85-1.50)*
Employed no access to money	*0.95 (0.72-1.25)*	*0.92 (0.69-1.22)*	*1.14 (0.88-1.50)*	*1.11 (0.85-1.46)*
Benefits but coping	*1.13 (0.88-1.45)*	*0.92 (0.70-1.21)*	*1.38 (1.08-1.76)*	*1.26 (0.97-1.64)*
Most deprived	*1.41 (1.06-1.87)*	*1.36 (1.00-1.86)*	*1.28 (0.96-1.69)*	*1.26 (0.93-1.70)*
Mother smoking during pregnancy				
No	*1.00 (ref)*		*1.00 (ref)*	
Yes	*1.02 (0.80-1.32)*		*1.00 (0.78-1.27)*	
Congenital anomalies			*0.86 (0.74-1.00)*	
No	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Yes	*1.78 (1.12-2.83)*	*1.63 (1.01-2.63)*	*1.78 (1.11-2.83)*	*1.57 (0.98-2.51)*
Gestational age				
Term/late term	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Early/pre term	*0.99 (0.82-1.20)*	*0.97 (0.80-1.18)*	*1.22 (1.01-1.46)*	*1.20 (1.00-1.45)*
Quarter of birth				
Jan-Mar	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	
Apr-Jun	*1.26 (0.99-1.60)*	*1.33 (1.04-1.69)*	*1.13 (0.89-1.42)*	
Jul-Sep	*0.99 (0.78-1.26)*	*0.99 (0.77-1.26)*	*1.20 (0.95-1.51)*	
Oct-Dec	*0.94 (0.74-1.18)*	*0.91 (0.71-1.15)*	*1.27 (1.01-1.59)*	
Delivery mode				
Vaginal	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Caesarean	*1.21 (0.99-1.49)*	*1.23 (1.00-1.53)*	*1.10 (0.90-1.35)*	*1.08 (0.88-1.32)*
Breastfeeding duration				
Less than 1 month	*1.29 (1.05-1.57)*	*1.21 (0.97-1.50)*	*1.29 (1.07-1.57)*	*1.22 (0.99-1.50)*
1 to 6 months	*1.17 (0.93-1.47)*	*1.11 (0.87-1.41)*	*1.06 (0.85-1.33)*	*0.98 (0.78-1.24)*
6 months & above	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Quartile of PM2.5 in relation to Bradford level [+]				

1st/2nd quartile of $PM_{2.5}$ (10.0 (9.1-10.5))	*1.00 (ref)*		*1.00 (ref)*	*1.00 (ref)*
3rd quartile of $PM_{2.5}$ (11.2 (11.1-11.4))	*1.11 (0.91-1.37)*		*0.99 (0.81-1.23)*	*0.94 (0.76-1.16)*
4th quartile of $PM_{2.5}$ (12.1 (11.9-12.6))	*1.03 (0.78-1.36)*		*1.03 (0.80-1.32)*	*0.97 (0.75-1.26)*
Formal childcare				
No	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Yes	*0.99 (0.79-1.25)*	*1.29 (1.00-1.66)*	*1.22 (0.97-1.53)*	*1.45 (1.12-1.87)*
Household mould/damp				
No mould or damp	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	
Mould or damp	*1.01 (0.82-1.23)*	*0.98 (0.80-1.21)*	*0.98 (0.79-1.21)*	
Number of people in household				
2-5 people	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	
6 or more people	*1.54 (1.27-1.86)*	*1.41 (1.14-1.74)*	*1.23 (1.02-1.49)*	
Cooking type				
Electric cooking only	*1.00 (ref)*		*1.00 (ref)*	
Electric and gas cooking	*1.14 (0.84-1.56)*		*1.18 (0.84-1.66)*	
Gas cooking only	*1.17 (0.90-1.54)*		*1.40 (1.05-1.86)*	
Intra-GP surgery correlation coefficient		*0.09 (0.06-0.15)*		*0.07 (0.04-0.11)*

Table 3 legend: Crude and mutually adjusted models for amoxicillin prescribing during the first and second years of life. All models included GP surgery as the mixed-effect.

Mutually adjusted models were adjusted for the mother's ethnic background, socio-economic status, and infant sex *a priori*, as well as:

1. First year of life: congenital anomalies, gestational age, quarter of birth, delivery mode, breastfeeding duration, formal childcare attendance, household mould or damp, and household overcrowding.
2. Second year of life: congenital anomalies, gestational age, delivery mode, breastfeeding duration, PM2.5 exposure, and formal childcare attendance.

OR are presented as OR (95% confidence interval). [+]The median and interquartile range (IQR) for the absolute PM2.5 levels corresponding to each quartile are displayed in the heading (median(IQR)), displayed in µg/m3. *Models for year 2 include variables imputed using multivariate imputation.

OR, odds ratio; GP, general practice; PM2.5, particulate matter 2.5