**Association between antibiotic exposure and “response failure” for subsequent respiratory tract infections in preschool children: an observational cohort study**

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**Abstract**

**Background**

Childhood antibiotic exposure has important clinically-relevant implications. These include disruption to the microbiome, antibiotic resistance and clinical workload manifesting as treatment “failure”.

**Aim**

To examine the relationship between the number of antibiotic courses prescribed to preschool children for acute respiratory tract infections (RTI) in the preceding year, and subsequent RTIs that fail to respond to antibiotic treatment (“response failures”)

**Design and setting**

Cohort study using UK primary care data (Clinical Practice Research Datalink, 2009-2016)

**Methods**

Children aged 12-60 months and prescribed an antibiotic for an acute RTI (upper and lower RTI or otitis media) were included. We selected one random index antibiotic course for RTI per child. Exposure was the number of antibiotic prescriptions for acute RTI up to 12 months prior to the index antibiotic prescription. The outcome was “response failure” up to 14 days after index antibiotic prescription, defined as: subsequent antibiotic prescription; referral; hospital admission; death; or emergency department attendance within three days. We used logistic regression models to estimate the odds between antibiotic exposure and “response failure”.

**Results**

From 114,329 children who were prescribed an antibiotic course for acute RTI, children who received two or more antibiotic courses for acute RTIs in the preceding year had greater odds of “response failure” (one antibiotic course: adjusted odds ratio (OR) 1·03 [95% CI 0·88-1·21], p=0.67,n=230 children; two or more antibiotic courses: OR 1·32 [1·04-1·66], p=0.02, n=97).

**Conclusion**

Childhood antibiotic exposure for acute RTI may be a good predictor for subsequent “response failure’’(but not necessarily because of antibiotic treatment failure). Further research is needed to improve our understanding of the mechanisms underlying “response failure”.

**Keywords**

children; antibiotic exposure, primary care; treatment failure

**How this fits in**

Theoretical predictions about the potential consequences of unnecessary antibiotic use and antibiotic resistance can seem abstract and remote to individuals with common infections in the community. Likewise, primary care clinicians report that they rarely encounter treatment failure -remote from their prescribing decisions. Yet we know that unnecessary antibiotic use and resistant infections have worse implications for patients’ illness burden in the community – even for common infections. A subset of the population that is at particular risk of receiving antibiotics unnecessarily is preschool children. Our findings suggest that children receiving more antibiotics for acute respiratory tract infections (RTIs) affects their likelihood of re-consulting a health professional and increases clinical workload. Incorporating antibiotic exposure data into clinical decision-support systems might prompt clinicians to implement strategies to support a non-antibiotic strategy (e.g. informing parents about the anticipated recovery period of common RTIs in children).

**Introduction**

Many antibiotic courses that do not benefit children are being prescribed for self-limiting acute respiratory tract infections (RTIs) in the community.1 At least 30% of antibiotics prescribed in outpatient settings in the USA, and between 9% and 23% in UK primary care are unnecessary.2,3 Children under 5 years old are prescribed proportionally more antibiotics for acute RTIs than any other age group.4-7 Antibiotic prescribing varies by country from around one in six children receiving at least one oral antibiotic prescription per year in the Netherlands 4, to around 57% of all acute RTIs in the USA, where this represents about 11.4 million potentially preventable antibiotic prescriptions annually.5

Many children, though, will have had multiple antibiotic courses within their early childhood.8 Such prescribing medicalises self-limiting RTIs in children and goes against recommendations of antibiotic prescribing guidance.9,10 However, in ambulatory care, unnecessary exposure to antibiotics is likely to have important clinically relevant implications such as treatment “response failure” mostly in the form of re-consultation and receipt of another antibiotic course.11-13 There is also robust evidence for an association between antibiotic use and resistant bacterial carriage.14,15 Antibiotic use may also disrupt the protective gut and lung microbiomes and potentially predispose young children to increased susceptibility to certain bacterial and opportunistic pathogens with adverse health outcomes such as higher rates of RTI 16, and subsequent RTIs which may which may be less responsive to antibiotic treatment.17,18

We therefore examined the relationship between the number of antibiotic courses prescribed to preschool children for acute RTIs in the preceding year, and subsequent RTIs that “fail” to adequately respond to antibiotic treatment (“response failures”).

**Methods**

*Study design*

This observational cohort study used routinely collected primary care data from the Clinical Practice Research Datalink (CPRD) in the United Kingdom. The CPRD ([www.cprd.com](http://www.cprd.com)) is a national database of electronic medical records that contains anonymised longitudinal data from over 670 GP clinics across the United Kingdom.19 The database includes records of all prescriptions issued, clinical diagnoses, referrals to secondary care, hospitalisations, and investigation results during consultations in primary care. Prescriptions are computer generated and are automatically incorporated into the patient medical record. The data have been extensively validated for pharmaco-epidemiological, clinical and health service usage research.20-22

*Study population*

We included children aged 12-60 months inclusive who were prescribed an antibiotic for an acute RTI (upper and lower RTI or otitis media) from January 2009 to September 2016. For the purposes of counting the number of antibiotic courses prescribed for acute RTIs in the preceding year before the start of the study period, data were included from January 2008 to end study date.

*Study definitions*

Acute RTIs were defined by one or more clinical diagnostic codes (Readcodes) relating to acute upper RTIs (e.g. rhinosinusitis) and lower RTIs (e.g. pneumonia, bronchitis), and acute otitis media. Antibiotic prescription included oral therapy with primarily antibacterial activity listed in the British National Formulary (BNF) for Children (Chapter 5.1) licensed for acute RTIs in young children and defined by means of CPRD *product codes*. There was no minimum antibiotic duration or dose to qualify for inclusion. Drugs with primarily antiviral or antifungal activity and drugs for non-acute RTI (e.g. tuberculosis) were excluded. Children who were prescribed an antibiotic at an index consultation that did not have an associated Read code or had an irrelevant (not RTI-related) Read code were excluded from the analysis. Children were also excluded where there was an inadequate follow-up period. All children had to be registered in the CPRD database for at least 14 days after index consultation to allow the outcome to occur and be recorded. Highly specific patient groups in whom specialised long-term antibiotic regimens are recommended for chronic respiratory diseases (e.g. tuberculosis) were excluded (Appendix 1).

*Antibiotic exposure*

Antibiotic exposure was measured as the number of antibiotic prescriptions for “acute RTI” up to 12 months prior to the index prescription (T0) (Fig. 1).

*Insert Figure 1.*

Antibiotic prescriptions for acute RTI episodes were selected at random. The selection of the random sample of episodes within children was derived using the STATA set seed randomisation command (www.stata.com/manuals13/rsetseed). To account for multiple individual RTI episodes presenting in each child, the index prescription (T0) was defined as the first antibiotic prescription for an acute RTI during the study period. All antibiotic prescriptions associated with acute RTIs up to 12 months prior to the index prescription were counted.

Covariates for adjustment were (further details in Appendix 1):

* age (years) at the time of index antibiotic prescription,
* sex,
* time of year (according to seasons: Dec-Feb = winter; Mar-May = spring; Jun-Aug = summer; Sept-Nov = autumn),
* RTI type (upper-, lower RTI, and otitis media),
* class of antibiotic (according to the BNFC classification),
* presence of one or more comorbidities,
* childhood vaccination status: diphtheria, tetanus, pertussis, polio and Hib (DTaP/IPV/Hib) and pneumococcal conjugate (PCV),
* social deprivation quintiles: based on patient-linked deprivation index score (IMD),
* number of previous “response failure” episodes during the 12-month period before the index prescription, and
* number of consultations for acute RTIs during the 12 months before the index prescription (baseline consultation rate).

*Outcome*

We conceptualised the term “response failure” in recognition that for many acute RTIs, failure may occur for reasons other than the antibiotic treatment itself. For the purposes of this analysis, “response failure” was defined as the earliest occurrence of any of:

1. prescription of a subsequent antibiotic within 14 days of the initial antibiotic being prescribed to that child,
2. GP record of hospital admission with an infection-related diagnostic code within 14 days of antibiotic initiation,
3. GP record of death with an infection-related diagnostic code within 14 days of antibiotic initiation,
4. GP record of referral to an infection-related specialist service within 14 days of antibiotic initiation, or
5. GP record of an emergency department visit within three days of antibiotic initiation

(the shorter time window likely reflects that the emergency event was related to the illness episode, and acknowledges that carers of young children tend to consult within a shorter period of time if their child’s symptoms do not improve).

Referrals to a specialist service in secondary care were taken were taken from CPRD’s Referral table.  This table contains information about who the referral is made to and is linked to a Readcode. We matched referrals to secondary care by index consultation dates and selected acute specialities relevant to acute infections with an RTI diagnostic code. Referrals for blood tests, microbiology (throat or ear swabs etc.) were excluded. Where it was not clear where the referral was being made to, referrals were based on probable acute RTI-related symptoms e.g. breathlessness. For each index antibiotic prescription (T0), “response failure” events were derived by searching forward 14 days from T0 for the first indication of “response failure” as per the definition thereof. For those children who fulfilled one of the criteria of “response failure”, any RTI-relevant Read code was sought immediately before or after the “response failure” event.

*Statistical* *methods*

Stata 13SE was used to carry out all statistical analyses. Data were summarised as numbers and percentages for categorical variables and means and standard deviations for continuous variables where appropriate. Two analyses were performed: a multivariable logistic regression analysis on a random index antibiotic course (prescription) for RTI per child (primary analysis) and multivariable logistic regression using a three-level mixed effects model (secondary analysis).

*(a) Primary analysis*

The primary analysis included one random index antibiotic course (prescription) for RTI per child during the study period. To examine the association between the number of antibiotic courses for acute RTIs in the preceding 12 months and “response failure”, we calculated unadjusted and adjusted odds ratios with 95% confidence intervals in relation to the study outcome using multivariable logistic regression.

*(b) Secondary analysis*

To account for multiple individual RTI episodes presenting in each child nested within each practice, we carried out multivariable logistic regression using a three-level mixed effects model to examine whether (i) GP practice-level, (ii) child-level factors and (iii) antibiotic prescriptions were associated with “response failure” adjusting for covariates.

*(c) Sensitivity analyses*

To assess the robustness of the primary analysis, sensitivity analyses were performed, which excluded data from:

1. index antibiotic prescribing episodes which were preceded by one or more antibiotic prescriptions within the last 14 days. These episodes may be response failures rather than index prescriptions based on our study definition;
2. index antibiotic prescribing episodes which were preceded by one or more antibiotic prescriptions during the 8-week period before the index prescription. Individuals with self-limiting respiratory tract infections may continue to experience symptoms such as persistent cough for up to eight weeks23,24;
3. children who were 12 months of age at the time of index prescription since these children would only have data from the time the child was registered at the GP surgery and may not have 12 months data in the CPRD.

An additional sensitivity analysis was also performed whereby the response failure outcomes were only defined as criteria ii-v of the outcome definition thereby minimising the behavioural aspects of parental consultation and antibiotic prescribing.

*(d) Subgroup analysis*

Subgroup analysis was performed by RTI type (upper RTI vs lower RTIs vs otitis media).

**Results**

There were 252,572 preschool children who had a total of 1,546,364 acute RTI consultations (upper and lower RTIs, AOM) during the study period. The proportion of children prescribed an antibiotic course during one of these consultations for acute RTI was 45% (114,329/252,572). Children had an average of six consultations for RTI over the 92-month study period (0.8 RTI consultations per year).

**Primary Analysis**

*Baseline characteristics*

There were 114,329 children prescribed an antibiotic course for RTI during the study period. Baseline characteristics of this cohort are shown in Table 1. The median baseline consultation rate for RTI was 4 (IQR 2 to 7) in the year previous to the index prescription. Asthma (n=3,134; 47·31%) was the most common comorbidity. A third of children with a comorbidity had a history of premature birth (n=2,201; 33·22%). Less than 3% of children had experienced one or two previous response failures during the 12 months prior to the index RTI consultation.

*Insert Table 1.*

*Antibiotic exposure*

There were 18, 946 (16·57%) children who received at least one antibiotic prescription for acute RTI in the preceding year (Table 1). The distribution of antibiotic exposure in the year prior to index prescription was positively skewed with a range of 0 to 12, a median of 0, and only 3% being exposed to two or more antibiotic courses in the 12 months prior to index prescription.

*Response Failure*

In the primary analysis, we observed 1,337 response failures (1·17% of 114,329 children prescribed an antibiotic course for RTI), of which 724 (52·58%) were referrals to an infection-related specialist service in secondary care, 306 (22·22%) were subsequent antibiotic prescriptions, 243 (17·65%) were emergency department visits within three days, 103 (7·48%) were hospital admissions, and one death (Table 2). Around half of referrals were to Paediatric and Ear Nose & Throat specialities. Around a third of referrals occurred on the same day as the index antibiotic prescription. Just under a quarter of referrals receiving an antibiotic course (23%; 167/724) were based on symptoms related to probable acute RTI. The remaining referrals had a linked RTI READ code. The absolute risk of response failure was respectively: referral (0.6%); second prescription (0.3%); emergency department visit (0.2%) hospital admission (0.1%), and death (<0.01%).

*Insert Table 2.*

*Odds of response failure*

Children who were prescribed two or more antibiotic courses for “acute RTI” in the preceding year had greater likelihood of “response failure” after adjusting for covariates (unadjusted odds ratio (OR) 2·22 [1·80-2·74], p<0.001; adjusted OR 1·32 [95% CI 1·04-1·66], p=0.02, n=97; Table 3). Children who had one antibiotic course during the previous year also had greater odds of response failure, but this was no longer statistically significant after adjustment (unadjusted OR 1·41 [1·22-1·62], p<0.001; adjusted OR 1·03 [95% CI 0·88-1·21], p=0.67).

*Insert Table 3.*

**Secondary analysis**

Incorporating multiple RTI episodes in each child, there were 190,290 acute RTI episodes in 114,329 children from 380 GP practices during the study period. Baseline characteristics of this cohort are detailed in Appendix 2 (Table S1).

*Response failure*

There were 3,709 response failures included in the secondary analysis. The median number of response failures per practice was 8 [IQR 4 to 14] during the study period. Subsequent antibiotic prescriptions (1,757, 47·37%) was the top criterion for response failure, followed by referrals to an infection-related specialist service in secondary care (1,359, 36·64%); emergency department visits within three days (426, 11·49%); hospital admissions (166, 4·48%) and one death (Appendix 2, Table S2).

*Odds of response failure*

When accounting for multiple individual RTI episodes presenting in each child nested within each general practice, secondary analysis supported the findings from the primary analysis. Greater odds of response failure were observed in children who had one antibiotic course during the previous year (one antibiotic course: unadjusted odds ratio (OR) 1·62 [1·50-1·75], p<0.001; adjusted OR 1·16 [95% CI 1·07-1·27], p<0.001, n=1,029. The likelihood of response failure was greater for children who had two or more antibiotic courses during the previous year: unadjusted odds ratio (OR) 2·92 [2·68-3·17], p<0.001; adjusted OR 1·92 [95% CI 1·75-2·10], p<0.001, n=820; Appendix 2, Table S3).

**Sensitivity analyses**

When excluding RTI-associated antibiotic prescribing episodes which were preceded by one or more antibiotic courses within the last 14 days, the association between ≥2 antibiotic courses and response failure was of borderline statistical significance: one antibiotic course: adjusted OR 1·00 [95% CI 0·85-1·18], p=0.98, n=217; two or more antibiotic courses: OR 1·28 [95% CI 1·01-1·61], p=0.046, n=90 (Appendix 3, Table S4a).

When excluding antibiotic prescribing episodes which were preceded by one or more antibiotic prescriptions during the 8-week period before the index prescription, a statistically significant association was not demonstrated between children receiving two or more antibiotic courses and “response failure”: two or more antibiotic courses: OR 1·13 [95% CI 0·86-1·47], p=0.38 , n=66 (Appendix 3, Table S4b).

Excluding children who were 12 months of age at the time of index prescription (14,438 excluded; 12·62%) did not change the overall results: one antibiotic course: adjusted OR 1·03 [95% CI 0·87-1·22], p=0.75,n=215; two or more antibiotics courses: OR 1·29 [95% CI 1·01-1·64], p=0.04, n=95 (Appendix 3, Table S5a).

By excluding children where the first criterion of our study outcome was used (i.e. prescription of a subsequent antibiotic within 14 days of the initial antibiotic being prescribed to that child; n=306 excluded), we observed that the prescription of one antibiotic course was associated with significantly increased risk of response failure (adjusted OR 1·21 [95% CI 1·02-1·44], p=0.03, n=198), as was prescription of two or more antibiotics (OR 1·54 [95% CI 1·20-1·98], p=0.001, n=91 (Appendix 3, Table S5b).

**Subgroup analysis**

Children who received two or more antibiotic courses specifically with a lower RTI (n=68,634) in the preceding 12 months were more likely to have “response failure” (one antibiotic course: OR 1·13 [95% CI 0·92-1·39], p=0.25; two or more antibiotic courses: OR 1·60 [95% CI 1·19-2·16], p=0.002. A statistically significant association was not observed for the other four categories of acute RTIs coded in the CPRD.

**Discussion**

*Main findings*

Children under 5 years old who received two or more antibiotic courses in the previous year for acute RTI had greater likelihood of “response failure” for subsequent acute RTIs compared to children that had received none. Our findings were supported after accounting for multiple individual RTI episodes in children nested within clinics. In the primary analysis, referrals to a specialist service in secondary care accounted for around half of response failures and one third of these occurred on the same day as the antibiotic prescription. Further studies are needed in which the reason for referral can be accurately elucidated.

*Comparison with existing literature*

Our findings are consistent with a recent study from the USA examining treatment failure rates within 14 days of over 30,000 children (aged 6 months to 12 years) with acute RTIs where around 3% required a new prescription for a systemic antibiotic.13 Through 30 days, 8.2% of children experienced treatment failure. The former study did not specifically look at other clinically-defined criteria (e.g. hospital admission) or antibiotic exposure in the previous year. Previous population-based studies in the UK found that around 1 in 10 patients of all ages prescribed antibiotics for an “acute RTI” (upper and lower RTIs, acute otitis media) in the community experience an antibiotic “treatment failure”.11,25 Close to 95% of these antibiotic “treatment failures” were in the form of re-consultation and receipt of a different antibiotic prescription within 30 days of their initial prescription. These previous studies found that the highest failure rates were for lower RTIs, which is similar to our findings. However, these studies did not focus on preschool children. We surmise that our lower rates of “failure” relate to a number of factors including a different outcome definition for failure (14 days instead of 30 days); other studies including both inpatient, outpatients, urgent care settings; prescription drug claims including injectable or intravenous antibiotics; and/or a focus on all children as opposed to preschool children.

Importantly, the underlying reasons for “response failure” events are complex and multifactorial. Possible explanations include that these “failures” are more to do parents’ healthcare seeking behaviour and that they are unaware of the normal duration of common RTI illness.26 Prescriber factors include the clinician’s inclination to prescribe an antibiotic because of diagnostic uncertainty coupled with concern that the infection might progress.27 Other factors might also include that antibiotic use in young children disturbs the fragile microbiome with subsequent increased susceptibility to infection28 or that antibiotic-resistant infections could have a role to play in leading to “response failures”.29

*Strengths and Limitations*

In the absence of routine microbiological sampling for acute RTIs in primary care , the estimates for “response failure” give a pragmatic, clinically relevant outcome measure that patients and clinicians in the community can relate to. A strength of this study is the scale and quality of primary care data to conduct this study and therefore the results are likely to be generalisable to similar paediatric populations. Our analysis adjusted for baseline consultation rate and previous response failures. A methodological strength is that the main findings are supported by the secondary analysis, where we have considered multiple RTI episodes in each child nested in GP practices over the study period. In addition, greater ORs were observed in the sensitivity analysis excluding children where the first criterion of our study outcome was used (i.e. antibiotic prescriptions, OR 1·32 [95% CI 1·04-1·66] vs OR 1·54 [95% CI 1·20-1·98]). This finding supports the primary analysis suggesting that patient demand for antibiotics is unlikely to be driving this association or perhaps that a child with a history of frequent antibiotic use may prompt the clinician to suspect an anatomical or immunity-related issue and seek specialist opinion. The absolute increase in the likelihood of ‘response failure’ between non-exposed and exposed preschool children is relatively low (0.3% based on an adjusted OR of 1.32 i.e. 0.94% (1050/111,281)\*1.32).

We accept there are important limitations. The true aetiology of these acute RTIs is not known. Therefore, evidence of antibiotic non-response may relate to sub-optimal diagnosis and inappropriate treatment and medicalisation of self-limiting RTIs in children rather than lack of treatment effectiveness. These data cannot report the relative contribution of bacterial resistance or answer the question of causality of the antibiotic prescription. Only children with acute LRTI treated with antibiotics were associated with ‘response failure’ and may reflect illness severity. Our findings, therefore, may be identifying children that are prone to infections (but without a relevant comorbidity) without identifying the association with number of antibiotic prescriptions. There was no association when excluding antibiotic prescribing patterns for the eight weeks prior to the index prescription and might contradict the antibiotic-microbiome theory.

In the primary analysis, referral to an infection-related specialist service was the most common reason for “response failure”. We acknowledge that the reason for referral may include other issues incidental to the acute presentation. Available data were unable to distinguish between urgent referrals and a routine specialist referral for an ongoing or unrelated RTI-associated problem. Likewise, we were not able to reliably exclude children on prophylactic antibiotics (e.g. flucloxacillin for cystic fibrosis). However, the number of children on prophylactic antibiotics is likely to be small in such a large cohort. Within our cohort study of nearly eight years, only 725 children (0·25%) were prescribed flucloxacillin of which only three children experienced a “response failure”. Lastly, although we adjusted for important covariates, it was not possible to account for confounding due to illness severity from routinely collected data.

*Implications for practice, policy and future research*

Previous antibiotic exposure for acute RTI in children may give an indication for subsequent “failure” (but not necessarily because of antibiotic treatment failure). Our findings suggest that children receiving more antibiotics affects their likelihood of re-consulting a health professional and increase clinical workload, even though the majority of RTIs in children are viral, self-limiting and would not be expected to have benefitted from antibiotic treatment. Indirectly, this points to the importance of appropriate safety-netting and informing parents (carers) of the natural recovery period of common RTIs in children.23 Incorporating these exposure data into clinical decision-support systems will prompt primary care clinicians to implement strategies to support a non-antibiotic strategy like informing parents about the anticipated recovery period of common RTIs in children.30 This is especially true where the child does not have clinical evidence of an infection which obviously requires treatment with antibiotics. Indirectly, this can help curb expectations for antibiotics 31, and facilitate better shared decision-making during consultations based on tangible outcomes that parents/carers and clinicians can relate to.32

Better quality indicators are needed for common infections to improve the appropriateness of antibiotic prescribing and reduce overall antibiotic prescribing.33 A recent UK database study found almost a third of antibiotic prescriptions could not be linked to a clinically-informative condition.34 Novel quality indicators should centre around acute RTIs, where the majority of unnecessary antibiotic prescribing occurs, and focus on the diagnostic process leading to a diagnosis and the decision to prescribe an antibiotic, rather than simply the choice of antibiotic.35

Routinely collected primary care data in its current format is unable to tease out the intricacies of everyday prescribing decisions. Large-scale observational studies in primary care settings are therefore needed to improve understanding of the mechanisms underlying “response failure”, how these may be addressed to minimise unnecessary antibiotic prescribing and use, and to determine the proportion of clinical response failures for common infections that are indeed attributable to antibiotic resistance and microbiome disruption.

*Contributors*

Dr van Hecke had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Ethics approval*

The study protocol was reviewed by the Independent Scientific Advisory Committee (ISAC) and approved 14 October 2016 (ISAC Protocol 16\_162R).

*Competing interests*

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Figure 1. Antibiotic exposure as the number of antibiotic prescriptions for acute RTIs up to 12 months prior to the index prescription (T0)

|  |  |  |
| --- | --- | --- |
| **Antibiotic exposure of interest** | **Index prescription (T0)** |  **Response Failure** |
|  |  |  |

**Table 1 Demographic and clinical characteristics of preschool children prescribed antibiotics for an acute RTI in the CPRD 2 January 2009 to 23 September 2016 (N=114,329)**

|  |  |
| --- | --- |
| **Characteristic** | **Number (%) or median (interquartile range)** |
| **Age in years (median, IQR)** | 2.39 yr (IQR 1.39 to 3.66) |
| **Gender (female)** | 54,379 (47·56%) |
| **Season a** Winter | 41,830 (36·59%) |
| Spring | 30,110 (26·34%) |
| Summer | 15,108 (13·21%) |
| Autumn | 27,281 (23·86%) |
| **RTI type** b URTI | 16,048 (14·04%) |
| LRTI | 68,634 (60·03%) |
| AOM | 28,604 (25·02%) |
| URTI & LRTI | 662 (0·58%) |
| Other mix | 381 (0·33%) |
| **Comorbidity** | 6,625 (5·79%) |
| **Antibiotic class** Cephalosporin |  847 (0·74%) |
| Macrolides | 11,571 (10·12%) |
| Broad-spectrum penicillin (amoxicillin; co-amoxiclav) | 87,723 (76·73%) |
| Penicillinase-resistant (flucloxacillin) | 275 (0·24%) |
| Penicillin V | 13,673 (11·96%) |
| Quinolones | 7 (0·01%) |
| Trimethoprim-cotrimoxazole | 233 (0·20%) |
| **Vaccination status at index date (complete)** | 43,401 (37.96%) |
| **Vaccination status at end of study period (complete)** c | 106,803 (93·42%) |
| **Social deprivation quintiles** d |  |
|  1 (least deprived) | 25,125 (21·99%) |
|  2  | 23,021 (20·15%)  |
|  3  |  20,935 (18·32%)  |
|  4  | 23,186 (20·29%)  |
|  5 (most deprived) | 21,994 (19·25%) |
| Not linked to IMD | 68 (0·06%) |
| **Previous response failures** e **in last 12 months** |  |
| None | 111,281 (97·33%)  |
| 1 |  3,011 (2·63%)  |
| 2 | 37 (0·03%) |
| **Previous RTI consultations in last 12 months (median, IQR)** | 4 (IQR 2-7) |
| **Number of children with an RTI-associated antibiotic prescription during the 12 months before the index consultation** |  |
| None | 95,383 (83·43%) |
| 1 | 14,929 (13·06%) |
| ≥2 | 4,017 (3·51%) |

a Seasons: Winter (Dec-Feb); Spring (Mar-May); Summer (Jun-Aug); Autumn (Sept-Nov)

b URTI: acute sinusitis, sore throat, laryngitis, coughs etc.; LRTI: pneumonia, bronchitis etc.; AOM: acute otitis media; URTI & LRTI: A small proportion of children had both LRTI and URTI READ codes on the same consultation day

c Complete set of specific vaccinations completed by age 5

d Index of Multiple Deprivation (IMD) quintile based on patient-linked IMD scores 2010

e Response failure is defined as the earliest occurrence of any of:

1. prescription of a subsequent antibiotic within 14 days of the initial antibiotic being prescribed to that child;
2. GP record of admission with an infection-related diagnostic code†
3. GP record of death with an infection-related diagnostic code†
4. GP record of referral to an infection-related specialist service†

(†all within 14 days of antibiotic initiation); or

1. GP record of an emergency department visit within three days of antibiotic initiation.

**Table 2 Antibiotic exposure in the 12 months prior to index consultation and response failure criteria. Values are numbers of children.**

|  |  |
| --- | --- |
|  | **Response failure** |
| **Antibiotic exposure** | Referral | Second prescription  | Emergency department visit  | Hospital admission | Death | **Total**  |
| None | 494 (68%)  | 268 (88%) | 209 (86%)  | 78 (76%)  | 1 (100%) | 1,050 |
| 1 | 153 (21%)  | 32 (10%) | 28 (12%) | 17 (16%)  | 0 | 230 |
| ≥ 2 antibiotic courses | 77 (11%)  | 6 (2%) | 6 (2%)  | 8 (8%)  | 0 | 97 |
| **Total** | 724a | 306b | 243c | 103d | 1e | 1,377 |

* a: Days to referral (median, IQR) = 2 days (0-7)
* b: Days to second prescription (median, IQR) =10 days (7-13)
* c: Days to emergency visit (median, IQR) = 2 days (1-7)
* d: Days to hospital admission (median, IQR) =2 days (1-9)
* e: Death occurred at day 5

**Table 3 Primary analysis: multivariable analysis of the association between RTI-associated antibiotic exposure in the previous year and subsequent “response failure” for acute RTI (n=1,377 response failures)**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Adjusted Odds Ratio [95% CI]** | ***P* value** |
| Number of RTI antibiotic courses in previous year (no. of children with response failure) |  |  |
| None (n=1,050) | 1 [Reference] |  |
| 1 antibiotic (n=230) | 1·03 [0·88 to1·21] | 0.67 |
| ≥2 antibiotics (n=97) | 1·32 [1·04 to 1·66] | 0.02 |
| Age at index consultation (years) | 0·95 [0·90 to 0.99] | 0.018 |
| Gender Male  | 1 [Reference] |  |
| Female  | 0·85 [0·76 to 0·95] | 0.003 |
| Season a Winter  | 1 [Reference] |  |
| Spring | 1·09 [0·96 to 1·26] | 0.18 |
| Summer | 1·22 [1·03 to 1·43] | 0.02 |
| Autumn | 1·00 [0·87 to 1·16] | 0.99 |
| RTI type b URTI | 1 [Reference] |  |
| LRTI | 0·88 [0·75 to 1·04] | 0.13 |
| AOM | 1·05 [0·88 to 1·25] | 0.60 |
| URTI and LRTI | 2·37 [1·48 to 3·79] | <0.001 |
| Other mix  | 0·84 [0·31 to 2·27] | 0.73 |
| Comorbidity None | 1 [Reference] |  |
| Present  | 1·20 [0·98 to 1·48] | 0.08 |
| Antibiotic drug class Cephalosporin | 1 [Reference] |  |
| Macrolides | 0·77 [0·50 to 1·19] | 0.25 |
| Broad spectrum penicillin(amoxicillin, co-amoxiclav) | 0·47 [0·30 to 0·71] | 0.001 |
| Penicillinase-resistant (flucloxacillin) | 0·46 [0·14 to 1·54] | 0.21 |
| Pen V (phenoxymethylpenicillin) | 0·60 [0·39 to 0·94] | 0.03 |
| Quinolones | 0 (empty) |  |
| Trimethoprim-cotrimoxazole  | 1·01 [0·41 to 2·53] | 0.98 |
| Number of response failures in previous year |  |  |
| None | 1 [Reference] |  |
| 1 | 2·08 [1·67 to 2·58] | <0.001 |
| 2 | 3·93 [1·18 to 13·12] | 0.03 |
| Number of acute RTI consultations in previous year | 1·03 [1·02 to 1·05] | <0.001 |
| Social Deprivation 1 (least deprived) | 1 [Reference] |  |
|  2  | 0·96 [0·81 to 1·13] | 0.61 |
|  3  | 1·08 [0·92 to 1·28] | 0.34 |
|  4  | 1·12 [0.95 to 1·32] | 0.17 |
|  5 (most deprived) | 0.99 [0.84 to 1·18] | 0.96 |
| Vaccination status at index consultation |  |  |
| Incomplete or none | 1 [Reference] |  |
| Complete | 1·41 [1·26 to 1·59] | <0.001 |

 a Seasons: Winter (Dec-Feb); Spring (Mar-May); Summer (Jun-Aug); Autumn (Sept-Nov)

b URTI: acute sinusitis, sore throat, laryngitis, coughs etc.; LRTI: pneumonia, bronchitis etc.; AOM: acute otitis media; URTI & LRTI: two separate RTI READ codes for antibiotic prescribing event on same day.