



Effect of antibiotics in preventing hospitalizations from respiratory tract infections in children with Down syndrome

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Abstract

Background: Children with Down syndrome (DS) are at high risk of respiratory tract infections (RTIs) due to anatomical variations, comorbidities, and immune system immaturity. Evidence on interventions to reduce this risk is incomplete. This study aims to quantify the effect of antibiotics prescribed for RTIs in primary care on the subsequent risk of RTI-related hospitalization for children with DS versus controls.

Methods: We conducted a retrospective cohort study of 992 children with DS and 4874 controls managed by UK National Health Service General Practitioners (GPs) and hospitals as identified in CALIBER (Clinical disease research using Linked Bespoke studies and Electronic health Records), 1997–2010. Univariate and multivariate logistic regression were undertaken.

Results: In children with DS, the prescription of antibiotics following an RTI-related GP consultation did not significantly reduce the risk of RTI-related hospitalization in the subsequent 28 days (risk with antibiotics, 1.8%; without, 2.5%; risk ratio, 0.699; 95% confidence interval, 0.471–1.036). Subgroup analyses showed a risk reduction only in infants with DS, after adjustment for covariates. There was no reduction in risk for controls, overall or across subgroups.

Conclusions: In conclusion, while prescription of antibiotics following RTI-related GP consultations were effective for infants with DS in reducing subsequent RTI-related hospitalization, this was not the case for older children with DS. We would encourage further high-quality cohort and randomized controlled trials to interrogate this finding, and to examine the impact of antibiotics on other endpoints, including symptom duration.

KEYWORDS

antibiotics, children, Down syndrome, hospitalization, respiratory

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1 | INTRODUCTION

With an incidence of 1 in 1000 live births, and prevalence of 6.3 in 10,000 people, Down syndrome (DS) is one of the most common genetic conditions in the UK.^{1,2} As of 2011, an estimated 37,090 people were living with DS in England and Wales, of whom approximately 10,438 were aged 0–18.³ It has been projected that the number of children with DS is increasing in the UK, with one analysis projecting 11,592 children 0–15 to be living in England and Wales by 2020.⁴ In addition, life expectancy of people with DS has doubled in the past six decades, increasing from 30 to 60 years,^{5,6} alongside advances in medical and surgical treatment, improved social inclusion and support, and general quality of life.^{5,6}

Children with DS are thought to be at an increased risk of frequent and severe respiratory tract infections (RTIs) due to anatomical variations (such as a narrow upper airway), complications from comorbidities (including congenital heart disease and reflux), and immune system immaturity.^{7,8} A study of 22 children with DS age-matched to 22 healthy siblings found children with DS had a significantly higher frequency of lower RTIs (LRTIs) compared to their siblings alongside observed immune parameter differences.⁷ These respiratory infections account for a large proportion of healthcare utilization in children with DS, especially at younger ages.⁹ In an Australian study of 3786 hospitalizations in 405 children with DS, 26.7% of all admissions were due to RTIs, with 52.6% of all children with DS experiencing any hospital admission due to an RTI.⁸ When compared to published admission rates for the pediatric population in Western Australia, significant differences were noted—the rate ratio for hospitalizations with respiratory system-related diagnoses in children with DS was 17.9. In particular, LRTIs result in longer length of stay and a high proportion of intensive care unit admissions (43% in one study) in children with DS.¹⁰

Despite this perceived risk, there is remarkably little evidence on interventions to reduce RTIs, with most trials for RTI treatments worldwide being less open to children and adults with DS than those without DS. There are many implicit barriers to research for individuals with learning disabilities,^{11,12} and barriers may also be explicit in the form of exclusion criteria. A 2019 review of over 26,000 studies in the NIHR portfolio found that 60.3% of all studies excluded learning disability groups, all studies investigating pneumonia excluded learning disability groups, and only 1.4% of studies were specifically targeted towards individuals with learning disabilities.¹³ Recent research on preventative and therapeutic interventions for RTIs in adults and children with DS is limited; a 2015 systematic review identified only five studies, from a search of 13,575 records, none of which focused on the effect of antibiotics.¹⁴ The impact of antibiotics prescribed for RTIs in primary care has been previously quantified for the general UK population,¹⁵ but given the differing prevalence and severity of RTIs in children with DS, the lack of evidence for the role of antibiotics in treating children with DS and RTIs therefore represents an important research gap.

Evidence in this area would be beneficial for patients, their families, and healthcare professionals (HCPs) to guide appropriate, timely and personalized treatment of RTIs in children with DS.

The present study utilizes routinely collected primary and secondary UK National Health Service health care data to address this study gap, estimating the effect of antibiotic prescription following RTI-related General Practitioner (GP) consultations in terms of reducing RTI-related hospitalizations in children with DS and controls.

2 | MATERIALS AND METHODS

2.1 | Objectives

This study aimed to (a) quantify the effect of antibiotics prescribed for RTIs in primary care on the subsequent risk of RTI-related hospitalization for children with DS compared to controls, and (b) to determine if the effect of antibiotics varies by type of RTI, and age group.

2.2 | Data sources

CALIBER is a database of linked routinely collected electronic health records from England,¹⁶ incorporating primary care (Clinical Practice Research Datalink [CPRD]),¹⁶ hospital admissions data (Hospital Episode Statistics [HES]),^{16,17} the Myocardial Ischaemia National Audit Project,¹⁸ and the Office for National Statistics national death registry. Healthcare utilization in this database is extrapolated from Read and ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th edition) codes which are used by GPs and hospital staff to classify healthcare encounters by theme and diagnosis. CPRD has been used by previous studies to quantify complications and characteristics of RTIs in the UK, as well as the efficacy of antibiotics in treating them.¹⁵

As part of this study a novel algorithm was developed which searched through symptom and diagnosis codes in CALIBER in line with the aims of this study, using the R CALIBERcode package.¹⁹ Individual codes (e.g., “bronchitis”) were classified as referring to a lower RTI (LRTI), an upper RTI (URTI), or unclassified RTI (i.e., not able to be clearly classified as either according to code list terms). The same process was used for DS and to identify other comorbidities, for example, congenital heart disease, using predefined Read and ICD-10 codes in CPRD and HES. Additionally, codes were labeled as referring to either probable or possible RTIs. Previous code lists from other similar works (published and unpublished, 42 in total) were consulted and merged and any new/unclassified/disputed codes were reviewed by two academics and adjudicated by a third in cases of disagreement. After finalization of code lists, they were reviewed in a consensus meeting with L. M., A. S., M. L., and A. H. (clinicians and academics with prior relevant expertise) to ensure agreement. See Table S1 for the code lists. This methodology is also reported in our paper investigating RTI-related healthcare utilization in children with DS.⁹

2.3 | Participants

CALIBER was searched between January 1st, 1997 and March 25th, 2010 for all adults and children with DS, as identified by all Read and ICD-10 codes related to DS in CPRD and HES. Individuals with an exit date before their entry date were removed, due to suspected data quality issues. For each remaining individual with DS, five controls without DS were frequency matched by GP, gender, birth year (± 5 years), and start of follow-up. Those who were over 18 years old at the entry date were excluded after this point.

2.4 | Definitions

Hospitalization rates were acquired from HES and prescription and consultation rates from CPRD, within CALIBER. Hospitalizations were defined according to HES coding of an event as a "hospital admission," which were then coded by diagnosis in line with the ICD-10 coding system. Length of stay was calculated as "discharge date – admission date + 1 day," and all admissions including those lasting only 1 day were included. When calculating baseline risk of hospitalization from a consultation, all GP consultations for RTIs were the exposure and all RTI-related hospitalizations were the outcome. Each RTI-related GP consultation was followed up for 28 days or until the first RTI-related hospitalization within that time period. Rates of hospitalization were calculated by dividing the number of episodes of hospitalization in 28 days by the total number of person-years in this time. Analyses were conducted across years, age groups, gender, and RTI type (i.e., URTI/LRTI/unclassified RTI). Age-groups were defined according to author consensus in the following four categories: infants (0–1 years old), toddlers (1–5 years old), juniors (5–10 years old), and young persons (10–18 years old).

A ranking system was used based on RTI-type (LRTI > URTI > unclassified), setting (secondary > primary care) and whether it was probable or possible (probable > possible) in the event of multiple RTI events being noted on the same day for the same patient (e.g., a probable URTI consultation and a possible LRTI hospitalization).

2.5 | Sample size

The Fitzgerald et al.⁸ Australian study of hospitalizations for children with DS was utilized to inform our sample size calculation. They found an average of 0.8 and 0.1 RTI-attributable hospital admissions in children with and without DS, respectively (with numbers representing the proportion of each population with an outcome of interest (e.g., a record of hospitalization)).⁸ To calculate our sample size, with the assumption UK hospitalization rates were similar, we estimated that at least 20 individuals per group were required to identify this difference in hospitalization rates between children with DS and controls at 80% power using

a significance level of 0.05. The number of individuals required increases by 10% for each variable considered for confounding.

2.6 | Statistical models

Univariate logistic regression was undertaken as the initial model to assess the effect of antibiotic prescriptions on the risk of subsequent RTI-related hospitalization in patients consulting for RTIs.

Multivariate logistic regression was undertaken in the final model. The covariates included in the final model (entered in a single step) were antibiotic prescription, age group, gender, presence of congenital heart disease, presence of asthma, and number of prior RTI-related hospitalizations and RTI-related GP consultations in the preceding 6 months. Comorbidities were identified if a relevant Read (i.e., GP consultation) or ICD-10 (i.e., hospitalization) code was recorded for a child at any point between their CALIBER entry and exit dates. Two further covariates were considered, but ultimately were excluded from the final model because there was insufficient power to detect difference due to the ratio of covariates to outcomes. These were the 28-day RTI-related Consultation Average, and the 28-day RTI-related Hospitalization Average.

Subgroup analysis was performed to assess the effect of antibiotics across age groups and RTI types. Where there was a reduction of sample size in subgroup analysis, post hoc power calculations were conducted to assess the risk of type II error.²⁰ Where a significant protective effect of antibiotic prescription was seen, the number needed to treat (NNT) was estimated. All data management and analyses were performed using STATA statistical software version 13 and R version 3.2.3 via the UCL Data Safe Haven.

2.7 | Study registration and ethics

The protocol for this study was approved by the CPRD independent scientific advisory committee, reference number 15_041R. The CALIBER record linkage has separate ethical approval (09/H0810/16) for observational clinical research. Informed consent from subjects or parents/guardians was not applicable; this study used routinely collected clinical data from CALIBER, which as mentioned has ethical approval for observational clinical research. This study was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

3 | RESULTS

3.1 | Cohort size, demographics, and comorbidities

A total of 992 children with DS and 4874 controls met the criteria for inclusion; their demographics are displayed in Table 1. In general, demographics were similar, although with regard to ethnicity, of those with

TABLE 1 Demographics and comorbidities of the study population

	Controls	Children with DS
Total (N)	4874 (100.0%)	992 (100.0%)
Gender		
Male	2626 (53.9%)	528 (53.2%)
Female	2248 (46.1%)	464 (46.8%)
Age group		
Infants (0–1 year)	1247 (25.6%)	252 (25.4%)
Toddlers (1–5 years)	1133 (23.2%)	224 (22.6%)
Juniors (5–10 years)	1044 (21.3%)	208 (21.0%)
Young persons (10–18 years)	1454 (29.8%)	308 (29.8%)
Ethnicity		
Asian or Asian British	211 (2.5%)	56 (3.3%)
Black or Black British	189 (2.4%)	48 (2.8%)
Chinese or “other” group	114 (1.35%)	30 (1.7%)
Mixed	393 (4.7%)	72 (4.2%)
Unknown	4005 (47.5%)	504 (29.5%)
White	3523 (41.8%)	1001 (58.5%)
Comorbidities		
Asthma	618 (12.7%)	136 (13.7%)
CHD	48 (1.0%)	393 (39.6%)
Diabetes	20 (0.4%)	11 (1.1%)
Epilepsy	34 (0.7%)	18 (1.8%)
Thyroid	11 (0.2%)	103 (10.4%)

Abbreviation: CHD, coronary heart disease.

records available, 41.8% of controls were white, compared to 58.5% of children with DS.

Over the study period, there were 2874 RTI-related consultations in which children with DS were prescribed antibiotics, and 1811 where they were not (see Table 2).

3.2 | Prescription of antibiotics following an RTI-related GP consultation and risk of subsequent hospitalization

In the overall population of children with DS, without adjustment for covariates, the prescription of antibiotics following an RTI-related GP consultation did not show any significant evidence for reduction in the risk of RTI-related hospitalization in the subsequent 28 days (risk, 1.8% (95% confidence interval [CI], 1.3%–2.3%), and 2.5% (95% CI, 1.9%–3.4%) respectively; risk ratio [RR], 0.699; 95% CI, 0.471–1.036). This finding also held true for controls (RR, 0.758; 95% CI, 0.482–1.191).

Among subgroups, without adjustment for prespecified covariates, antibiotics did not provide a significant protective effect against hospitalization across any type of RTI and any age group for children with DS or controls (see Table 3).

TABLE 2 Risk of RTI-related hospitalization within 28 days of an RTI-related GP consultations in children with DS and controls

Classification	With antibiotic treatment		Without antibiotic treatment		With antibiotics versus without	
	# of consultations	# of hospitalizations	# of consultations	# of hospitalizations	Risk ratio [95% CI]	p value
Children with DS	2874	51	1811	46	0.699 [0.471-1.036]	.0913
Controls	5527	31	6350	47	0.758 [0.482-1.191]	.2553
Children with DS						
URTI	1610	20	1159	22	0.654 [0.359-1.193]	.2068
LRTI	566	12	55	3	0.389 [0.113-1.336]	.1396
Unclassified RTI	698	19	597	21	0.774 [0.420-1.425]	.4249
Controls						
URTI	3806	19	4109	24	0.855 [0.469-1.558]	.6485
LRTI	724	5	114	2	0.394 [0.077-2.005]	.2444
Unclassified RTI	997	7	2127	21	0.711 [0.303-1.667]	.5430

Abbreviations: DS, Down syndrome; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Classification	Children with DS		Controls	
	Odds ratio [95% CI]	p value	Odds ratio [95% CI]	p value
All	0.693 [0.463-1.037]	.0747	0.756 [0.480-1.192]	.2291
URTI	0.650 [0.353-1.197]	.1667	0.854 [0.467-1.561]	.6082
LRTI	0.375 [0.103-1.373]	.1387	0.389 [0.075-2.032]	.2632
Unclassified RTI	0.768 [0.409-1.442]	.4107	0.709 [0.300-1.674]	.4327
Infants	0.319 [0.100-1.016]	.0532	0.382 [0.086-1.684]	.2034
Toddlers	0.862 [0.488-1.523]	.6096	1.346 [0.762-2.376]	.3058
Juniors	1.453 [0.560-3.768]	.4425	0.858 [0.261-2.819]	.8011
Young person	0.725 [0.204-2.584]	.6204	-	-

Note: (-) Small sample counts prevented analyses in certain subgroups.

TABLE 3 Unadjusted protective effect of prescribing antibiotics following an RTI-related GP consultation on RTI-related hospitalization in children with DS and controls

After adjustment for all seven covariates (see Section 2.6), antibiotics did not protect against RTI-related hospitalization for the overall group of children with DS or for controls.

However, subgroup analysis by age after adjustment for covariates revealed a protective effect for infants (0–1 years; see Table 4). RTI-related hospitalizations for infants with DS were reduced when antibiotics were prescribed (adjusted odds ratio, 0.260 (95% CI, 0.077–0.876); NNT, 11.9 (95% CI 6.0–1708.7)). There was no protective effect at other ages, or by type of RTI, or in controls (see Table 4).

Post hoc power calculations were conducted across RTI subgroups for both children with DS and controls. Study power was higher for analyses in children with DS (range, 11.4%–37.3%) than in controls (range, 7%–21.2%), due to the relative infrequency of hospitalization in controls (see power calculations in Table S2).

4 | DISCUSSION

In this large population of 992 children with DS and 4874 controls, the prescription of antibiotics following RTI-related GP consultations did not reduce the overall risk of subsequent RTI-related

hospitalization. However, subgroup analyses showed a reduction in risk of hospitalization for infants with DS (0–1 year of age). There was no reduction in risk when analysing across RTI subtypes. The present findings therefore suggest a possible risk reduction for infants with DS which warrants further research and subsequent consideration in updated guidelines.

In terms of strengths, this study is the first to assess the effect of antibiotics in reducing the risk of hospitalization from RTIs in children with DS, and addresses the pressing need for evidence-based interventions to treat RTIs in children with DS. A major strength of this study is the utilization of CALIBER, which allowed for analysis of a large and recent sample. A 2007 study used CPRD primary care data to assess the effect of antibiotics in preventing serious complications following RTIs in the general population, and found a limited benefit, with an NNT of over 4000.¹⁵ That study did not link primary to secondary care data, thereby potentially underestimating complication rates and overestimating the NNT. The present study overcomes this limitation by successfully linking primary and secondary care data.

Limitations of our study relate the small number of individuals with LRTI-related hospitalizations identified, that is, 15 hospitalizations in

Classification	Children with DS		Controls	
	Odds ratio [95% CI]	p value	Odds ratio [95% CI]	p value
All	0.769 [0.511-1.157]	.2074	0.901 [0.569-1.426]	.6554
URTI	0.748 [0.403-1.390]	.3587	1.033 [0.561-1.901]	.9175
LRTI	0.470 [0.121-1.833]	.2772	0.610 [0.114-3.270]	.5644
Unclassified RTI	0.784 [0.412-1.492]	.4593	0.752 [0.318-1.781]	.5175
Infants	0.260 [0.077-0.876]	.0297	0.409 [0.091-1.846]	.2451
Toddlers	0.841 [0.472-1.497]	.5557	1.316 [0.744-2.328]	.3448
Juniors	1.422 [0.544-3.716]	.4731	0.772 [0.232-2.571]	.6739
Young person	0.705 [0.197-2.528]	.5918	-	-

Note: (-) Small sample counts prevented analyses in certain subgroups.

TABLE 4 Adjusted protective effect of prescribing antibiotics following an RTI-related GP consultation on RTI-related hospitalization in children with DS and controls

children with DS, and seven in controls: this has affected the power in this domain (see post hoc power calculations above²¹). These small numbers could be explained by misclassification of GP diagnoses or reasons for hospitalization (e.g., sepsis). Differential misclassification bias could have occurred if consultation codes are more accurately recorded in patients who are prescribed antibiotics compared to those who are not. General errors in coding accuracy may have affected the analysis (a 2017 study found that specific asthma coding in CPRD had a positive predictive value of 86.4%²²). The protective effect observed for infants should be interpreted with caution, due to multiple significance testing. Additionally, after their initial presentation to their GP for an RTI, some untreated children may ultimately have been prescribed antibiotics in other settings, and it is not possible to tell whether prescribed antibiotics were ultimately taken as prescribed, meaning that risk reduction could have been underestimated.

There are a number of implications from this study for clinical practice and future research. Previously, scientific literature has indicated that antibiotics have a limited role in reducing complications in children from the general population with RTIs.^{23–25} A secondary analysis of 8320 children presenting with cough and respiratory symptoms found that antibiotics were prescribed immediately in 28% of cases and delayed in 9% of cases, but did not reduce hospitalizations in either case (Immediate: RR, 0.83; 95% CI, 0.47–1.45; delayed: RR, 0.70; 95% CI, 0.26–1.90).²⁵ A Cochrane review found insufficient evidence for antibiotics as a means to reduce the risk of pneumonia in children up to 5 years of age.²⁴ These findings however had not been personalized to children with DS since they have been excluded from the majority of studies so far. UK National Institute for Health and Care Excellence (NICE) recommendations for antibiotic prescribing in RTIs state that antibiotics should be prescribed immediately if any child is either systemically unwell or at high risk of serious complications due to pre-existing comorbidities, such as congenital heart disease.²⁶ This study indicates that other than in infancy children with DS do not receive an observable benefit with regard to hospitalization after being prescribed antibiotics for RTIs in primary care. This finding has added significance because children with DS may be more at risk of antibiotic resistance given immune system immaturity and increased likelihood of receiving multiple antibiotic courses.^{27–30} Despite this, children with DS are prescribed antibiotics for RTIs more frequently than healthy controls, at a rate of 42 per 100 person years for children with DS versus 19 per 100 person years for controls (adjusted RR, 2.26).⁹ The reasons for this are unclear and may be due to perceived benefits in other areas that have not been well-studied. Previous studies have suggested that prescribing decisions are also related to parental expectation, uncertainty, and pressure from employers.^{31,32} Clinical uncertainty in children with DS is likely to be higher than the general population, with a greater prevalence of comorbidities and possible practitioner uncertainty; hence, practitioners may be adopting a risk-averse approach. Qualitative studies investigating practitioner decision-making, and parental health-seeking behavior, would be very valuable.

To build a more rounded picture of whether antibiotics help children with DS and RTIs in other ways than reducing hospitalizations, future cohort studies and randomized controlled trials should

examine the effect of antibiotics on the duration of RTI-related symptoms, and on days lost at school or at work due to RTIs. Studies should also investigate the impact of prescribing in different settings (e.g., Urgent Care, A&E), differing impacts by duration of antibiotics, and whether prescribed antibiotics are ultimately taken. The existing NICE guidelines on antibiotic prescribing and guidance disseminated by the Down Syndrome Medical Interest Group could then be adapted to incorporate these new findings, with consideration of the limitations of our study.³³ HCPs caring for children with DS could equally be empowered to give more appropriate advice on the efficacy of antibiotics. On the basis of our initial findings, professionals are encouraged to use alternative safety-netting avenues in addition to antibiotic prescriptions, when managing older children with DS suffering from RTIs.

5 | CONCLUSIONS

In conclusion, HCPs and families should be aware that prescribing antibiotics for RTIs in older children with DS does not appear to prevent subsequent RTI-related hospitalization, irrespective of RTI type. This study provides new evidence that antibiotics may be beneficial for infants with DS.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Logan Manikam, Anne G. M. Schilder, Monica Lakhanpaul, Peter Littlejohns, and Andrew Hayward led the study conception and design, and acquisition, analysis and interpretation of data, with contributions from Meghan A. Cupp and Emma C. Alexander. Material preparation, data collection and analysis were predominantly performed by Logan Manikam with advice from all other authors. The first draft of the manuscript was written by Emma C. Alexander and Logan Manikam and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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