Respiratory Tract Infections in Children with Down's Syndrome

Dr Logan Nishant Manikam

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

UCL Great Ormond Street Hospital (GOSH) Institute of Child Health, Population Policy and Practice

UCL Farr Institute of Health Informatics Research

UCL Ear Institute, evidENT

KCL Department of Primary Care and Public Health Sciences

Supervisors:

Professor Monica Lakhanpaul

Professor Anne Schilder

Professor Andrew Hayward

Professor Peter Littlejohns

Declaration

I, Dr Logan Nishant Manikam confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Candidate's signature

About Me

I am an ST4 Public Health Speciality Registrar, UCL National Institute for Health Research Doctoral Research Fellow (DRF) and Interim Child Public Health Lead at London Borough of Newham.

My initial exposure to academic paediatrics dates back to 2008, when I undertook a survey of health information needs of parents attending a paediatric A&E as a medical student. I progressed successfully through the NIHR academic training pathway from an Academic Foundation Doctor into an Imperial College London Academic Clinical Fellow (ACF) in Paediatric Infectious Diseases. I then identified my passion for population health and secured a King's College London ACF in Public Health. Ultimately, I secured a NIHR DRF which led to the following PhD thesis.

Alongside the DRF, I consult for a variety of clients, particularly through my role as the Interim Child Public Health Lead at the London Borough of Newham working closely with Newham Clinical Commissioning Group and Bart's Health NHS Trust. In this role, I have steered public health policy for a diverse yet deprived London borough with some of the worst public health indicators for child health.

I also have a special interest in participatory research and have completed numerous projects ascertaining the views of children, young people and their families; I therefore felt it was vital to develop and consult a Patient and Public Involvement panel from inception until the completion of this work. I have also cultivated an interest in global child health after working as an Intern with the UNICEF Maternal and Newborn Health Team during my time in this fellowship.

I continue to practice clinically in neonatal intensive care and paediatrics as a medical locum. My numerous encounters with children with DS presenting with RTIs in paediatric ED over the years has therefore shaped both my fellowship application and PhD thesis completion. Alongside my academic and public health commitments, I undertake a pastoral role in mentoring numerous medical students and junior doctors in medical academia.

Acknowledgements

ACADEMIC SUPPORT

I would like to thank my PhD supervisors Prof. Monica Lakhanpaul, Prof. Andrew Hayward, Prof. Anne Schilder and Prof. Peter Littlejohns for their advice and support in preparing my fellowship application and during my PhD.

I would also like to thank my colleagues at UCL and KCL: Dr Hannah Evans, Emma Alexander, Meghan Cupp, Prof. Rolf Groenwold, Dr Spiros Denaxas, Giovanna Ceroni, Denise Beales, Natalie Fitzpatrick, Dr Stefano Cacciatore, Arturo Gonzales, Dr Kate Reed, Kunjshri Kumari Singh, Dr Roderick Venekamp, Nischay Mehta, Dr Chidi Amadi and others I have worked with.

FINANCIAL SUPPORT

I am in receipt of a National Institute for Health Research (NIHR) Doctoral Research Fellowship (DRF-2014-07-005) hosted at the UCL GOS Institute of Child Health. Whilst preparing my fellowship application, I was in receipt of a NIHR Academic Clinical Fellowship in Public Health at King's College London.

CALIBER is a collaboration between UCL, the London School of Hygiene and Tropical Medicine (LSHTM) and the Clinical Practice Research Datalink (CPRD). CALIBER is funded by a Wellcome Trust project grant (086091/Z/08/Z) and a NIHR programme grant (RP-PG-0407-10314).

This study was supported by the UCL Farr Institute of Health Informatics Research by providing both infrastructure, access and technical support in utilising CALIBER.

PATIENT PERSPECTIVE

The inception of this project was informed by concerns from parents of children with DS in both acute and outpatient settings that they were receiving mixed messages on how to manage RTIs in their children with DS, including the use of antibiotics.

A Patient and Public Involvement (PPI) panel was therefore set up at the project's outset to assist in research design, analyses, interpretation and dissemination. This consisted of 2 parents of children with DS (Ms Donna Self and Lindsey Fairchild) and a representative

from the Down's Syndrome Association, the largest UK-based charity of adults and children with DS (Ms Vanda Ridley).

Aside from commenting and approving both the systematic review and CALIBER project protocols, they were instrumental in interpreting findings and its implications for clinical practice across all chapters.

Thesis Abstract

BACKGROUND

Children with Down's Syndrome (DS) are prone to respiratory tract infections (RTIs), yet there is little evidence to guide clinical practice.

AIMS

For children with and without DS, this thesis aims to use routinely collected data to identify RTI-related healthcare utilisation, those most at risk of RTI-related healthcare utilisation, and the effects of antibiotics in preventing RTI-related hospitalisation.

METHODS

A systematic review of existing interventions and a retrospective cohort study based on routinely collected primary and secondary care data (CALIBER).

KEY FINDINGS

The CALIBER cohort comprised 992 children with DS and 4874 controls. Children with DS consulted their GP for RTIs twice as often as controls, were prescribed antibiotics twice as often, and were hospitalized six times as often. In children with DS, younger age, congenital heart disease and asthma were risk factors for RTI-related healthcare utilisation. Using multivariate analysis, this study found that for infants with DS, the prescription of antibiotics significantly reduced subsequent RTI-related hospitalisation - the number needed to treat is 11.9. Separate analysis, inverse probability of treatment weighting, found that the protective effect for infants with DS was not significant. When prescriptions were analysed by type of RTI, the prescription of antibiotics for upper RTIs did not reduce the risk of hospitalization for children with DS or controls. This was also the case for lower RTIs, although with a small sample.

CONCLUSION

For children with DS over the age of one presenting with RTIs to primary care, antibiotic treatment does not prevent subsequent RTI-related hospitalisation. There is conflicting evidence from two separate analysis methods as to whether treating infants with DS with antibiotics prevents RTI-related hospitalisation, so further research is recommended.

Further prescribing strategies (i.e. rescue antibiotics) should be explored to broaden the evidence base for this at-risk group.

TABLE OF CONTENTS

List of Figures

List of Tables

Abbreviations

A&E	Accident & Emergency
AVSD	Atrio Ventricular Septal Defect
CBA	Controlled before-after
CHD	Congenital heart disease
CI	Confidence interval
CLD	Chronic lung disease
CPG	Clinical Practice Guideline
CPRD	Clinical Practice Research Datalink
CwDS	Children with Down's Syndrome
DS	Down's Syndrome
DS	Down Syndrome Association
EHR	Electronic Health Record
GP	General Practice
HES	Hospital Episode Statistics
HRQoL	Health-related quality of life
IMD	Index of Multiple Deprivation
IPTW	Inverse Probability of Treatment Weighting
ISAC	Independent Scientific Advisory Committee
LRT	Lower respiratory tract
LRTI	Lower respiratory tract infection
MINAP	Myocardial Ischaemia National Audit Project
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NNT	Number Needed to Treat
ONS	Office of National Statistics
OOH	Out of Hours
OR	Odds Ratio
PCV	Pneumococcal conjugate vaccine
PPI	Patient and Public Involvement
PS	Propensity Score
RCPCH	Royal College of Paediatrics and Child Health
RTI	Respiratory tract infection
RSV	Respiratory Syncytial Virus
RR	Relative Risk
RRTI	Recurrent respiratory tract infection
SMD	Standardised Mean Difference
UCL	University College London
URT	Upper respiratory tract
URTI	Upper respiratory tract infection

Aims and Objectives

AIMS

For children with and without Down's Syndrome (DS), this thesis aims to use routinely collected data to identify RTI-related healthcare utilisation, those most at risk of RTI-related healthcare utilisation, and the effects of antibiotics in preventing RTI-related hospitalisation.

OBJECTIVES

1. To undertake a systematic review of the literature on the effectiveness of preventative and therapeutic interventions for respiratory tract infections (RTIs) in adults and children with DS (**Chapter 2**);
2. To quantify NHS healthcare utilisation attributable to RTIs in children with and without DS from 1997 to 2010 (**Chapter 5**);
3. To ascertain which children, with and without DS, are most at risk of increased RTI-related NHS healthcare utilisation (**Chapter 5**);
4. To assess the effects of antibiotic prescriptions in RTI-related GP consultations for preventing RTI-related hospitalisations, in children with and without DS (**Chapter 6**).

Chapter 1: Background

1.1 CHAPTER OUTLINE

In this chapter, I outline the historical context and current organisation of care of children with Down's Syndrome (DS) in the UK. I subsequently give a brief overview of RTIs in children together with a comparison on how RTIs differ in children with DS.

1.2 DOWN'S SYNDROME

Historical context

DS or trisomy 21, is a genetic condition that was first described by Sir Langdon Down in 1866 (1).

With an incidence of 1 in 1000 live births in 2008, DS is one of the most common genetic conditions in the UK (2). A recent population study conducted by the National Congenital Anomaly and Rare Disease Registration Service estimated the number of people living with DS in the UK to be almost 50,000; of which, approximately 10,500 are children (under the age of 18) (3).

Despite advancements in antenatal screening (e.g. non-invasive prenatal diagnostic testing) from 1990 to date, the number of births of children with DS in the UK has remained constant (2). During the same period however, advances in medical and surgical treatment, social inclusion and public understanding of DS have allowed for significant improvement in life expectancy of these children from 30 to nearly 60 years (4, 5). Alongside this, there has been a corresponding improvement in quality of life (4, 5).

Current organisation of care

In the UK, children with DS are provided structured child and family-centred medical care via multi-agency collaboration to maximise their physical, educational and health outcomes (6).

This is enshrined in the Royal College of Paediatrics and Child Health (RCPCH) and Down Syndrome Association (DSA) Paediatric Service Specification for Children and Young People with DS, a non-mandatory specification designed to assist commissioners in service delivery to this at-risk group (6).

Some of the common co-morbidities that are seen in children with DS include; congenital heart disease (CHD), hypothyroidism, learning difficulties, sleep apnoea, gastroesophageal reflux disease and recurrent otitis media. Managing these particular conditions requires a multi-disciplinary approach led by a paediatrician (e.g. community paediatrician, paediatrician specialising in neurodisabilities, or a general paediatrician). Due to the potential frequency of multi-organ complications, specialist involvement is common (e.g. ENT, Cardiology, General Surgery and Gastroenterology).

There are various models of service provision for children with DS. In some areas, there are dedicated unified multi-disciplinary DS clinics. In others, children with DS are seen by community paediatricians in generic child development centres who may then refer children with DS on to specialists using local care pathways based on the Service Specification detailed above (6).

The RCPCH guidance states that all children with DS should be cared for and reviewed by a paediatrician with particular expertise in DS. Children should be reviewed once every three months up to the age of one, and then subsequently at least once a year. Specialist involvement must include Speech and Language Therapy, paediatric cardiology, ophthalmology, and audiology. Other services should be commissioned as and when required, including physiotherapy, medical specialists, sexual health services, occupational therapy, special needs dentistry, and Child and Adolescent Mental Health Services (6).

A number of regional audits relevant to the routine care of children with DS have been published. A 2012 audit of the Nottingham Down Syndrome Children's Clinic found that 97.9% of children were visited by the Down's Syndrome team after birth, with 87.5% receiving a health visitor home visit at 2 weeks of age (7). Various healthcare elements were audited, with some areas of good practice – for example, 94.9% received regular audiology assessment, and 91.9% were offered speech and language therapy; however, only 32.9% received regular check for symptoms of cervical spine instability (7). As with other studies, it appears that rates of monitoring for complications are variable (8, 9).

A 2014 audit in Wales found that 86% of identified children with DS were followed up by community paediatricians, with 88% of these having regular follow up (10). However,

only 15% of sampled case notes included the local health board guideline for health surveillance, indicative of a potential difficulty with the dissemination of guidelines.

There is little information in existing literature examining the role of General Practice for children with DS in the UK. A study from 1981 found that children with DS saw their GP a mean of 5.6 times in a year, with 4.4 visits to the GP surgery and 1.2 visits by the GP to patients' homes (11). A 2007 study of adults with DS in Newcastle found that 20% had seen both a General Practitioner and a specialist in the previous 12 months; 18% had only seen their General Practitioner; and 14% had only seen a specialist physician. 48% had seen no medical doctor at all in the previous 12 months, and 38% had seen no doctor for the past 3 years (9). In contrast, an American study found that 40% and 60% of the cohort of 62 patients were cared by Family Physicians and medical specialists respectively (8). Both recent studies found that rates of monitoring for common complications of DS were highly variable.

The Patient and Public Involvement (PPI) Panel for this thesis, consisting of two parents of children with DS and a representative from the Down's Syndrome Association, reflected on the role of the GP for children with DS. They reported that interactions with GPs are mostly good for most parents, who may frequently attend for home visits if a child is unwell or prescribe antibiotics without consultations.

The full recommended specifications for surveillance and management of specific medical problems associated with DS, from diagnosis to transition at 18 years of age, are listed below in **Table 1**.

Table 1. Service standards for specific medical problems associated with children with DS from diagnosis to transition.

Adapted with permission from RCPCH Paediatric Service Specification: Services for Children and Young People with Down Syndrome (6)

System	First year of life	Early years / pre-school	School Age
Thyroid	All children with DS must undergo the routine newborn blood spot screening test to exclude congenital hypothyroidism.	Thyroid function must be reviewed either: • Annually, on the basis of annual thyroid stimulating hormone blood spot test; or • Biennial serum thyroid function and antibody tests	

Vision	All children with DS must undergo an examination for red reflex to exclude congenital cataract, as part of the routine newborn examination.	By 2 years of age, children with DS must undergo a formal eye and vision test, including squint assessment. All children must also undergo a detailed visual assessment before school age (4 years), to include squint assessment, refraction and acuity.	School aged children with DS must undergo a detailed ophthalmological/optometric assessment a minimum of once every two years.
Hearing	All children with DS must undergo the routine newborn hearing screening test to exclude hearing impairment. Before the child's first birthday, children with DS must undergo a formal audiological review, including hearing assessment and impedance check.	Between one and four years of age, children with DS will undergo an annual audiological review, including hearing assessment and impedance check.	School age children with DS will undergo an audiological review, including hearing assessment and impedance check, a minimum of once every two years.
Breathing	Children with DS must be assessed for symptoms of sleep-related breathing disorder annually until commencing school, with further assessment (including overnight pulse oximetry) arranged where clinically indicated.		School-age children with DS who develop symptoms of sleep-related breathing disorders must be investigated (including overnight pulse oximetry) and managed promptly, including referral to ENT if appropriate.
Heart	By 6 weeks of age, all children with DS must have a formal cardiological assessment (including echocardiography) to exclude congenital heart disease.	Children with DS must be reviewed annually for signs and symptoms of acquired valvular heart disease, with further assessment (including echocardiography and specialist cardiology referral arranged where clinically indicated).	
Growth	Children with DS will undergo monitoring of height and weight (plotted on a UK DS-specific growth chart) on an annual basis.		
Haematology	All children with DS will have a blood film assessment in the neonatal period to exclude related blood disorders.	N/A	
Gastrointestinal	Assessment (and investigation as required) of common gastrointestinal problems, such as constipation, feeding difficulties and coeliac disease, must take place during each regular medical review.		
Spinal	Assessment (and investigation as required) of developing disorders of the cervical spine must take place during each regular medical review.		

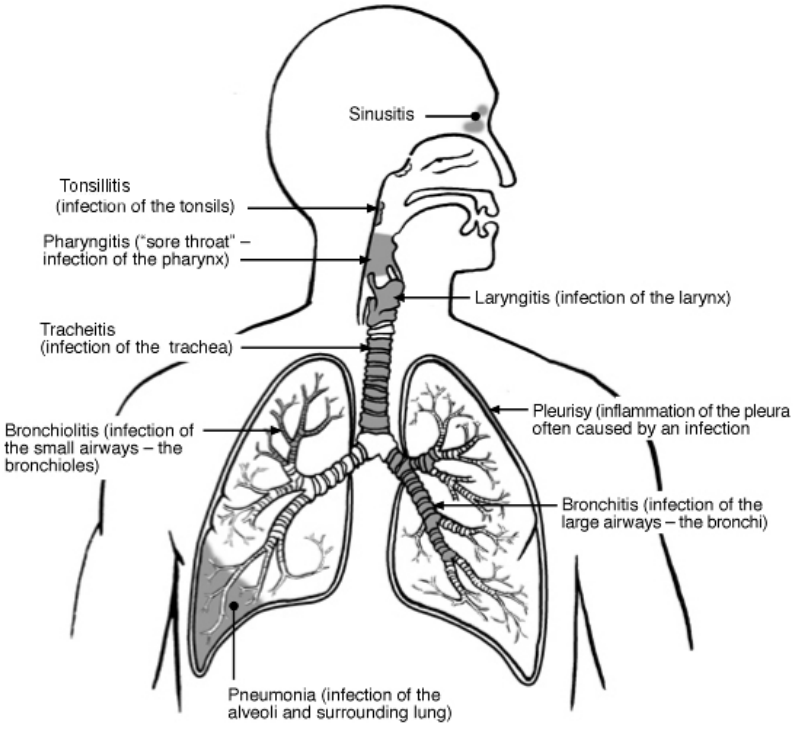
1.3 RESPIRATORY TRACT INFECTIONS

1.3.1 Overview

RTIs are infections of the respiratory system which can occur at any point along the respiratory tract (12). They can be split into upper respiratory tract infections (URTIs), and lower respiratory tract infections (LRTIs). URTIs include; rhinitis (common cold), sinusitis, otitis media, tonsillitis, pharyngitis, tracheitis and laryngitis; and LRTIs include bronchitis, bronchiolitis and pneumonia. These can be bacterial, viral or fungal in pathogenic origin. This is illustrated in **Figure 1** below (13).

Figure 1. Respiratory tract infections.

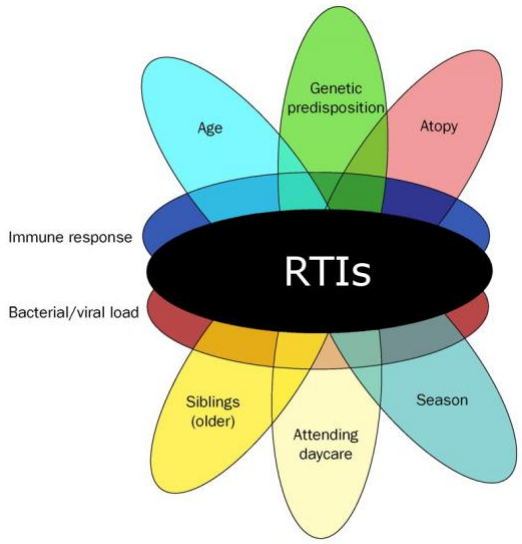
Adapted with permission from Patient.info (13)



There are numerous risk factors for RTIs as illustrated in **Figure 2**. These include; young age, environmental tobacco smoke, home-dampness, attending day-care centres, atopy, genetic predisposition, seasonality and exposure to others with RTIs (such as having siblings) (14).

Figure 2. Risk factors for RTIs.

Adapted with permission from The Lancet (15).



Most URTIs are viral in origin and are commonly due to *Rhinoviruses*, *Coronaviruses*, *Parainfluenza* viruses, Respiratory Syncytial Virus (RSV), *Adenoviruses* and *Influenza* viruses. In a US study, the annual isolation rates per 1000 person-years was 113.2 for *Rhinoviruses*, 53.8 for *Parainfluenza* viruses, 55.7 for RSV, 33.4 for *Adenoviruses* and between 16.7 and 3.7 across different *Influenza* sub-types (16). URTIs which are commonly non-viral include epiglottitis, laryngotracheitis and pharyngitis; these are commonly caused by bacteria such as *Haemophilus influenzae* type b., *Streptococcus pyogenes* or *Streptococcus pneumoniae*. In contrast, the aetiology of LRTIs is more mixed with a study of hospitalised children noting a bacterial (25%), viral (25%) or mixed (20%) cause for RTIs (17). Incidence of *Haemophilus influenza* type b. ranges from 0.02 to 0.74 per 100,000 in children 0-19, and for *Streptococcus pyogenes* the range is from 0.5-5 per 100,000 across the same age group (18, 19). Incidence of *Streptococcus pneumoniae* infection per 100,000 ranges from 59.7 per 100,000 for neonates to 0.8 for children aged 10-14 (20). With the higher relative incidences of viral relative to bacterial pathogens observed, continued high rates of antibiotic prescriptions for RTIs are therefore unwarranted (21).

According to a 2007 study utilising the General Practice Research database, the overall risk of complications is low following acute respiratory tract infections (22). In children 0-4 and 5-15, when antibiotics were not prescribed, the risk of pneumonia after URTI when was low at 10.74 and 4.45 per 10,000 cases respectively; the risk of quinsy after sore

throat was 1.57 and 5.99 per 10,000 respectively; and mastoiditis after otitis media was 1.33 and 2.39 per 10,000 respectively. The most common investigated complication was pneumonia after a chest infection with a risk of 125.92 and 127.31 per 10,000 in the respective age categories, when antibiotics were not prescribed (22).

Interventions to prevent RTIs

Interventions targeted at preventing RTIs are focused on reducing transmission of pathogens between individuals (e.g. infection control measures), stimulating immune response (e.g. immunostimulants, passive and active immunisation) and antibiotic prophylaxis for individuals.

Infection control measures such as hand and respiratory hygiene, cough etiquette, and personal protective equipment (e.g. gloves, apron and eye protection) are proven to reduce the transmission of RTIs. For example, in a 2006 systematic review, pooled results noted that hand washing could reduce the risk of RTIs by 16% (95% Confidence Interval (CI) 11–21%) (23). In another 2009 systematic review, physical measures were noted to be highly effective in reducing the risk of RTIs (24). These include handwashing more than ten times daily (Odds Ratio (OR) 0.45; 95% CI 0.36-0.57), masks (OR 0.32; 95% CI 0.25-0.40) and gloves (OR 0.43; 95% CI 0.29-0.65) (24).

Immunostimulants are drugs whose mechanism is primarily to stimulate the immune system. Although there are many different types, in general their mechanisms of action remain poorly understood (25). An example of an immunostimulant is pidotimod, which works by stimulating Tumour Necrosis Factor α, a signalling protein that regulates cells of the immune system (25). Another example is Isoprinosine, which stimulates the immune system by mimicking hormones of the thymus gland. There is published evidence on the use of immunostimulants for children at risk of RTIs. For example, in a 2012 Cochrane systematic review, non-specific immunostimulants were noted to reduce RTI incidence by 40% on average in susceptible children (i.e. children who are known and/or expected to suffer from at least three RTIs per winter season) (25). In a 2010 systematic review, a specific bacterial immunostimulant was noted to reduce the risk of recurrent RTIs (i.e. at least three RTIs per winter season) by 26.2% in at-risk children (26). However, safety profile concerns (i.e. risk of agranulocytosis) of immunostimulants have thus far precluded their use in routine clinical practice (25).

In contrast, vaccinations are of considerable importance in preventing RTIs. There are vaccines developed to prevent both bacterial (e.g. *Streptococcus pneumoniae*, *H. influenzae* type b, and more recently nontypeable *H. influenza*) and viral (e.g. *Influenza* or RSV) causes of RTIs. Vaccinations are active – they stimulate a host immune response leading to long-lasting protection. This compares to passive immunity, such as by providing IgG antibodies, which leads to immediate, but short-lived protection.

Numerous systematic reviews have been published on the effectiveness of these vaccines. For example, a 2012 systematic review noted the effectiveness of live attenuated influenza vaccines in reducing the risk of influenza-related illness in children by 83% (95% CI 69–91%) (27). Similar findings were observed in a 2014 systematic review of the pneumococcal conjugate vaccine (PCV), which reduced the risk of invasive pneumococcal disease by 88% (95% CI 83- 94%) (28).

Specific to RSV, palivizumab is a monoclonal antibody designed to provide RSV-specific passive immunity. There have been several published systematic reviews noting its effectiveness in reducing the risk of severe RSV infections in high-risk children by 55% (95% CI 38-72%) (29, 30). However, a 2011 systematic review demonstrated that, unlike other devices for generating immunity that are administered population-wide (such as PCV and influenza vaccines), palivizumab was not considered good value for money in the UK when used non-selectively. This review suggests its use should be restricted to at-risk subgroups such as those with chronic lung disease (CLD) and CHD (30).

Finally, antibiotic prophylaxis aims to achieve sufficient blood concentrations of antibacterial agents to prevent bacterial infection and their subsequent growth. Whilst its use is commonly seen in high-risk groups, a recent 2015 systematic review noted inconclusive evidence that antibiotic prophylaxis in certain high-risk groups can reduce the rates of pneumonia, disease exacerbations, hospital admissions and mortality (31).

Interventions to treat RTIs

Interventions targeted at treating RTIs are predominantly focused on antivirals and antibiotics that aim to reduce either illness duration and/or severity.

In the UK, the National Institute for Health and Care Excellence (NICE) produces clinical practice guidelines (CPGs) on the use of such interventions. These are developed through an extensive review of the literature and where evidence is lacking, by consensus

methodology (32). In 2008, a NICE CPG on antibiotics to treat upper and lower RTIs in children was produced. It recommended that antibiotics should be prescribed in children who are; (a) unwell, (b) have signs/symptoms suggestive of LRTIs or RTI-related complications such as mastoiditis or (c) at high risk of RTI-related complications (e.g. children with CHD) (33). This was updated in 2014 with the same recommendations in place (33).

For antivirals, a NICE CPG, produced in 2009 and updated in 2014, recommends that antivirals should be prescribed in children at high risk of RTI-related complications within 48 hours of onset of an influenza-like illness (34).

1.3.2 Antimicrobial Resistance

The increasing prevalence of antimicrobial resistance is a global problem. With a diminishing number of new antimicrobials available to use, antimicrobial resistance is now widely recognised as a major public health threat (35).

In the UK, despite the Chief Medical Officer's 2011 report and NICE CPGs advocating antimicrobial stewardship, recommendations are often not followed. This is reflected by a continuing high rate of RTI-related antibiotic prescribing, particularly in children (36).

This is despite evidence noting the marginal benefit of prescribing antibiotics for RTIs to children in primary care (37). For example, in a large retrospective cohort study using CPRD, it was estimated that to prevent one case of pneumonia, 4,400 episodes of URTIs in primary care would have to be treated with antibiotics (38).

The reasons for these high rates of antimicrobial prescribing are explored in several systematic reviews. For example, a 2011 systematic review of GP views determined uncertainty and previous experience of RTI management significantly influenced the decision to prescribe (39). Similar findings were seen in a 2013 systematic review exploring parental, physician and healthcare provider perceptions of factors influencing antibiotic prescribing decision making (40). More recently, in a 2015 systematic review of parents' and clinicians' views, prescribing using a "just-in-case" approach was common, even when neither group believed that antibiotics were clinically indicated (41, 42).

When faced with at-risk children with recurrent RTIs such as children with co-morbidities, antibiotic stewardship is arguably even more challenging (36).

1.4 RESPIRATORY TRACT INFECTIONS IN DOWN'S SYNDROME

The relationship between DS and RTIs is complex. Whilst structural variations of the respiratory, cardiovascular and gastrointestinal system may play a role in making them more susceptible to recurrent RTIs, immune system immaturity in children with DS may also contribute to different responses to treatments, such as antibiotics, when compared to children without DS (43). In the remainder of the chapter, what is known about the factors that influence the risk of RTIs in children with DS, epidemiology of RTIs in children with DS, and prevention and treatment options for RTIs in children with DS are discussed.

1.4.1 Impact of anatomical variation, immune system immaturity and co-morbidities on risk of RTIs

Respiratory system

The upper airway is often narrower in children with DS compared to controls without DS. This may result from a range of phenotypic variations, such as midfacial hypoplasia, that may cause a child with DS to have recurrent RTIs even in the presence of normal sized tonsils and adenoids (similar to a child without DS with enlarged tonsils and adenoids) (43). Other associated phenotypic features or associated conditions include macroglossia, midface hypoplasia, choanal stenosis, narrow nasopharynx, enlarged tonsils and adenoids, lingual tonsils and shortening of the palate (44).

Congenital anomalies such as tracheal bronchus are often common in DS; this is an aberrant or accessory bronchus arising from the trachea with an incidence of between 2 to 5%, which is often associated with recurrent right upper lobe pneumonia (43, 45).

A unique pattern of pathological and histological abnormalities has been demonstrated in children with DS. This includes a double capillary network, porous appearance and enlargement of the alveolar ducts and alveoli macroscopically, and reduced numbers of alveoli and acinar microscopic complexity (43). The effect of these abnormalities on lung function has not been clearly established.

In addition to the general porosity of the lungs, DS has been associated with subpleural cysts. However, these are often not recognised since they are not normally apparent on a plain chest radiograph and are generally thought to have limited or no clinical significance (46).

Laryngomalacia, namely a soft and immature laryngeal cartilage, is the commonest cause of airway obstruction in children with DS under the age of two years (43, 47) with a prevalence of 5-10% (48). Laryngomalacia, together with tracheomalacia, are common in DS due to a combination of hypotonia, gastroesophageal reflux disease and lack of coordination, and may first be recognised after presentation with stridor (49).

In addition, due to the smaller trachea seen in children with DS, there is an increased incidence of subglottic stenosis and a corresponding increased susceptibility to intubation trauma (43, 47). Finally, children with DS have been noted to have increased mucus secretions and reduced ciliary beat frequency when compared with controls without DS (43, 47).

Immune system

Variations in immunological parameters in children with DS have been well described, with both the increased severity and frequency of RTIs postulated to be partially due to immune system immaturity. These include reduced T and B cell subpopulations, decreased neutrophil chemotaxis, thymic abnormalities, and altered of levels of immunoglobulin sub-classes (50-53).

T cells are white blood cells that are involved in regulating and signalling in the immune system, as well as killing infected cells. For children with DS, T cells are particularly reduced in the first two years of life relative to children without DS (54). A number of other differences have been observed, including significantly higher numbers of IFN-gamma producing $CD4^+$ T cells (involved in regulation) and $CD8^+$ T-cells (involved in killing infected or damaged cells) (55). The thymus gland, the site of the maturation of T cells, is typically smaller and of an abnormal shape relative to children without DS, and thymocytes, the cells of the thymus, have been found to have altered receptor expression which could affect functionality (52).

B cells are white blood cells that secrete antibodies or immunoglobulins. In children with DS they do not undergo the typical rapid expansion in numbers of infancy that occurs in children without DS, with one study finding that 61% of observed B cell numbers in children with DS were in the 5^{th} percentile relative to the general population (54). It has been hypothesised that the reduced numbers of B cells occurs primarily due to the reduction in T helper cells, rather than due to additional factors (56).

There are inconsistent results regarding immunoglobulin levels in children with DS, with some studies reporting that levels of immunoglobulins such as IgA, IgG and IgM in children with DS are not significantly different from children without DS, and other studies reporting that IgA, IgD and IgG levels are elevated (57, 58).

Neutrophils, white blood cells that can ingest and kill foreign microbes, are reportedly affected with a reduced level of overall functioning (59), reduced levels of chemotaxis (directed movement around the body), increased levels of chemokinesis (random movement) (60), and altered oxidative metabolism (61).

Additionally, it has been suggested that there is accelerated progression to senescence in the immune systems of adults and children with DS, given that many of the haematological parameters found in DS are also observed in ageing (62).

All of these abnormalities are thought to be linked to differing frequency and severity of infections in children with DS. In a recent study comparing respiratory infections and corresponding immune parameters in children with DS and their siblings, children with DS were noted to have a significantly higher frequency of LRTIs compared to their siblings alongside observed immune parameter differences (63).

Cardiac system

CHDs are present in just over 40% of children with DS. Airway and respiratory function may be affected by CHD surgical complications. For example, as part of surgical corrections of Atrio Ventricular Septal Defects (AVSDs), a CHD commonly seen in children with DS, surgical trauma may lead to chylothorax, injury to the recurrent laryngeal nerve, diaphragmatic paralysis, and subglottic stenosis (64). These complications may result in less compliant lungs (restrictive defects) which reduces oxygen intake and leads to hypoxaemia. Cardiac problems have been linked to worsening of other symptoms, such as obstructive sleep apnoea, in children with DS (65).

Finally, children with DS are more susceptible to pulmonary vascular problems compared to children from the general population with CHD (66, 67).

Cardiac problems, especially haemodynamically significant AVSDs, are associated with increased hospitalisations and chest infection rates due to left to right shunting leading to pulmonary oedema and subsequently increasing the risk of infections (68). Furthermore, in the presence of pulmonary oedema, a mild infection may result in

tachypnoea in contrast to a child with DS unaffected by CHD. Physiologically, this effect may be more evident in younger children with immature immune systems and narrower airways.

A large Australian population-level study, including 1282 children and 871 adults with DS, compared the risk of cardiovascular events in hospitalised patients with and without DS. Significantly higher rates of CHD were detected in children with DS, at 35.2%, compared to 0.8% in those without DS (69). Rates of other cardiovascular diseases were also examined, with 41.7% of children with DS possessing at least one cardiovascular risk factor (such as high blood pressure, diabetes, sleep apnoea) compared to 5.6% of those without DS; additionally 4.7% of children with DS had pulmonary hypertension, 0.8% a cardiac arrhythmia, and 1.4% high blood pressure specifically (69).

Gastrointestinal system

Congenital defects of the gastrointestinal system in DS include oesophageal atresia, duodenal atresia, ano-rectal malformations and Hirschsprung's disease. Of these, surgical repair of oesophageal atresia may lead to surgical complications that impact upon pulmonary function, such as post-surgery bronchitis that occurs with an incidence of 0.5-0.9% (70).

Children with DS may have swallowing abnormalities, oesophageal dysmotility or gastro-oesophageal reflux. With a combined prevalence of 75% in these three conditions, any of which giving rise to aspiration in children with DS, the inhalation of foreign material is common – particularly the inhalation of liquids into the lower airway (49).

This may lead to chronic recurrent aspiration, causing children with DS to present with wheeze, chronic cough, recurrent pneumonia, pulmonary scarring or impaired lung function (49). It is therefore a diagnosis to be considered when a child with DS encounters significant or recurrent respiratory problems.

Others

The intrinsic structural problems described above may be exacerbated by hypotonia and obesity, which affect the size and shape of the pharyngeal airway. This consequently increases the risk of aspiration (43, 47). As a higher proportion of children with DS are overweight when compared with the general population, obesity is another important factor to consider (43).

1.4.2 What is known on the epidemiology of RTIs in Down's Syndrome

To date, there has been no epidemiological study of RTIs in children with DS in the UK. However, there have been several studies abroad on RTI-related secondary healthcare utilisation in children with DS.

For example, in an Australian study of 3,786 hospitalisations in 405 children with DS, it was noted that almost one third of admissions were for respiratory tract infections, affecting 52.6% of all children with DS hospitalised for any reason, with an admission rate of 11.4 per 1,000 person-years at risk (71). When compared to published admission rates for the paediatric population in Western Australia, significant differences were noted - hospitalisations with respiratory system related diagnoses in children with DS were 17.9 times higher.

In a USA study of hospitalisations in 217 children with DS, 64.9% of admissions were due to RTIs such as pneumonia, acute bronchitis or bronchiolitis (72). Furthermore, in children with CHD, higher rates of RTI-related hospitalisations were observed (72).

RSV is the most common cause of childhood LRTI. It is also a major cause of hospital admissions in children with co-morbidities, likely due to both the variations in innate and adaptive immune systems and differences in respiratory function in terms of anatomical, histological and physiological factors (73, 74). In a population-based cohort study investigating RSV related hospitalisations, children with DS were noted to have a 5.5-fold (95% CI 2.5-12.3) increased risk of hospitalisation due to RSV LRTIs in their first two years of life in the absence of other co-morbidities, such as CHD (75).

A prospective multicentre Spanish study published in 2017 compared hospitalisation rates due to RSV infection and the corresponding severity of disease. A total of 93 infants with DS and 68 controls matched by sex and age were followed up to one year and during a complete RSV season (76). It was found that respiratory-related hospitalisations were significantly higher in the DS cohort, at rates of 44.1% compared to 7.7%. RSV-related hospitalisations were also significantly higher in children with DS, at rates of 9.7% compared to 1.5% (76).

With a focus on hospitalisations, the epidemiology of RTIs in DS in the UK has not been studied thoroughly nor compared with children without DS. Therefore, uncertainty about the burden of RTIs to children with DS, their families and the NHS in both primary and

secondary care remains. It is also unclear whether the incidence of RTIs are higher in children with DS, or whether they have a larger proportion of serious complications (i.e. hospitalisations) from RTIs compared to children without DS.

1.4.3 Prevention and Treatment: Comparison with the general population

In contrast to the numerous systematic reviews on interventions to prevent RTIs in children from the general population, there appears to be little published evidence specifically on children with DS. Moreover, in CPGs produced by NICE on interventions to treat RTIs, there is little by way of evidence based recommendations for at-risk children.

Since most research on such infections has excluded children with DS, clinicians are therefore unsure how best to prevent and treat them.

For example, in a 2006 systematic review and meta-analysis of all quantitative studies on antibiotics for RTIs, it was noted that there was no published evidence on the use of antibiotics for children with DS, despite the evident clinical need for it (77).

This is further compounded by the uncertainty of extrapolating effects of treatments from published studies in other at-risk children with a single co-morbidity to children with DS. Children with DS are known to have multiple anatomical and immunological variations and therefore may respond differently to interventions, such as vaccines and antibiotics (43).

Additionally, there have been several published clinical opinions recommending an aggressive antimicrobial prescribing approach, such as prophylactic antibiotics over the winter months, stronger antibiotics (e.g. Co-Amoxiclav rather than Amoxicillin), and rescue packs of antibiotics to be kept at home (43, 78). Whilst this may be indicative of how the effects of antibiotics are different in children with DS in clinical practice, this has not been substantiated by research to date (43, 78).

Similarly, interventions to prevent RTIs, such as vaccines, are known to produce different results in children with DS. For example, poor responses to vaccines have been noted in children with DS, such as to influenza A and Hepatitis B vaccines (79, 80). These have largely been attributed to reduced immunoglobulin A and G levels (50-52). In recent years, it has been recommended that children with DS undergo regular serological testing

to assess vaccine responses (*e.g.*, antibody functionality) and repeat vaccinations accordingly (81).

Whilst RSV is a prominent cause of severe RTIs in children with DS, studies of Palivizumab have thus far been restricted to healthy and other at-risk children (e.g. CHD) with limited evidence of its use in children with DS (30).

A need for research to improve the evidence base for prevention and treatments for RTIs in children with DS therefore remains. This forms the basis of the subsequent chapters of this thesis.

Chapter 2: Interventions to Prevent or Treat RTIs in Down's Syndrome: A Systematic Review

ABSTRACT

Background

Despite a high frequency and severity of RTIs observed in children with DS, an absence of evidence based recommendations for optimal management of RTIs is noted. It has been presumed that this is due to limited research into preventative and therapeutic interventions for RTIs in this at-risk group, but this has not been formally assessed in a systematic review of the literature.

Methods

PubMed, Embase.com, Cochrane Library and CINAHL were searched from the time of inception until February 2015 using a broad strategy combining the terms "Down's syndrome", "Respiratory Tract Infections", and relevant synonyms. The initial search was updated in October 2017. Studies were considered eligible if they were randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs), controlled before-after studies (CBAs), or cohort studies assessing any intervention to prevent or treat RTIs in individuals with DS irrespective of age.

The bibliographies of eligible included studies were then hand searched for other potentially relevant studies. ClinicalTrials.gov and the World Health Organization ICTRP were searched for ongoing studies.

Data extraction was completed using a customised data extraction sheet and relevant Cochrane 'Risk of Bias' tools were utilised to assess the risk of bias within eligible studies. Studies with a critical risk of bias were subsequently excluded from the analyses.

Results

A total of 17,731 records were identified from which seven studies fulfilled the eligibility criteria. All seven studies focused on preventative strategies for RTIs in

children with DS. No RCTs, non-RCTs, CBAs or cohort studies on therapeutic interventions were identified.

One RCT of moderate risk of bias compared prophylactic zinc therapy with placebo. Outcome data were reported for 50 (78%) children who presented with extreme symptoms: no benefit of prophylactic zinc therapy was found on URTI episodes, doctor visits, antibiotic use, and school absence.

One non-RCT with serious risk of bias included 26 children and compared prophylactic treatment with pidotimod, an immunostimulant, with no treatment. Treatment with pidotimod was associated with fewer URTI recurrences compared with no treatment (1.43 vs. 3.82 parent-reported episodes).

A prospective cohort study with serious risk of bias compared a cohort of 532 Canadian children with DS treated prophylactically with palivizumab with a cohort of 233 Dutch children with DS who did not receive this intervention. The cohort treated with palivizumab was found to have fewer RSV-related hospitalisation (23 untreated, 8 treated) but the same number of overall RTI-related hospitalisations (73 untreated, 74 treated) in the first two years of life.

The four further studies, one on a school-based infection control programme, one on prophylactic zinc therapy, and two on prophylactic palivizumab therapy, were subsequently excluded due to critical risk of bias.

Discussion

The evidence base for the management of RTIs in people with DS is incomplete. Methodologically rigorous studies are warranted to guide clinicians in how best to prevent and treat RTIs in both children and adults with DS.

2.1 CHAPTER OUTLINE

In this chapter, I review the literature on preventative and therapeutic interventions for RTIs in adults and children with DS. This work was published in *Paediatric Infectious Diseases Journal* in 2016 (82).

2.2 BACKGROUND

One in three of all hospitalisations of children with DS below the age of three years are due to RTIs (71, 72). When admitted for RTIs, children with DS spend two to three times more time in hospital, on average, than those without DS (43, 47). In children with DS up to the age of 18 years, pneumonia and other RTIs are the leading cause of death (83).

Despite this, key clinical trials of preventative and therapeutic interventions for RTIs have excluded adults and children with DS. The absence of evidence based recommendations for the management of RTIs in DS, and the diversity of expert based prescribing strategies, paves the way for mixed patient information and variation in the management of RTIs.

In this chapter, I provide a thorough overview of the evidence base for the management of RTIs in this at risk-group by systematically reviewing the literature on the effectiveness of interventions to prevent or treat RTIs in adults and children with DS.

2.3 AIMS & OBJECTIVES

2.3.1 Aims

To undertake a systematic review of the literature on the effectiveness of preventative and therapeutic interventions for RTIs in adults and children with DS.

2.3.2 Objectives

1) To design and perform systematic searches to identify original studies on preventative and therapeutic interventions for RTIs in adults and children with DS;
2) To extract data from studies meeting inclusion criteria using a purpose-designed data extraction tool；
3) To synthesise findings by study design；
4) To perform a meta-analysis of data by study design (where able);
5) To critically appraise quality of evidence.

2.4 METHODS

2.4.1 Data sources and searches

The effectiveness of preventative and therapeutic interventions for RTIs in children with DS were systematically reviewed using a broad search strategy combining the terms "Down's syndrome", "Respiratory Tract Infections", and relevant synonyms (82). DS-related co morbidities such as Sleep-Disordered Breathing, CLD and CHD were also included in the syntax. This broad strategy ensured that all studies on management of RTIs in children with DS with and without these co-morbidities were captured (e.g. antibiotic prophylaxis in CHD and CLD).

The following electronic databases were searched for published, unpublished and ongoing studies: PubMed, Embase, Cochrane Library, CINAHL. Trial registries (WHO ICTRP and ClinicalTrials.gov) were also searched.

To identify any additional relevant studies, reference lists of all included articles were screened together with targeted searches of the grey literature using Google Scholar, SIGLE, and official research websites (NIHR, Wellcome Trust, NIH, NHMRC, Medical Research Council, Down Syndrome Association, and National Down Syndrome Association). Additionally, I liaised with research networks and charities, such as Trisomy 21 Research Society, Down Syndrome International, Down's Heart Group, Mosaic Down's Group, and Down's Syndrome Medical Interest Group (84-87).

All searches were conducted from the time of inception of that particular information source, up until February 2015.

An update of the initial search was conducted in October 2017, searching the same electronic databases (PubMed, Embase, Cochrane Library, CINAHL) and trial registries (WHO ICTRP and ClinicalTrials.gov) for published, unpublished and ongoing studies.

2.4.2 Study selection

The inclusion criteria for considering studies for this review consisted of:

2.4.2.1 Types of studies

Randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs), controlled before after studies (CBAs) and cohort studies. Non-RCTs were defined as

studies that involved allocation to different interventions using methods that are not random.

2.4.2.2 Population

All children and adults with DS irrespective of age.

2.4.2.3 Intervention

Any intervention (medical and surgical) for the prevention or treatment of RTIs. This included active observation and supportive care.

2.4.2.4 Comparison

Any comparator group (or none) was considered for inclusion.

2.4.2.5 Outcomes

Outcome measures were not pre-specified. This was chosen as articles were expected to cover a broad range of interventions and therefore encompass a broad range of outcome measures.

I excluded studies not published in English (unless a translation was available). No limits on the publication year or status restrictions were set.

2.4.3 Data extraction

I screened titles and abstracts retrieved from the database searches along with the reference lists of the included studies and relevant systematic reviews, alongside a second independent reviewer (Kate Reed; KR). We both independently reviewed the full text of potentially relevant studies against the pre-defined eligibility criteria. A third review author (Roderick Venekamp; RV) reviewed any discrepancies and the differences were resolved by consensus.

Data extraction was performed by myself and was independently checked by KR and RV. Quality assessment of included studies was performed by myself and RV independently.

In the 2017 update, screening of titles and abstracts was done by myself and a second independent reviewer (Kunjshri Kumari Singh; KKS). A third review author (Emma Alexander; EA) reviewed any discrepancies. Data extraction was performed by myself and checked by EA. Quality assessment of included studies was performed by myself and EA independently.

For data collection, I used a standardised data extraction form including information on study characteristics, setting, design, randomisation, inclusion and exclusion criteria, data-analysis methods, interventions, outcomes, and results.

2.4.4 Assessment of heterogeneity

I assessed clinical heterogeneity across the included studies by reviewing differences in populations, interventions, and outcomes measured. In view of the marked differences in the interventions and study types used in the individual studies, I did not perform a meta-analysis.

2.4.5 Assessment of Risk of Bias

I assessed risk of bias in RCTs using the 'Risk of Bias' tool described in Chapter 8 of the Cochrane Handbook of Systematic Reviews and Interventions (88). Six components were classified as either high, moderate, low or unclear risk of bias: (i) Random sequence generation, (ii) Concealment of allocation, (iii) Blinding, (iv) Incomplete outcome data, (v) Selective outcome reporting and (vi) Additional sources of bias. Components (i) and (ii) accounted for sequence bias, (iii) encompassed performance and detection bias, (iv) attrition bias, and finally (v) covered reporting bias. Any study with a high risk of bias in multiple domains was classified as having a High Overall Risk of Bias and was excluded from the data synthesis.

For non-randomised studies, I used the Cochrane Risk Of Bias assessment tool for non-randomized studies of interventions (ACROBAT-NRSI) and looked at bias due to (i) Confounding, (ii) Participant selection, (iii) Intervention measurement, (iv) Departures from intended interventions (v) Missing Data, (vi) Outcome measurements and (vii) Reporting of study results (89). These were classified as critical, serious, moderate, low or unclear risk of bias. Any study with a critical risk of bias in any domain was judged to have a critical Overall Risk of Bias, and thus was excluded from the data synthesis.

2.5 RESULTS

2.5.1 Study selection

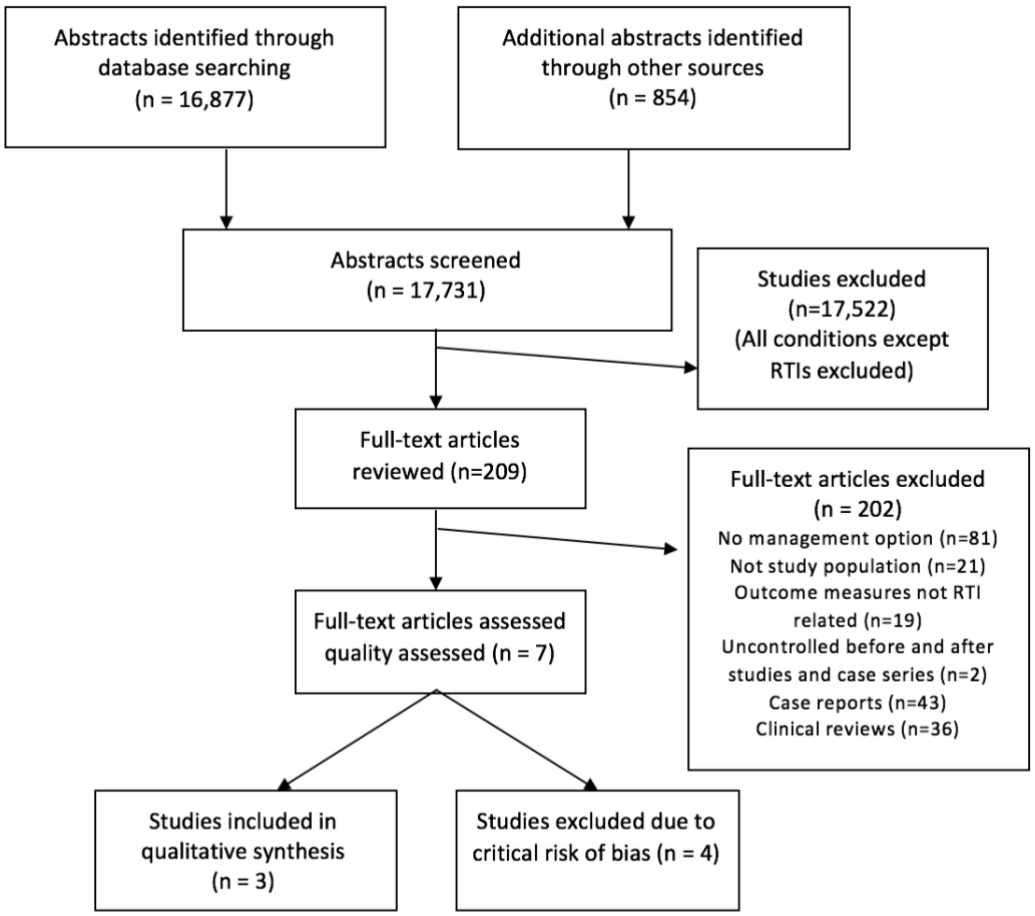
Database searches in 2015 identified 13,575 articles. After screening of titles and abstracts, 157 potentially relevant published articles were identified. This substantial drop was due to a significant number of studies identified with no interventions

described. After reviewing the full texts, five published studies were considered eligible for inclusion (90-94).

The 2017 update identified a further 3,302 abstracts from database searching. After initial title and abstract screening, 3,250 abstracts were excluded. A total of 52 full text articles were reviewed. Of these, 50 were excluded. This left a further two studies eligible for inclusion.

Figure 3 reflects the number of records identified, included, and excluded with reasons. The number of records incorporates results from both the 2015 review and the 2017 update.

Figure 3. Systematic literature searches for inclusion in review.



2.5.2 Description of included studies

Table 2 shows the main characteristics of the seven eligible published studies (five from the 2015 review and two from the 2017 update). All seven studies evaluated preventative

(i.e. prophylactic) interventions against RTI in children with DS; none focused on therapeutic interventions. Three studies focused on palivizumab, a human monoclonal antibody. For two of these studies, the primary outcome was RTI-related hospitalisation (76, 90). The third study was a post-marketing observational study assessing the effectiveness of palivizumab in preventing LRTIs caused by RSV in children who had DS or were otherwise immunocompromised (95).

Two studies assessed the effectiveness of prophylactic treatment with an oral zinc supplement (92, 94) on number of URTIs. One study focused on the effectiveness of pidotimod, an immunostimulant, on number of URTIs (91). Finally, one assessed the effectiveness of a school-based infection-control programme on rates of RTIs (93).

All studies exclusively studied individuals with DS under the age of 19 years. The seven studies varied in terms of design (one RCT, one non-RCT, three cohort studies, and two CBA studies), age range of included participants, and duration of follow-up. Two studies were conducted in Italy (91, 94), one in Canada (92), one in Canada and the Netherlands (90), one in the USA (93), one in Japan (95), and one in Spain (76).

Table 2. Characteristic of studies included in review.

Study	Study Design	Population Characteristics	Intervention	Control	Outcome Measures	Risk of bias
Lockitch 1989 (92)	RCT	64 children with DS (1-19yr)	Zinc Sulphate supplements 25 mg/day for 1–9 yrs and 50 mg/day for older children for 6	Placebo (identical lactose pills)	Number of children with URTI (days and episodes), doctor visits, antibiotic use, and school absence	Moderate
Yi 2014 (90)	Prospective cohort study	765 children with DS (2-18m)	Palivizumab for 9 months	No treatment	RSV-related hospitalisation Respiratory infection-related hospitalisation	Serious
La Mantia 1999 (91)	Non-RCT	26 children with DS who had at least 6 URTIs in preceding 6 months (3-13y)	Pidotimod 400 mg/day for 3 months	No treatment	Number of URTI episodes ('relapses') and days with fever	Serious
Sanchéz-Luna 2016 (76)	Prospective cohort study	97 children with DS and 70 without DS (0-1y)	Between 1 and 6 doses of palivizumab	No treatment	Hospitalisations due to acute respiratory tract infections and RSV	Critical
Kashiwagi 2017 (95)	Prospective cohort study	138 infants with DS and 167 immunocompromised infants (0-2y)	Palivizumab 15mg/kg once per month during RSV season	n/a	RSV infections and hospitalisations	Critical
Krilov 1996 (93)	CBA study	71 children with DS (0–5y)	Infection Control Programme over 1 year	n/a	Respiratory illness rate, doctor visits, antibiotic use, and school absence	Critical
Licastro 1994 (94)	CBA study	21 children with DS (7–15y)	Zinc Sulphate supplements 1 mg/kg/day for 4 months	n/a	Infection rate (mainly URTI) and days with fever	Critical

2.5.3 Risk of bias across studies

Table 3 shows the Risk of Bias for Lockitch's RCT (1989) using the Cochrane Risk of Bias tool (92). The overall risk of bias was moderate with incomplete outcome data in 14/64 children (22%) and insufficient information on co-interventions, allocation and analyses (e.g. whether intention-to-treat analyses were undertaken). Reasons given for failure to

complete the study included major illness, moving to other cities, and intolerance of the supplements.

Table 3. Risk of bias assessment for Lockitch's RCT (1989) using the Cochrane Risk of Bias tool.

Domain	Judgement
Random sequence generation (selection bias)	Unclear risk
Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Low risk
Blinding of outcome assessment (detection bias)	Low risk
Incomplete outcome data addressed (attrition bias)	High risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk
Overall	**Moderate risk**

Table 4 shows the Risk of Bias for the non-randomised studies using the ACROBAT-NSRI tool (89).

Table 4. Risk of bias assessment for non-randomised studies using the ACROBAT-NSRI.

Domain	Yi 2014	La Mantia 1999	Sanchéz-Luna 2016	Kashiwagi 2017	Krilov 1996	Licastro 1994
Bias due to confounding	Moderate	Serious	Serious	Critical	Serious	Moderate
Bias in selection of participants into the study	Serious	Moderate	Critical	Moderate	Critical	Serious
Bias in measurement of interventions	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Bias due to departures from intended interventions	Moderate	Moderate	Moderate	Moderate	No Information	Moderate
Bias due to missing data	Moderate	Low	Moderate	Moderate	Moderate	Critical
Bias in measurement of outcomes	Moderate	Serious	Low	Critical	Moderate	Serious
Bias in selection of the reported result	Low	Low	Moderate	Serious	Moderate	Low

Overall	**Serious**	**Serious**	**Critical**	**Critical**	**Critical**	**Critical**

The overall risk of bias for Yi *et al.* (90) was serious with the absence of a true internal comparator (i.e. control population with a similar demographic profile in the same geographic area). This made it impossible to assess whether the differences in RSV-related hospitalisations were due to palivizumab or due to unmeasured differences in baseline risk and exposure to RSV in different countries (e.g. differences in participant characteristics, healthcare system or seasonality).

The overall risk of bias for La Mantia *et al.* (91) was judged as serious due to subjective outcome measurement (e.g. parent reported URTI episodes), imbalanced baseline characteristics between the intervention and control groups and no adjustments for confounding.

As per guidance from Cochrane, I excluded four studies with a critical risk of bias from the subsequent narrative.

For the two CBA studies by Licastro *et al.* (94) and Krilov *et al.* (93), the risk of bias was critical. In the former, this was due to the large amount of missing data whilst in the latter there was no detailed information on how the school was selected for inclusion in the study (i.e. non-random selection of the school for the study).

In the prospective cohort study Kashiwagi *et al.* the risk of bias was also critical (95). Although the study aimed to assess the effectiveness of palivizumab in RSV infections and hospitalisations, there was no control group, and thus it was not possible to judge the efficacy of the treatment. The study only reported the percentage of participants who received palivizumab and then later went on to have RSV infections or hospitalisations, with no statistical analysis.

The overall risk of bias for Sanchéz-Luna *et al*. (76) was judged as critical due to selection bias. The study was observational only and there was a lack of information as to why a sub-sample of participants were prescribed palivizumab as RSV prophylaxis. It was stated that there were few differences at baseline between the groups that received prophylaxis, but these were not adjusted for, and residual confounding due to selection (by indication) cannot be excluded.

2.5.4 Results from included studies

2.5.4.1 Zinc

Lockitch *et al.* randomised 64 children with DS to prophylactic oral zinc therapy for six months or placebo. However, they reported only on the 50 children (23 treated with zinc and 27 with placebo) who had 'extreme' numbers of days/episodes of illness (i.e. the number of days or episodes of illness exceeded the 90th percentile value for siblings and age-matched unrelated children). In this subset of children with DS, during six months of treatment, no significant differences in terms of URTI episodes, doctor consultations, and antibiotic use were found between those receiving zinc and children receiving placebo (92).

2.5.4.2 Pidotimod

In a non-RCT, La Mantia *et al.* followed 26 children with DS who had experienced at least six URTIs in the preceding six months; they received either the immunostimulant pidotimod for three months (14 children) or no treatment (12 children). While on pidotimod, children with DS had fewer parent-reported URTI recurrences (mean 2.7, standard deviation (S.D.) 1.1 vs mean 6.8, S.D. 1.3) and days with fever (mean 4.5, S.D. 3.5 vs mean 16.9, S.D. 6.7) compared to those not receiving this treatment (91).

2.5.4.3 Palivizumab

In a prospective cohort study, Yi *et al.* followed a cohort of 532 Canadian children with DS treated prophylactically with palivizumab for nine months and 233 Dutch children with DS who did not receive this monoclonal antibody. In the first two years of life, treatment with palivizumab resulted in a 3·6-fold reduction in the incidence rate ratio (adjusted incident rate ratio (IRR) 3.63; 95% CI 1.52- 8.67) of RSV-RTI hospitalisations. Palivizumab however did not reduce overall hospitalisations for RTI (adjusted IRR 1.11; 95% CI 0.80 to 1.55) (90).

2.5.5 Results from excluded studies

Given the minimal amount of data available in the field, the results from the excluded studies are presented, but should be interpreted with caution given the critical risk of bias for these studies.

2.5.5.1 Zinc

In the CBA study using oral zinc supplementation, Licastro *et al.*, 21 children with DS aged 7 to 15 were recruited. The number of RTI episodes in the past 12 months was assessed at baseline and a year after treatment cessation. The number of infective episodes significantly decreased after one year of follow up in male children (3.1±0.7 before, 1.6±0.9 after, $p<0.025$) with no significant difference for female children observed (94).

2.5.5.2 Infection control programme

The CBA study Krilov *et al.* investigated the efficacy of a school-based infection control programme on the number and type of infectious illnesses experienced by its sample of children with DS aged 6 weeks to 5 years, with 33 baseline responders and 38 intervention responders. At baseline it was reported that there were a median of 0.67 respiratory infections per child per month with a non-significant reduction to 0.42 per child per month in the intervention year ($p=0.07$) (93).

2.5.5.3 Palivizumab

The prospective cohort study Kashiwagi *et al.* aimed to assess the safety and effectiveness of monthly doses of palivizumab during the RSV season for the prevention of LRTIs caused by RSV in children with DS (n=138) or other immunocompromising conditions (n=167). Overall, 5 patients (1.7%) across both groups had an RSV infection during the study period, and 2 patients (0.7%) were hospitalised (95).

In another prospective cohort study, Sanchéz-Luna *et al.* followed a cohort of 161 infants for one year, 93 of whom had DS and 68 others without DS who were age- and sex-matched. Of those with DS, 33 received palivizumab as RSV prophylaxis. Hospitalisation rates for any acute RTI and due to RSV were recorded. The rate of hospitalisation for any acute RTI was 3.0% (1/33) in children with DS who received palivizumab versus 15.0% (9/60) in those without RSV prophylaxis. However, in a further logistic regression analysis, adjusted by DS status, prophylaxis against RSV was not a predictor of subsequent hospitalisation due to RSV infection (76).

2.6 DISCUSSION

2.6.1 Summary of findings

My systematic review of the literature identified one RCT, one non-RCT, three cohort studies, and CBA studies on the prevention of RTIs in individuals with DS.

Four assessed passive immunotherapies (three palivizumab, one pidotimod), two looked at prophylactic treatment with oral zinc supplements, and one at the effectiveness of a school-based infection-control programme. Due to a critical risk of bias, four studies were not included as part of the main results (zinc therapy, infection-control programme, and two palivizumab studies).

Pidotimod, an immunostimulant, and palivizumab, a human monoclonal antibody, showed some benefit in individuals with DS, on URTI episodes and RTI hospitalisations respectively, when used prophylactically for three and nine months. They therefore may have a role in preventing RTIs in individuals with DS.

Although the included RCT assessing zinc over six months showed no effect on URTI episodes, the excluded CBA study assessing the effects of zinc over four months showed a significant reduction in episodes. In view of the critical risk of bias in the latter, these results should be interpreted with caution.

2.6.2 Strengths and Weaknesses

I chose a very broad search strategy including DS-related co-morbidities such as CHD, to ensure a thorough and comprehensive search of all potential management options for RTIs in people with DS to inform clinical practice and future research. Whilst this search identified numerous studies (n=17,731 incorporating the 2017 update), the majority did not report on any interventions to prevent or treat RTIs.

Limitations of the review are likely to stem from restricting to studies published in English and publication bias. The latter is owing to anecdotal evidence that most studies on individuals with DS involve small samples, which may limit publication potential. Whilst one may argue that a rigorous approach to assessment of the risk of bias is unnecessary in the light of limited evidence in the field, it was important to clarify both the quality and quantity of evidence to assist in informing current clinical practice and future directions for research.

2.6.3 Comparison with previous research

In contrast to adults and children with DS, there is an abundance of high quality research into medical and surgical interventions for (recurrent) RTIs in the general population. With this high-level evidence, CPGs such as the NICE CPG [CG69] on prescribing antibiotics in RTIs in the general population have been developed (33). Similarly, numerous studies have highlighted the effectiveness of preventative measures for RTIs such as vaccination in the general population (33). However, how these recommendations can be translated to people with DS is unclear since their functional anatomy and immunity profile may both predispose them to RTIs differently and may make them respond differently to treatments.

2.6.4 Implications for practice

I found no randomised controlled trials, controlled before-after studies and cohort studies on therapeutic interventions for RTIs in children with DS, suggesting that there is no high-quality evidence to guide clinicians in managing children with DS.

From the prophylactic treatments identified, I found some evidence for the use of palivizumab in preventing RSV-RTIs. Due to the absence of a true internal comparator in one study (e.g. comparing treated vs. untreated populations between Netherlands and Canada with differing healthcare practices and seasonal patterns), the causal inferences of palivizumab on children with DS are limited.

Furthermore, whilst palivizumab was effective in reducing RSV related RTI hospitalisations, overall RTI-related hospitalisations were unaffected, except in one study that had a critical risk of bias where a reduction was observed. Currently, American Academy of Pediatrics guidance recommends palivizumab as prophylaxis in children with DS only when there are concurrent comorbidities (e.g. CHD, CLD, prematurity) (96).

Pidotimod shows encouraging results in preventing RTIs, however as with most immunostimulants it is currently only licensed for research purposes in several European countries and the USA, due to a lack of high quality evidence as to its efficacy and its side effect profile (97).

Finally, with a high quality RCT showing no significant effect of prophylactic zinc therapy in preventing RTIs, it is not recommended for clinical practice (92).

2.6.5 Implications for research

With no high quality, therapeutic intervention studies identified from this systematic review, clinicians are faced with little evidence to guide them in the treatment of RTIs in children with DS. A particularly relevant decision is that of prescribing antibiotics for RTIs where concerns about antimicrobial resistance exist. It is disappointing that, in the two years since the original review took place, no additional studies were identified that met the quality criteria for inclusion.

Whilst randomised controlled trials remain the gold standard in providing robust clinical and cost-effectiveness estimates, due to the fluctuating nature of RTIs, substantial numbers of children with DS would need to be recruited. Cohort studies utilising population wide electronic health records may therefore be a viable alternative.

This exemplifies the need for the subsequent phases of my thesis that focus on establishing RTI healthcare utilisation in primary and secondary care and the effectiveness of antibiotics in preventing hospitalisations in children with DS compared to children without DS using routinely collected EHRs.

Chapter 3: The CALIBER Database

3.1 CHAPTER OUTLINE

This chapter outlines the CALIBER database, including the general characteristics of its source datasets, the points to consider in analysing and interpreting findings from EHR research, and the process of identifying or "phenotyping" variables of interest in CALIBER.

3.2 INTRODUCTION

CALIBER (CArdiovascular disease research using LInked Bespoke studies and Electronic health Records) is a database of linked routinely collected electronic health records (EHR) from England (98), comprising data from primary care (Clinical Practice Research Datalink, CPRD) (98), hospital admissions (Hospital Episode Statistics, HES) (98, 99), the Myocardial Ischaemia National Audit Project (MINAP) (100) and the national death registry at the Office for National Statistics (ONS).

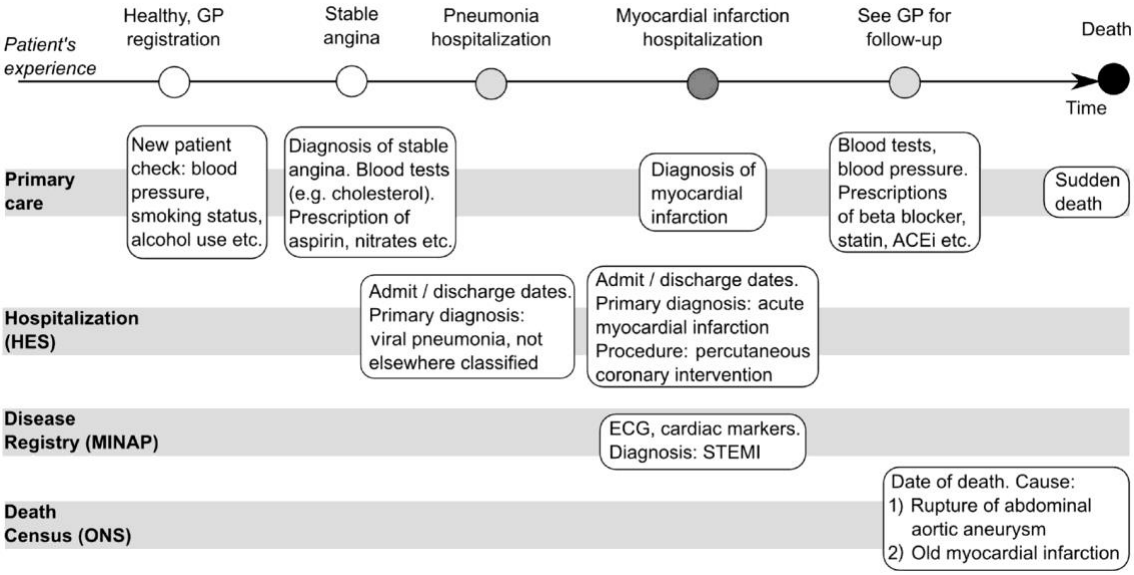
It is housed at the UCL Farr Institute of Health Informatics Research and made sharable and research ready by defining and curating with meta-data variables (categorical, continuous, event) on >300 risk factors, CVDs and non-cardiovascular comorbidities.

CALIBER also holds small-area indices of deprivation from ONS (Index Of Multiple Deprivation, IMD) linked by the patient's postcode (101). The IMD is a score calculated for each patient's neighbourhood based on social indices such as income, education, and employment.

The data sources complement each other in providing different types of information about a patient's medical history longitudinally (**Figure 4**) (102).

For example, CPRD provides information on primary care encounters, encompassing diagnoses, observations and prescriptions. HES complements this with its stored records on secondary care and hospitalisations, A&E attendances, and outpatient appointments. MINAP stores information on all patients suspected of suffering an ischaemic cardiac event. ONS provides information on deprivation using the IMD score, and on date and cause of death if applicable. Through all these sources, researchers can learn about progress of illness, healthcare utilisation, interventions received and mortality and morbidity outcomes.

Figure 4. How a patient's medical history may be recorded in the CALIBER data sources.



The CALIBER dataset is pseudo-anonymised with key identifiers removed; patients' and general practices' location can only be identified at a very crude level (one of 10 regions in England).

In the 2010 version of the CALIBER dataset (used for the subsequent chapters of this thesis), the entire cohort (100%) was linked via CPRD, HES, ONS and MINAP.

There are several advantages to using CALIBER over a general CPRD-HES linked dataset, with 100% data linkage between all four data sources being one of these (102). Novel methods of data linkage can be error-prone, whereas CALIBER has been tried and tested in many other studies (103-105). Another key reason is that CALIBER allows researchers to use preselected and validated codelists for conditions such as diabetes, which would have to be created from scratch if a researcher used CPRD alone.

3.3 SOURCE DATASETS

3.3.1 Primary care data: Clinical Practice Research Datalink (CPRD)

CPRD is an ongoing primary care database of anonymised medical records from general practitioners, with coverage of over 11.3 million patients from 674 practices in the UK (England, Wales, Scotland and Northern Ireland) (102). It represents one of the largest databases of longitudinal medical records from primary care in the world.

The population of active patients (alive and currently registered) on July 2013 was 4.4 million (6.9% of the UK population) and is broadly representative in terms of age, sex and ethnicity of the total UK population. The CPRD is therefore a rich source of health data for research, including data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours and referrals to secondary care.

Primary care clinical encounters are entered onto the CPRD database using Read codes. Read terminology is a structured hierarchy of both medical and non-medical terms covering categories for signs and symptoms, diagnoses, investigations, treatment and therapies, drugs and appliances, occupations and administrative processes. They therefore offer a comprehensive list of clinical terms that can be used to describe the care and treatment of patients.

However, in contrast to ICD-10 codes, which are structured according to disease groups, Read codes encompass all clinical terminology used in primary care with approximately 100,000 codes available to utilise. Huge variation in coding practices for the same disease is therefore common with detailed search strategies therefore necessary to phenotype a disease of interest (detailed further below).

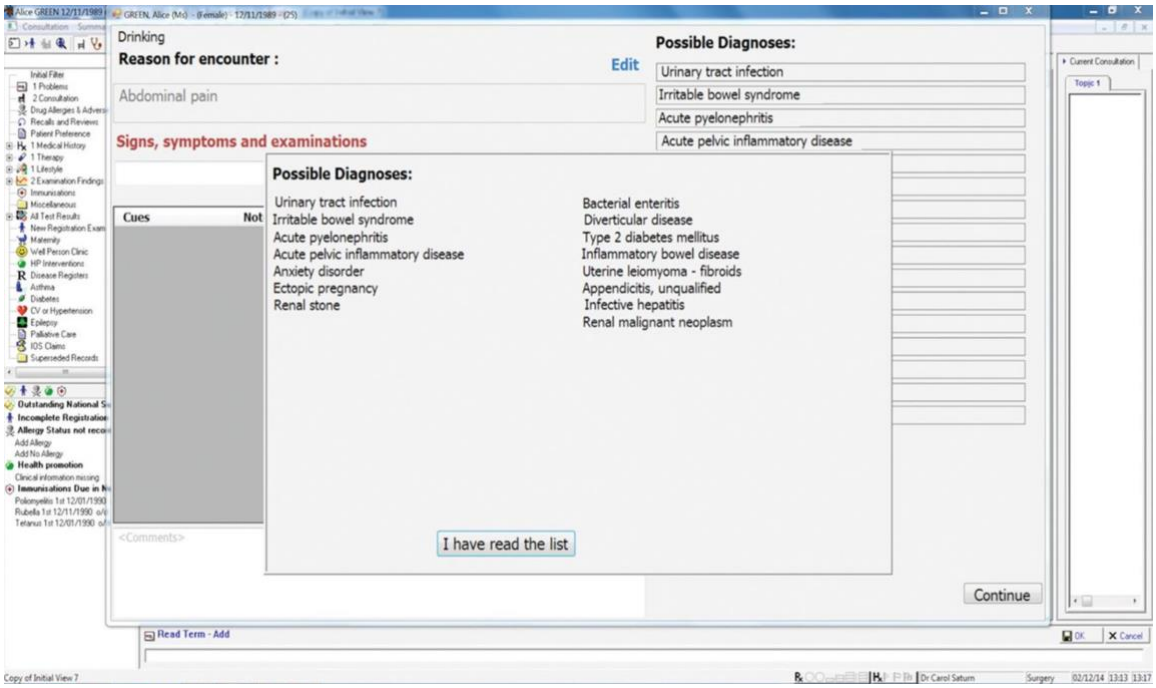
Information in the CPRD database is recorded in a number of tables, which can be linked by the pseudonymised patient identifier in order to build up a complete picture of a patient's healthcare experience.

- **Patients** – one row per patient, with demographic details such as year of birth, date of death and registration dates.
- **Practices** – one row per practice, giving details such as region of the UK and the date when the practice achieved 'up-to-standard data' (see further below).
- **Consultations** – each patient episode is considered a 'consultation' and all data are entered in consultations (face-to-face, telephone or administrative). This table allows diagnoses and prescriptions entered in the same consultation to be identified.
- **Staff** – one row per staff member, with gender and role.
- **Events** – there are a number of event tables with a patient having any number of events. Each event is linked to a single consultation and an event date, a medical dictionary code (Read code), product dictionary code (Multilex) and/or associated information in free text.

- **Clinical** – Read coded diagnoses entered by the GP with additional data such as observations.
- **Referrals** – referrals to secondary care, with the indication recorded as a Read code.
- **Immunisations** – records of immunisations.
- **Therapy** – prescriptions.
- **Test** – results of laboratory tests, each with a Read code.

A screenshot illustrating how information may be entered in practice by a GP in consultation is denoted in **Figure 5** below. This is a screenshot using the Vision clinical system (106).

Figure 5. Screenshot of the Vision clinical system utilised by GPs to enter clinical information (e.g. Read codes).



Practices participating in CPRD are assigned an "up-to-standard" date by CPRD custodians based on the date on which acceptable standards are met on ten practice-based measures of quality, completeness and representativeness. Once deemed "up-to-standard", their data is marked as suitable for longitudinal data research. Hence, conventionally, clinical data from patients are restricted from the date their practice were deemed "up-to-standard".

Practice data are checked once delivered to CPRD for data quality issues (98). Any practice submitting poor data is provided feedback and if coding practices are not rectified, data from their practice are subsequently removed from CPRD (107).

Despite these quality measures, data quality within CPRD is variable because data are entered by GPs during routine consultations and not specifically for the purposes of research. For example, when faced with a patient with tonsillitis, via look-up tables, rather than selecting the most accurate Read code, GPs may select a multitude of codes ranging from symptom codes such as sore throat to throat soreness and diagnostic codes such as throat infection, pharyngitis and/or tonsillitis. Furthermore, whilst data completeness within practices contributing to CPRD is better compared to those that do not, a lot of data is written in free-text and therefore not freely accessible. In addition, clinical observations such as pulse, blood pressure, and temperature are rarely recorded.

There have been numerous CPRD studies that have undertaken validation of Read coded diagnoses against anonymised requested GP paper records or electronic free text. A systematic review of these CPRD validation studies found that diagnoses were generally reliable (108). Across all diseases and all validation studies, a median of 89% of records were validated, with a range of 24-100%. For respiratory disorders, the median was 88% with a range of 26-100% (108). To my knowledge, no validation study in DS has been conducted to date.

Free text can no longer be requested from CPRD for validation purposes due to changes in information government requirements, and no free text validation was undertaken in the course of this thesis.

3.3.2 Secondary care data: Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) is a database warehouse containing details of all admissions, procedures, outpatient appointments and Accident & Emergency (A&E) attendances at NHS hospitals in England (102). It is a records-based system that covers all NHS trusts in England, including acute hospitals, primary care and mental health trusts with information on each hospitalisation stored as a large collection of separate records (one for each period of care) in a secure data warehouse. This data is collected during a patient's time at hospital and utilised to allow hospitals to be paid for the care they deliver.

Data on diagnoses is logged using the ICD-10 coding system whilst information on procedures is stored using the OPCS4 coding system (102). ICD-10 is the 10th revision of the World Health Organizations' medical classification system (102). It contains codes for diseases, signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease. OPCS-4 is the coding system for operations, procedures and interventions performed during inpatient stays, day case surgery and some outpatient treatments in NHS hospitals (102). Similar to CPRD, patients are identified by their NHS number.

Validation studies in the field of RTIs have confirmed that HES records on RTIs appear to be both reliable and complete (109). However, its primary purpose is as an administrative dataset for financial payments. The research utility of HES is therefore limited by data granularity and limitations of the ICD-10 coding system. Moreover, data quality is known to be variable with inaccurate and/or incomplete clinical coding common due to data being inputted by clinical coders who have very little contact with front line clinicians and have to work from clinical notes which are normally inadequate and/or unstructured. Therefore, caution is advised when analysing and interpreting results for clinical research purposes.

3.3.3 Death registry & deprivation: Office of National Statistics (ONS)

The death registry for England and Wales curated by the Office for National Statistics (ONS) includes the date of death and the causes entered on the death certificate. A single underlying cause of death is allocated according to the WHO ICD-10 algorithm based on the information recorded on the death certificate, likely causal sequence and ICD selection rules (110).

Deaths in England and Wales have been coded using ICD-10 since 2001 and ICD-9 in previous years (85). Due to a change in the rules for selecting the underlying cause from ICD-9 to ICD-10, the causes of deaths are not directly comparable between 2001 onwards and previous years (110).

The IMD is a composite measure of deprivation calculated by ONS using indicators for super output areas (postcode areas). It covers the following domains; (i) Income, (ii) Employment, (iii) Health and disability, (iv) Education, skills and training, (v) Barriers to housing and services, (vi) Crime and (vii) Living environment (101).

3.4 ACCESS TO CALIBER DATA

Access to CALIBER data operates by a 'safe haven' model, where the data is stored, processed and managed within the security of a walled garden system, avoiding the complexity of assured end point encryption. A file transfer mechanism enables aggregate data to be transferred out of the walled garden simply and securely (86).

CALIBER researchers are provided with pseudo-anonymised data (i.e. identifiers such as date of birth, name and address removed). Whilst the free text associated with coded data is not currently available to researchers, historically it was possible to request it (with a cost for manual anonymisation) and it has been used for validation studies in the past (111).

3.5 ETHICAL AND SCIENTIFIC APPROVAL

CPRD has Multi-centre Research Ethics Committee approval for all purely observational research using its linked EHRs (CPRD, HES, ONS) (112). The CALIBER dataset comprises CPRD data linked to HES, ONS and MINAP by a trusted third party with the final dataset held in a pseudonymised form. The CALIBER record linkage has therefore had separate ethical approval (09/H0810/16) for observational clinical research.

Raw data are available for use by researchers, subject to approval of the protocol by, and payment to, the bodies governing access to the constituent data sets. For CPRD, this involves scientific approval of the protocol by the Independent Scientific Advisory Committee (ISAC) and a signed licence outlining scope and data confidentiality of use of CPRD data (113).

Following ISAC approval, an application to the CALIBER Scientific Advisory Committee is made in order to use the curated CALIBER dataset.

3.6 PHARMACOEPIDEMIOLOGY USING EHRs

The CALIBER dataset has been developed and used for numerous studies investigating risk factors and the onset of cardiovascular diseases (114-118). More widely, it has been utilised successfully in assessing healthcare utilisation and prescribing trends for a range of other diseases including infections (119), mental health (e.g. depression (120)) and cancer (121).

Increasingly, EHRs such as CALIBER are being used to estimate the effects of interventions on outcomes in populations particularly due to its advantages in overcoming limitations in RCTs, such as the difficulties of including restricted patient groups (e.g. elderly, rare diseases), assessing intervention efficacy in real world settings, and insufficient power to assess rare outcomes.

However, as EHR data is collected for reasons unrelated to research, data quality is often insufficiently detailed, which limits its efficacy in assessing quality of care and the community burden of disease. There may be missing, limited, or inaccurate information on exposures, outcomes and potential confounding variables such as ethnicity, body-mass index, co-morbidities and disease severity (122, 123). These issues are discussed further below.

3.6.1 Misclassification

CALIBER researchers need to rely on Read codes that GPs have assigned to consultations, or ICD-10 codes that hospital coders have assigned to hospitalisations. In routine practice, they are unlikely to apply strict case definitions when allocating diagnostic codes. Misclassification can therefore occur.

Misclassification can occur in the selection of the patient population, exposure, confounders and outcomes. It is commonly categorized as either non-differential or differential misclassification. For example, in non-differential exposure misclassification, the misclassification is deemed unrelated to the occurrence or presence of disease. In contrast, if the misclassification of exposure is different for those with and without disease, it is differential.

In non-differential misclassification, this mostly produces a bias in favour of the null hypothesis. Differential misclassification can result in bias both for and against the null hypothesis (124, 125). An example of differential misclassification in routinely collected data would be if a clinician is more likely to spend time accurately inputting codes for a person with a disease than a person who is perceived as healthy.

It is crucial therefore that phenotyping algorithms are developed rigorously with sensitivity analyses undertaken to assess the impact of varying codelists on findings. An advantage of using routinely collected data for healthcare utilisation studies is that coders are effectively blinded for an individual study, and this means that such studies

are not vulnerable to certain subtypes of bias that can secondarily cause misclassification bias. These other types of bias include observer bias (the knowledge of the hypothesis results in an interviewer emphasising certain questions), recall bias (knowledge of a disease state results in a participant 'joining the dots') and reporting bias (participants report certain exposures because they are aware they are of interest) (126).

3.6.2 Missing data

Missing data is defined as occurring when no data value is stored for the variable in the current observation. Occasionally, the level of missingness is so substantial that EHRs may not be sufficiently internally valid to undertake research (127, 128).

For example, a patient may be White but his ethnicity may never be recorded in the EHR. This will lead to that patient's ethnicity being classified as Unknown. If ethnicity is an important confounder in an analysis, (e.g. when analysing the impact of ethnicity on cardiovascular disease outcomes) but the proportion of missing or unknown ethnicity is high, the analyses may be compromised.

A commonly used method to handle missing data is multiple imputation; creating multiple complete versions of the dataset with missing values imputed by random draws from distributions inferred from observed data (129). However, this is subject to limitations, with biased results from multiple imputation likely if significant proportions of the data are missing or if the recording of the variable differs between different groups (e.g. if BMI is more likely to be recorded in individuals who are obese rather than individuals who are not).

Alternatively, in some instances, use of multiple linked data sources to cross-reference may increase the overall completeness of the data. For example, combining CPRD and HES increased completeness of ethnicity to 97%, with 85% of patients having the same ethnicity recorded in both databases (130). There can also be large differences in incidence estimates when utilising linked databases; for example community acquired pneumonia incidence was 39% higher when using linked databases compared to a single source (131).

Data completeness is a key advantage to the use of multiple linked data sources. However, there are consequently effects of such an approach on sample sizes, and hence the ability of a study to have sufficient power to detect differences. If the aim of a study

is to stratify by ethnicity or some other factor that can be drawn from multiple sources, or if these variables are considered important confounders, then linked data may be considered a necessity.

However, it should also be noted that even if linked data sources are utilised, then recording will remain imperfect. A total of 85% of patients having the same ethnicity recorded in two databases means that 15% of patients do not, and there may not be an easy way to adjudicate these differences without having a further negative impact on sample sizes. In the above study concordance of ethnicity was driven largely by patients who were coded as White, and minorities had reduced concordance. If the aim is to stratify an analysis by ethnicity, then misclassification bias may occur as a result (130). If data linkage means that all patients classified as having a disease state in either database are classified as having it overall, then incidences may be overestimated; otherwise, there has to be some way in which to adjudicate differences, which may be resource intensive and unreliable, or there will be a smaller sample size.

3.6.3 Confounding

A direct comparison between treatment groups will likely be affected by inaccuracies caused by confounding (132-134), namely a factor that varies between two groups in addition to those under investigation. In clinical practice, treatment assignment is generally based on the physician's perception of a patient's risk of a particular outcome (132, 133) and prognostic patient characteristics that are typically unevenly distributed among the treatment groups. When applied to treatment, this sort of confounding is often known as confounding by indication.

Whilst there are numerous methods known to detect or control for measured confounding, there may also be unmeasured or poorly measured risk factors (e.g. patient's clinical observations) of the outcome that are also associated with the exposure (134). These are referred to as unmeasured, unobserved, or residual confounders.

Confounding by indication is particularly hard to address and arises from the fact that individuals who are prescribed a medication or who take a given medication are inherently different from those who do not take the drug, because they are taking the drug for a reason (e.g. individuals prescribed an antidepressant).

A recently developed method that aims to address confounding is propensity score

methods (134). This aims to weight or match treated and untreated patients in such a way as to make results more comparable to a randomised controlled trial.

The propensity score (PS) is a score applied to every person within the dataset. In the context of studies aiming to understand the effect of treatment, the PS is applied to each person in the dataset and represents their probability of receiving treatment.

For example, in a RCT, everyone gets an equal chance of being allocated the treatment and therefore has a PS of 0.5. In contrast, in non-randomised studies, if a particular group of patients were more likely to receive treatment than healthier patients with little/no co-morbidities then they are likely to have a higher PS.

The score is based on knowledge of factors that predict treatment and can therefore be utilised in a number of ways to tackle confounding (134, 135).

There are four ways that PS can be utilised to reduce the effects of confounding when estimating the effects of treatment on outcomes: matching, inverse probability of treatment weighting (IPTW), stratification, and co-variate adjustment (136).

IPTW using the PS uses weights based on the PS to create a synthetic sample in which the distribution of measured baseline co-variates is independent of treatment assignment. This analysis approach is utilised in Chapter 6 of my thesis; “Effects of Antibiotics in Preventing Hospitalisations in Children with Down’s Syndrome” and discussed in more detail in the methods section of the same Chapter.

There is a lack of consensus in the applied literature as to which variables to include in the PS model. Possible sets of variables for inclusion in the PS model include the following: all measured baseline co-variates, all baseline co-variates that are associated with treatment assignment, all co-variates that affect the outcome (i.e. the potential confounders), and all co-variates that affect both treatment assignment and the outcome (i.e. the true confounders).

In a recent review, IPTW and matching was deemed equivalent with minimal bias noted when both were utilised with a correctly specified PS model (135).

However, it is important to note that despite its advantages as an analytical technique for EHR research, the usefulness of PS is limited by EHR data quality. For example, in acute events, GPs do not code signs and symptoms that may be indicators of illness severity

(e.g. shortness of breath). Whilst PS may take account of the fact that some patients may be generally sicker, because of absent information on illness severity on the day of treatment allocation, it may not adequately predict treatment probability.

3.7 PHENOTYPING ALGORITHMS

The phenotype of an individual in the context of EHR research is the set of observable characteristics as recorded in EHR about that person. This may include clinical measurements such as pulse or blood pressure, or diagnoses such as acute myocardial infarction. It is therefore crucial to understand the process by which information about a subject enters the record, in order to be able to interpret and infer the phenotype correctly (137).

Frequently, it is necessary to make assumptions based on clinical knowledge and develop a strategy for allocating a diagnostic label to the patient (e.g. probable angina, possible angina). This is called a phenotyping algorithm.

There are few diseases or conditions for which it is possible to create a 'perfect' phenotype (i.e. identifying all disease cases with perfect accuracy), because it relies on having accurate information in the GP/hospital and for it to be entered consistently and accurately in the EHR.

Instead, a phenotyping algorithm may choose to maximise either diagnostic specificity or sensitivity. EHR based studies therefore typically include sensitivity analyses using different phenotyping algorithms (e.g. using different data sources, or using restricted or expanded sets of diagnoses codes). This can be used to show that the limitations of the phenotyping process have not introduced bias into the results.

The use of CALIBER to cross-reference between linked data sources therefore provides an inherent advantage rather than utilising a single data source to be able to look at other information, which might give clues (e.g. primary care or medication in linked data) (138).

3.8 CODE LISTS

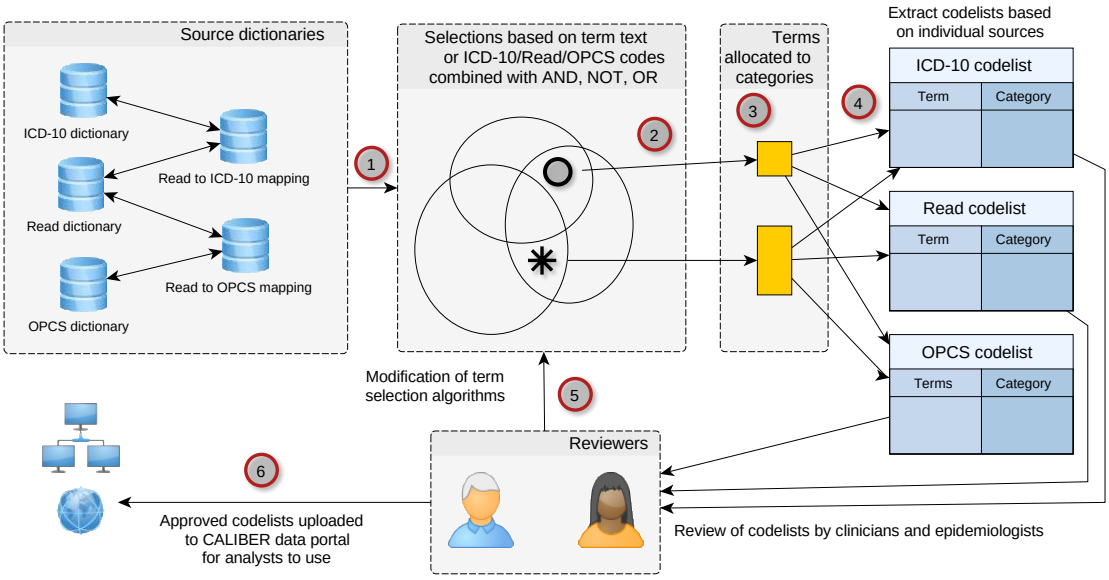
As part of the phenotyping process, codes of interest (e.g. diagnostic, symptom, medications) need to be identified and listed according to the relevant source dataset terminology (e.g. selecting all ICD-10 terms for RTIs to assess RTI-related hospitalisations). There are thousands of potential terms per terminology, with a varying

number of terms (ranging from a handful to hundreds) required depending on what the disease state is, and how specific a researcher is aiming to be.

Codelists are created using an iterative process; terms are searched for in dictionaries, and then combined to produce an optimal set which is then categorised or labelled.

In CALIBER, the production of code lists is assisted by the use of; (1) the CALIBER Data Portal, a web portal for researchers to access descriptions of contributed CALIBER clinical phenotypes (phenotypes), the underlying development process and codelists of Read, ICD-10 or OPCS codes used to define them and (2) R packages created by Dr Anoop Shah; the R CALIBERcodelist package (139, 140). The process of code list production is illustrated in **Figure 6**, which is followed by an explanation of each of the labelled steps.

Figure 6. Process for generating a codelist using the R CALIBER codelists package.



1) Review source dictionaries and decide which ones to use, e.g. READ, ICD-10 and/or OPCS dictionaries.
2) Use these source dictionaries to create a selection of terms relevant to the individual query (e.g. by selecting all terms containing the word 'infections' or all ICD-10 codes beginning with 'I10'). Combine selections using Boolean operators such as AND, OR or NOT to identify exactly which terms are of interest, or to exclude confounding terms. For example, if investigating respiratory tract infections, 'urinary tract infections' would be excluded.

3) Create a category name for terms in a particular selection, e.g. ‘URTIs’ or ‘Down’s Syndrome’
4) Set the metadata for the codelists under construction (version number, category descriptions, author name, date). Extract the READ, ICD-10 and OPCS codelists and save in a standard format.
5) Undertake a consensus meeting with clinicians and epidemiologists who have expertise in the relevant field in order to review the codelists and suggest any changes. The algorithm may be iteratively changed with results compared with previous versions if necessary, which may prompt a return to Step 2 of the codelist generation process.
6) Approved codelists with documentation can be shared on the CALIBER data portal for use in subsequent studies.

Chapter 4 describes the codelist generation process for the relevant codelists for the remainder of this thesis.

Chapter 4: Down's Syndrome and RTIs in CALIBER

4.1 CHAPTER OUTLINE

In preparation for the remainder of the next chapters of this thesis, which assess RTI-related healthcare utilisation and effects of antibiotics on reducing RTI-related complications, this chapter describes the process of defining clinical phenotypes for RTIs, Down's Syndrome and other variables of interest (e.g. co-morbidities), the selection of the study population (i.e. children with Down's Syndrome and controls), exposures (e.g. consultations, antibiotic prescriptions) and outcomes (e.g. hospitalisations).

4.2 PHENOTYPING RESPIRATORY TRACT INFECTIONS

In this section, I detail the process of developing the phenotyping algorithm for RTIs used for the next chapters in this thesis.

In cases of cardiovascular disease, MINAP, the gold standard in recording acute coronary events, is utilised alongside CPRD and HES within CALIBER. In contrast, for RTIs, only CPRD and HES data sources are available to classify whether a patient has an RTI at a particular point in time and attempts to identify the type of RTI.

RTIs can be classified using either diagnostic or symptom codes or both, each of which has potential limitations:

Diagnosis codes: Assuming the patient and/or healthcare professional know what type of RTI the patient has, it can theoretically be coded using the specific Read or ICD-10 code. However, some codes are still non-specific, for example 'respiratory tract infection' could either mean URTI or LRTI. In addition, some patients may have conflicting diagnostic codes issued on the same day.

Symptom codes: In contrast to diagnostic codes, these do not clearly identify the clinical diagnoses and may range from 'cough' to 'fever'. For example, based on clinical knowledge, blocked nose can be a symptom of seasonal rhinitis or URTI and may be classed as either. Similarly, fever, a sensitive but non-specific marker for an infection, may be a possible RTI.

In developing the algorithm, I reviewed previously published code lists for identifying RTIs in UK primary and secondary care datasets. Where code lists were unpublished, authors

(26 in total) were contacted to provide code lists (16 provided). After merging duplicate code lists, a unique code list was compiled.

Concurrently, diagnostic and symptom codes were searched through the Read and ICD-10 dictionaries using the R CALIBERcode package using the search terms listed in the Appendix. Codes identified were marked as “definite exclude”, “definite include” and “unsure”. Codes from the latter two categories were subsequently merged with the unique code list compiled above.

All Read and ICD-10 codes ever recorded in the cohort of adults and children with DS and controls in CALIBER were then sourced, collated and merged with the unique code list derived above. Any matches were deemed as “marked”.

All unmarked Read and ICD-10 codes (i.e. codes that were being recorded in the population of interest in the CALIBER dataset but not identified to be of interest in the earlier steps) were then reviewed by myself and Dr Nischchay Mehta, an ENT Registrar and Wellcome Trust Fellow to identify codes that may have been missed. These were again marked as “definite exclude”, “definite include” and “unsure”.

Codes that both reviewers marked as “definite exclude” were dropped. Any discrepancies between codes marked as “definite exclude” by one reviewer but not by another were discussed and resolved. These codes were subsequently reviewed by an academic GP, Dr Mark Ashworth, at King’s College London Department of Primary Care and Public Health Sciences.

At a consensus meeting that included my academic supervisors; an ENT surgeon (Prof. Anne Schilder), paediatrician (Prof. Monica Lakhanpaul) and an infectious diseases epidemiologist (Prof. Andrew Hayward), these codelists were discussed and finalised.

Codes were classified as either “URTI”, “LRTI” or “Unclassified RTI” (i.e. Uncertainty on whether it was a URTI or LRTI) and then sub-categorised as either “Probable” or “Possible”.

I performed a sensitivity analysis by different levels of certainty of RTIs (i.e. “Probable” vs. “Possible”) and in view of similar findings, a sensitive code list incorporating both categories were utilised for subsequent chapters of this thesis. This is detailed in the Appendix.

4.3 DOWN'S SYNDROME & CO-MORBIDITIES

A similar process was undertaken to phenotype DS and co-morbidities. In the latter, a review of publications on respiratory disorders in DS was undertaken to compile a list of co-variates that could influence either the frequency or severity of RTIs (43, 47, 141). This is detailed in **Table A 1**. The codelist for Down's Syndrome is included in **Table A 2.**

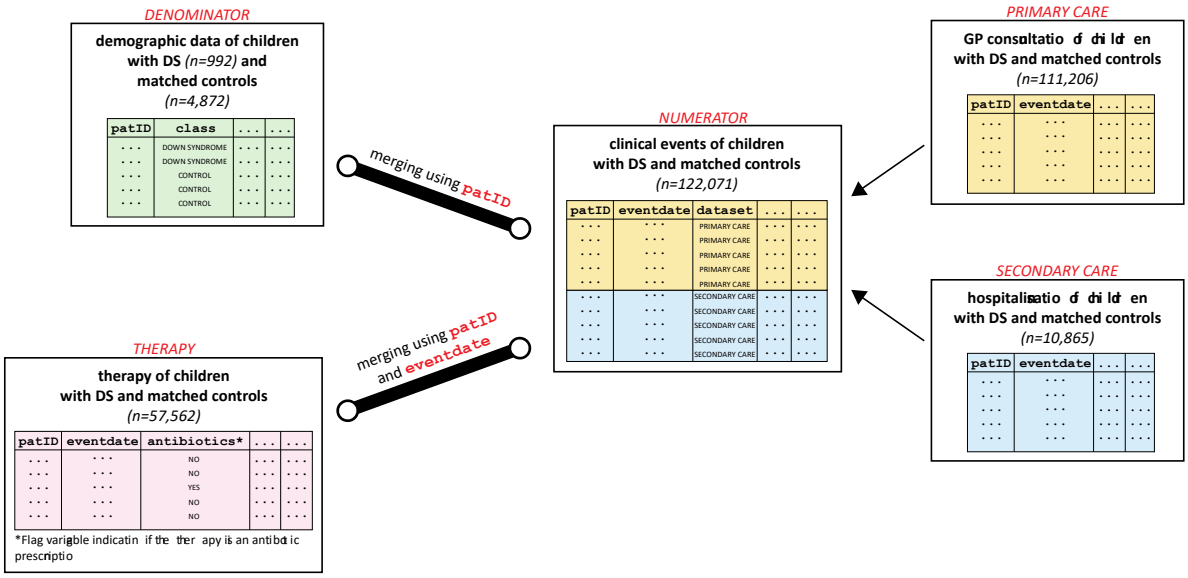
4.4 ANTIBIOTICS

I identified antibacterial agents listed in any chapter of the British National Formulary (BNF) using Multilex codes described above (142). Analyses were subsequently restricted to antibacterial agents listed in chapter 5.1 of the BNF excluding antituberculous and antileprotic drugs (BNF chapters 5.1.9 and 5.1.10). The class of a given antibacterial prescription is based on subchapters of BNF Chapter 5.1, the titles of which I have used in subsequent chapters of this thesis. All antibiotics were considered, in line with the approach of previous CPRD studies of antibiotic prescribing, and it was assumed there were no *a priori* differences in prescribing trends and patterns for children with DS (21).

4.5 STUDY POPULATION

The selection process of children with DS and controls from the CALIBER dataset alongside GP consultations, hospitalisations and primary care prescriptions is described in **Figure 7** below.

Figure 7. Overarching Diagram of Cohort, Consultation, Hospitalisations and Therapy.

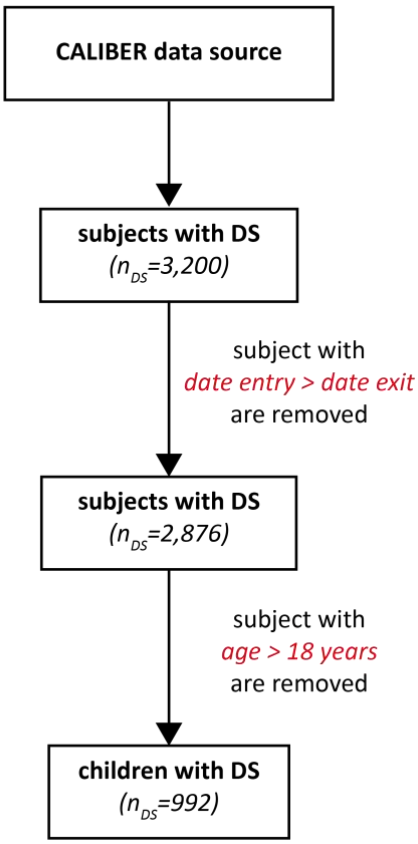


This cohort is utilised as the basis for all subsequent analyses with all baseline characteristics (e.g. Date of Birth, Cause of Death, Date of GP registration, IMD) of both children with DS and controls incorporated in a CALIBER data file labelled "DENOMINATOR".

4.5.1 Down's Syndrome

Figure 8 denotes the selection process of adults and children with DS from CALIBER.

Figure 8. Selection process of children with DS from the CALIBER dataset.



Adults and children with DS were identified in any of the CALIBER data sources between 1st January 1997 to 25th March 2010 by searching for any of the Read codes for DS in CPRD and by ICD-10 codes in HES recorded as either the primary or secondary discharge diagnosis.

Patients started contributing study data from either the latest date of: (i) 1 January 1997, (ii) the date at which the GP practice provided "up-to-standard" data, (iii) the date the patient registered with the GP practice or (iv) their date of birth.

This was deemed their date of entry into the cohort (i.e. entry date).

Patients were followed up while registered at the practice until the earliest date of: (i) 25 March 2010, (ii) the last date of data collection from the GP, (iii) the date the patient transferred out of the database (i.e. leaves the GP practice) or (iv) their date of death.

This was deemed their date of exit from the cohort (i.e. exit date). Individuals with an exit date prior to their entry date (i.e. patient records with data quality issues) were removed (n=324). A total of 2,876 adults and children with DS remained. Those who were more than 18 years old at the entry date were subsequently excluded from the study. A total of 992 children with DS remained.

4.5.2 Controls

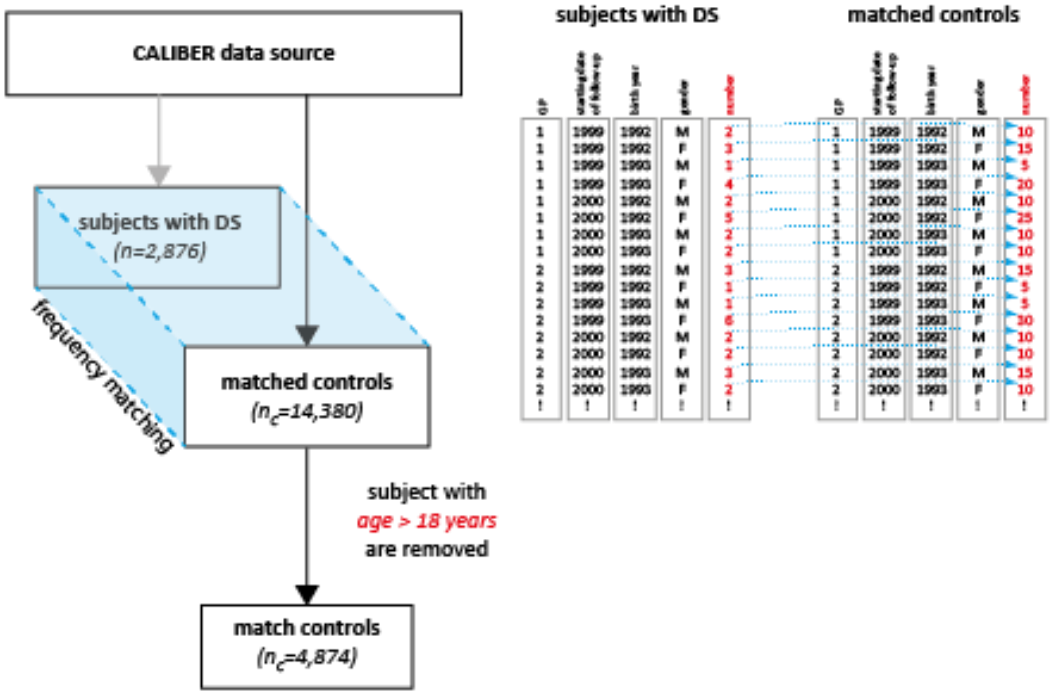
For each of 2,876 adults and children with DS, five controls were frequency matched by GP, gender, birth year (±5y) and starting date of follow-up totalling to 14,380 controls.

In frequency matching, matching is done by groups of subjects rather than individually. For example, if there are 50 children with DS, a control population with the same age distribution is selected. Whilst both individual and frequency matching have their relative advantage and disadvantages, the latter was chosen as it was easier to perform than individual matching and it allowed subsequent analysis of the effects of matching variables on the outcomes.

Similar to adults and children with DS, only individuals with an exit date after their entry date were selected. Individuals older than 18 years old at the entry date were subsequently excluded from the study. A total of 4,874 controls remained.

The flow diagram of the selection process of controls is shown in **Figure 9**.

Figure 9. Selection process of controls from the CALIBER dataset.



4.5.3 Clinical and Demographic Characteristics of the Cohort

Age

I categorised age at entry into the cohort into four age-bands based on clinical consensus of the impact RTIs may have on different age groups; infants (0 to 1-year-old), toddlers (1 to 5 years old), juniors (5 to 10 years old) and young persons' (10 to 18 years old).

This stratification was chosen in order to group by known risk of RTIs across age groups. Children are at the highest risk for RTIs in the first year of life, with respiratory infections being the greatest cause of morbidity and mortality in this age group, hence the 0-1 category. Risk is also increased, although less so, in the 1-5 year old category relative to older children (143). There is less evidence of varying risk between the 5-10 and 10-18 years old age categories, so these divides were chosen because of the behavioural and educational changes relevant to these age groups. From 5 to 10, most children will have commenced regular education. Between the ages of 10 to 18, children go through adolescence and may commence secondary education.

Due to the length of follow-up in this longitudinal cohort, these children may have participated in several age groups over time. For example, a child who entered the cohort at age three and was followed up for ten years in CALIBER would have his or her follow-

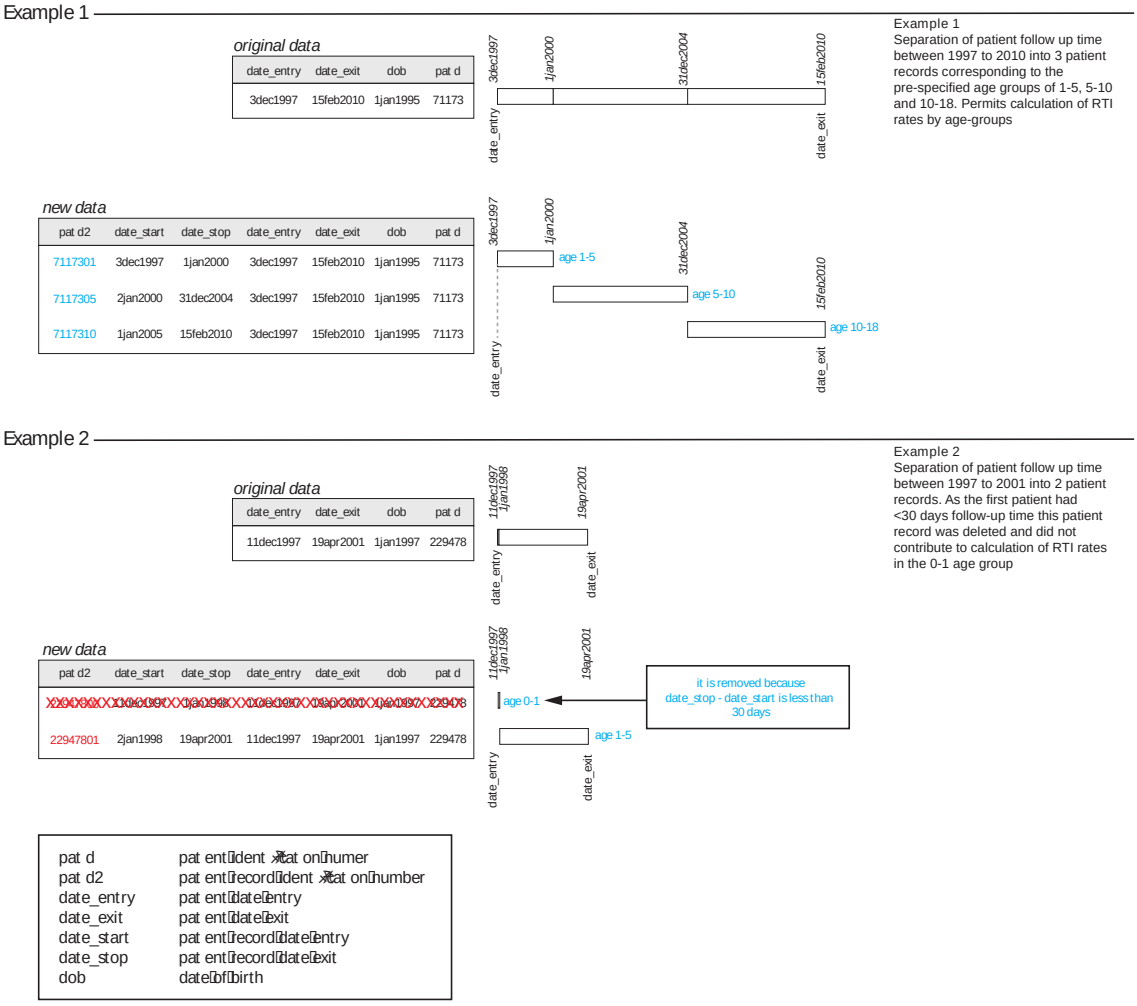
up time segregated across the 1-5 (toddlers), 5-10 (juniors) and 10-18 years (young persons) age groups.

To prepare for analyses, a separate patient record with unique identifiers was created for each age category with entry and exit dates corresponding to when the child entered and exited the age group.

Using the example above, three patient records would be created corresponding to age 3-5, 5-10 and 10-13. Patient records with a follow up time of less than 30 days were not included in subsequent analyses.

In **Figure 10** two examples are illustrated. I created a total of 1,711 patient records for the 992 children with DS and 8,435 patient records for the 4,874 controls for analyses in the subsequent chapters of my thesis.

Figure 10. Process for creating patient records for subsequent consultation/hospitalisation rates calculations.



Co-morbidities

I deemed study participants to have a co-morbidity of interest (e.g. CHD) if a relevant READ (i.e. GP consultation) or ICD-10 (i.e. hospitalisation) code was recorded at any point between their entry and exit dates. Details of how each condition was phenotyped and subsequently selected is described above.

IMD quintile

In CALIBER, Index of Multiple Deprivation (IMD) information is supplied by the ONS. IMD scores are calculated using a number of indicators; (i) Income, (ii) Employment, (iii) Health and disability, (iv) Education, skills and training, (v) Barriers to housing and services, (vi) Crime and (vii) Living environment (101). These then produce an overall score for an individual postcode which represents the level of deprivation in that area. IMD scores are commonly stratified into quintiles, with Quintile 1, a score of ≤ 8.49, representing the least deprived quintile, and Quintile 5, a score of ≥ 34.18, representing the most deprived quintile. I established the IMD quintile of children with DS and their controls by separating them out according to their IMD scores into an individual Quintile.

Ethnicity

I established the ethnicity of adults and children with DS and their controls using the method described by Jensen, *et al.* (141) which assessed the completeness and consistency of ethnicity recording in the CALIBER dataset.

In CALIBER, ethnicity data is provided in the HES dataset under 16 ethnic categories and in CPRD as Read codes. Relying on HES data alone, the 56.4% of individuals (3264 out of 5783) with Unknown ethnicity recorded consisted of 60.0%) of controls and 39.0% of children with Down's Syndrome.

Using the process illustrated in **Table 5**, this was reduced to five categories consisting of; (1) White, (2) Black or Black British (i.e. Bl_Afric, Bl_Other, Bl_Carib), (3) Mixed (4) Asian or Asian British (i.e. Pakistani, Bangladeshi, Indian, Oth_Asian) and (5) Chinese or Other Group (i.e. Chinese and Other).

Table 5. The 16 groups of the 2001 Census for England and Wales mapped to the 5 collapsed categories.

16 groups	**5 Categories**
1 British	**1.White**
2 Irish	
3 Any other White background (write in)	
4 White and Black Caribbean	**2. Mixed**
5 White and Black African	
6 White and Asian	
7 Any other mixed background (write in)	
8 Indian	**3. Asian or Asian British**
9 Pakistani	
10 Bangladeshi	
11 Any other Asian background (write in)	
12 Caribbean	**4. Black or Black British**
13 African	
14 Any other Black background (write in)	
15 Chinese	**5. Chinese or Other Group**
16 Any other ethnic group (write in)	

4.6 STUDY EXPOSURES AND OUTCOMES

All GP consultations, hospitalisations and primary care prescriptions on the cohort were extracted from the CALIBER database as separate data files. The steps below detail the process of preparing these data files for analyses in the next chapters of my thesis into a single CALIBER data file.

4.6.1 Primary care

In total, there were 1,507,367 entries in primary care within the CALIBER dataset, of which 340,712 were from children with DS and 1,166,655 were from controls. The process of curating these data is illustrated in **Figure 11**. **Table 6** shows the consultation IDs used in selecting relevant consultations of interest.

Figure 11. Selection process of GP consultations of RTIs and co-morbidities of interest in children with DS and controls within the CALIBER dataset.

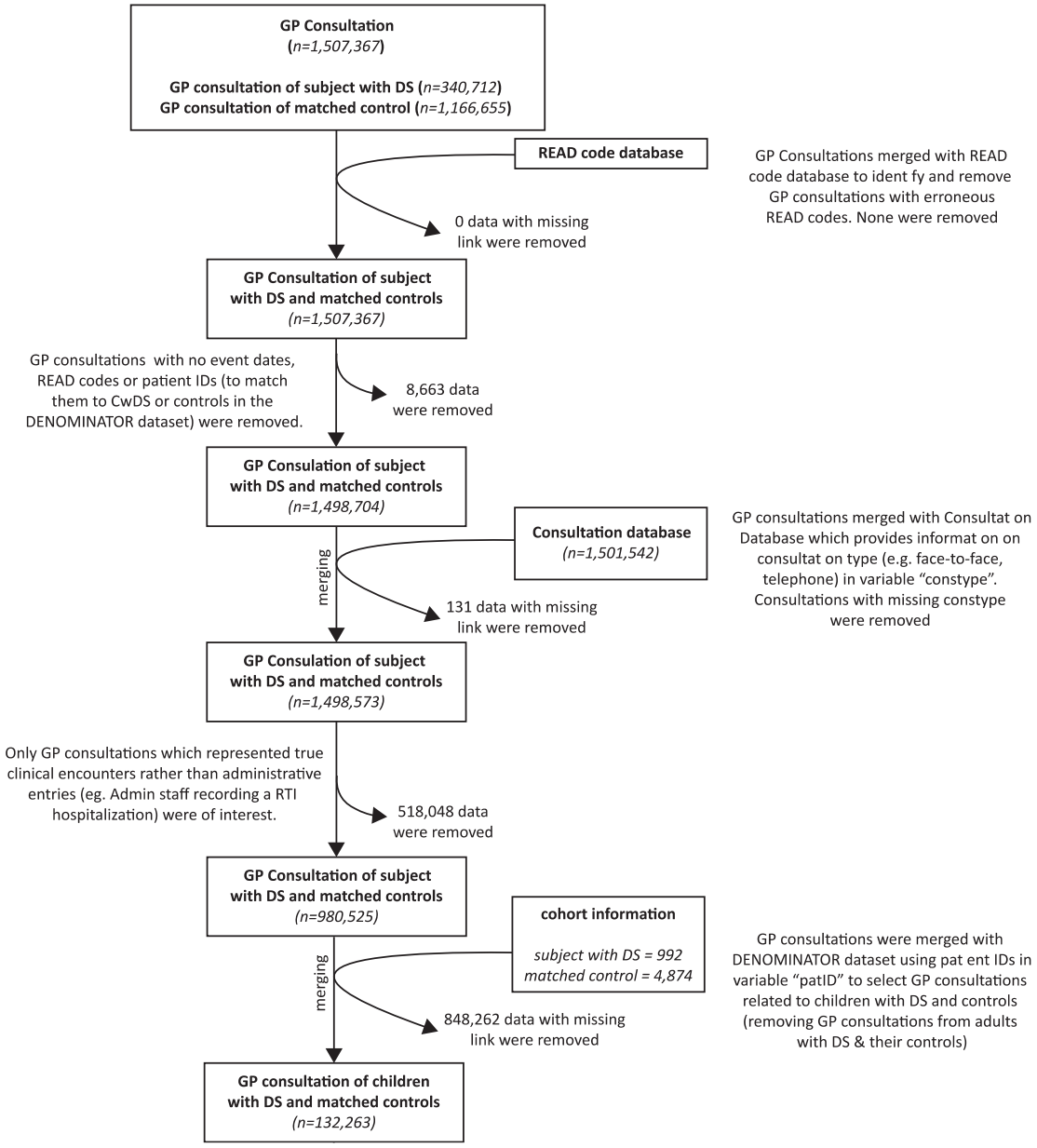


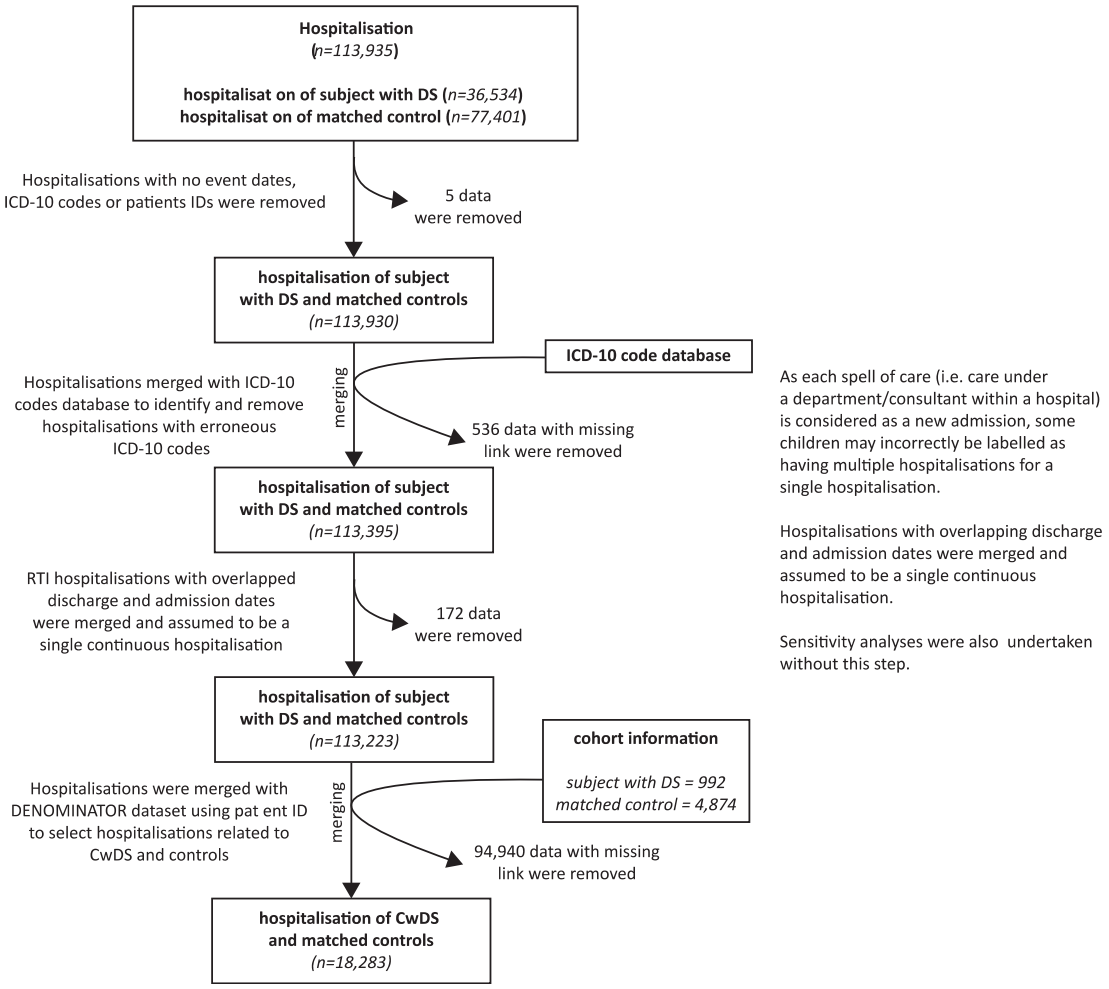
Table 6. Consultation IDs utilised in selecting relevant GP consultations of interest (e.g. Inputted by a clinician rather than administrative staff).

Clinical episode	constype
Clinic	1
Night visit, Deputising service	2
Follow-up/routine visit	3
Night visit, Local rota	4
Night visit, practice	6
Out of hours, Practice	7
Out of hours, Non-Practice	8
Surgery consultation	9
Acute visit	11
Emergency Consultation	18
Casualty Attendance	20
Hospital Admission	23
Children's Home Visit	24
Home Visit	27
Hotel Visit	28
Nursing Home Visit	30
Residential Home Visit	31
Twilight Visit	32
Triage	33
Walk-in Centre	34
Co-op Surgery Consultation	36
Co-op Home Visit	37
Minor Injury Service	38
Community Clinic	40
Initial Post Discharge Review	48
Night Visit	50

4.6.2 Secondary care

There was a total of 36,534 hospitalisations in children with DS and 77,401 from controls. The process of curating these data is denoted in **Figure 12**.

Figure 12. Selection process of hospitalisations due to RTIs and co-morbidities of interest in children with DS and controls within the CALIBER dataset.



4.6.3 Respiratory Tract Infections

A proportion of RTI events were noted to have been recorded on the same date for the same patient. For example, a probable URTI consultation and a possible LRTI hospitalisation could be recorded in the same data for the same patient.

RTIs were therefore categorised following a ranking system based on RTI-type, setting and whether it was probable or possible (based on codelists developed earlier). This is illustrated in **Table 7** below. For example, based on the previous example of a probable URTI consultation and possible LRTI hospitalisation on the same day, the latter would prevail.

This led to a reduction in the total number of RTI-related GP consultations analysed from 20,889 to 19,970 (-4.4%) and RTI-related hospitalisations from 826 to 800 (-3.1%), a total of 945 events, of which 83 were LRTIs, 373 were URTIs, and 489 were unclassified RTIs.

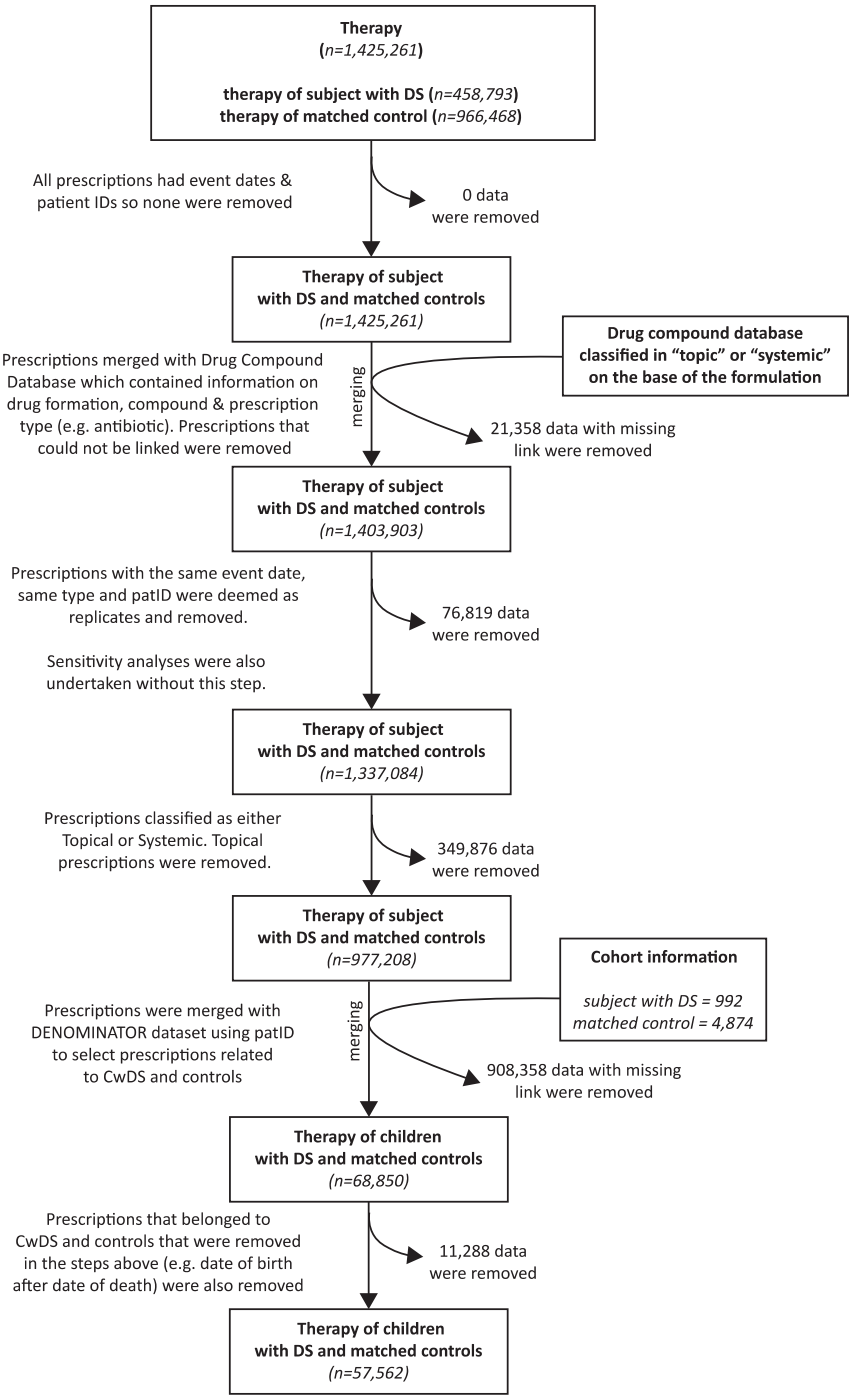
Table 7. RTI ranking system utilised in prioritising RTI types and settings where conflict arose.

	Disease	Probable/Possible	Dataset
1	LRTI	Probable	SECONDARY CARE
2	LRTI	Possible	SECONDARY CARE
3	URTI	Probable	SECONDARY CARE
4	URTI	Possible	SECONDARY CARE
5	Unclassified RTI	Probable	SECONDARY CARE
6	Unclassified RTI	Possible	SECONDARY CARE
7	LRTI	Probable	PRIMARY CARE
8	LRTI	Possible	PRIMARY CARE
9	URTI	Probable	PRIMARY CARE
10	URTI	Possible	PRIMARY CARE
11	Unclassified RTI	Probable	PRIMARY CARE
12	Unclassified RTI	Possible	PRIMARY CARE

4.6.4 Prescriptions

There was a total of 458,793 prescriptions in children with DS and 966,468 prescriptions in controls issued in primary care. The process of curating these data is denoted in **Figure 13.**

Figure 13. Selection process of all prescriptions of interest (e.g. Systemic) in children with DS and controls within the CALIBER dataset.



Chapter 5: RTI-Related Healthcare Utilisation in UK Children with Down's Syndrome

ABSTRACT

Background

Children with RTIs present often to GP services in the UK, particularly in the winter months when there are higher levels of circulating respiratory tract viruses. For most children, RTIs are commonly a mild and relatively short viral illness. In some children, particularly 'at-risk' children such as those with DS, RTIs can quickly become more serious and result in hospital admissions.

This retrospective cohort study aims to quantify RTI-related primary and secondary healthcare utilisation and treatments (e.g. antibiotics) in children with DS and controls alongside the risk of RTI-related hospitalisation, time to RTI-related hospitalisation, and re-consultation with their GP.

Methods

I used a longitudinally linked primary care, hospital admission, disease registry, and mortality dataset for England (the CALIBER programme). The study population comprised children aged 0-18 with at least one record of DS matched with five controls from the same GP, gender, birth year, and date of entry into CALIBER.

I followed up individuals for occurrences of RTIs and antibiotic prescriptions recorded in either the primary or secondary care dataset between 1997 and 2010. I used Poisson regression to calculate consultation, hospitalisation, and antibiotic prescription rates. I used the Wilcoxon test to compare hospitalisation length of stay. I stratified analyses according to year, age, gender, RTI type (e.g. URTI, LRTI, and unclassified RTI), season (e.g. seasonal influenza/RSV), and co-morbidities (e.g. CHD).

I assessed the proportion of RTI-related consultations leading to an RTI-related hospitalisation in children with DS and controls, the time to hospitalisation following an RTI-related GP consultation, proportion of RTI-related hospitalisations occurring without a prior RTI-related GP consultation and proportion of RTI-related consultations with a subsequent GP re-consultation.

Results

RTI-related healthcare utilisation (i.e. GP consultations, hospitalisations) is significantly higher in children with DS compared to controls for both GP consultations (Adjusted RR 1.73; 95% CI 1.62-1.84) and hospitalisations (Adjusted RR 5.70; 95% CI 4.82-6.71). This was consistent throughout the study period (1997-2010) and was most pronounced for LRTI-related GP consultations (Adjusted RR 3.59; 95% CI 3.19-4.04) and hospitalisations (Adjusted RR 11.30; 95% CI 8.45-15.10). Overall, the length of stay in hospital due to RTIs was longer for children with DS (Mean 5.2; 95% CI 5.0-5.4 days per admission) compared to controls (Mean 2.4; 95% CI 2.2-2.6).

Children with congenital heart disease (CHD) and DS had higher rates of RTI-related hospitalisations compared to children with CHD and without DS (Adjusted RR 3.15; 95% CI 1.02-9.68), but there was no difference in RTI-related GP consultations. Children with asthma and DS had higher rates of RTI-related hospitalisations (Adjusted RR 4.03; 95% CI 2.79-5.83) and RTI-related GP consultations (Adjusted RR 2.11; 95% CI 1.78-2.51) compared to children with asthma and without DS.

The risk of an RTI-related hospitalisation following an RTI-related GP consultation was higher in children with DS compared to controls (Adjusted RR 3.15; 95% CI 2.35 – 4.24). In those hospitalised, the time to hospitalisation was similar in children with DS (median of 8.0 days; 95% CI 3.0-19.0) and in controls (median of 8.0 days; 95% CI 2.0-18.0).

The odds of re-consultation with a GP for an RTI following an initial RTI-related GP consultation was higher in children with DS with 24.3% re-consulting compared to 16.0% of matched controls (OR 1.69; 95% CI 1.57-1.82).

A high proportion of RTI-related hospitalisations were not preceded by a RTI-related GP consultation in both children with DS (74.1%; 95% CI 68.9-78.5%) and matched controls (73.4%; 95% CI 67.0-78.8%).

Antibiotic prescribing was markedly higher in children with DS compared to controls over the entire study period (Adjusted RR 2.34; 95% CI 2.19-2.5). When restricted to antibiotics prescribed on the same day as an RTI-related GP consultation, this relationship persisted (Adjusted RR 2.26; 95% CI 2.1 – 2.43).

Differences in RTI-related antibiotic prescriptions were more apparent in LRTIs (Adjusted RR 3.74; 95% CI 3.3-4.25) compared to other RTIs. Infants with DS were prescribed the most antibiotics for RTIs compared to all other age groups.

Discussion

This is the first study of RTI healthcare utilisation in children with DS compared to controls utilising linked primary and secondary care data. Children with DS have higher rates of primary care consultations, antibiotic prescribing, hospitalisations, and longer hospital stays compared to controls.

Children with DS are also more likely to be hospitalised following an RTI-related GP consultation and to re-consult with their GP for an RTI compared to controls.

In the next chapter, I will build on this to assess the effects of antibiotic prescribing in reducing the risk of RTI-related hospitalisation in children with DS compared to controls.

5.1 CHAPTER OUTLINE

This chapter aims to establish RTI-related healthcare utilisation in children with DS and compares this to controls. I have applied a retrospective cohort study design using CALIBER. Details of this data source, together with phenotyping algorithms for RTIs, Down's Syndrome, co-variates and selection of the study population and exposures (i.e. consultations, hospitalisations and prescriptions), are reported in Chapter 4.

5.2 BACKGROUND

Thus far, only international studies of RTI-related hospitalisations in children with DS have been undertaken, with no comparisons to controls and no epidemiological studies of RTIs in children with DS in the UK published.

Uncertainty therefore remains around the burden of RTIs on children with DS in both primary and secondary care. Moreover, in the absence of comparisons to controls, clinicians and healthcare professionals are unable to quantify the relative risk of RTI-related hospitalisation and re-consultation in children with DS to families and carers, or which children with DS are most at-risk.

This chapter aims to address the evidence gap by utilising the longitudinally linked CALIBER dataset, encompassing records of over 10 million individuals across both primary and secondary care, to undertake a retrospective cohort study of children with DS compared to controls.

5.3 AIMS & OBJECTIVES

5.3.1 Aim

To quantify NHS healthcare utilisation attributable to RTIs in children with and without DS from 1997 to 2010 and to ascertain which children, with and without DS, are most at risk of increased RTI-related NHS healthcare utilisation.

5.3.2 Objectives

1. To investigate whether RTI-related GP consultations and hospitalisations differed in children with DS and controls;
2. To investigate whether RTI-related GP consultations and hospitalisations varied by gender and co-morbidities that influence RTI-related healthcare utilisation；
3. To assess whether RTI-related GP consultations and hospitalisations varied between and across age groups in children with DS and controls;
4. To explore whether hospital length of stay differed between children with DS and controls;
5. To investigate whether children with DS were more likely to be hospitalised following an RTI-related GP consultation compared to controls;
6. To establish how soon after a RTI-related GP consultation were children with DS and controls hospitalised for an RTI;
7. To examine the proportion of children with DS and controls who attended their GP for an RTI-related consultation preceding a RTI-related hospitalisation;
8. To identify what proportion of children with DS and controls re-consult with their GP following an initial consultation for an RTI;
9. To examine whether antibiotic prescribing and RTI-related antibiotic prescribing differed between children with DS and controls;

5.4 METHODS

5.4.1 Data Management

5.4.1.1 Participants

I described the selection of the study population together with assessment of the clinical and demographic characteristics of the cohort in the previous chapter, Chapter 4, "Down's Syndrome and RTIs in CALIBER".

5.4.1.2 Sample size

An Australian study of hospitalisations noted an average of 0.8 and 0.1 RTI-attributable hospital admissions in individuals with and without DS, respectively (71). To identify a difference in hospitalisation rates as large as this between the two groups at 80% power using a 5% significance level, 20 individuals per group with the hospitalisation rates above would be required. If confounding and effect modification are accounted for in this analysis, the sample size required to detect this difference increases by 10% for each variable considered and is increased four-fold if an effect modifier is included using an interaction term. There are approximately 992 children with DS in the CALIBER linked dataset to account for this.

5.4.1.3 Respiratory Tract Infections

Read and ICD-10 codes used to select RTIs are listed in **Table A 2** and **Table A 3** (Appendix), respectively. The processes for selecting RTI-related GP consultations and hospitalisations are described in further detail in the previous chapter.

5.4.1.4 Antibiotic treatment

I selected and categorised antibiotic prescriptions into nine classes as detailed in the BNF; Benzylpenicillin & Phenoxymethylpenicillin, Broad-Spectrum Penicillins, Cephalosporins and Other Beta-Lactams, Macrolides, Metronidazole & Tinidazole, Penicillinase Resistant Penicillins, Quinolones, Sulphonamides & Trimethoprim and Tetracyclines.

I linked these nine classes with all GP consultations irrespective of Read codes (i.e. reason for prescribing an antibiotic). This therefore included consultations with no relevant Read codes for RTIs and was utilised to ascertain differential coding behaviour for the two groups in general.

Identified consultations with same-day antibiotic prescriptions were subsequently linked with GP consultations corresponding with Read codes for RTIs to determine RTI specific prescribing rates.

This approach matched that of other papers investigating RTI-related antibiotic prescribing, which also matched relevant RTI codes with antibiotic prescriptions occurring on the same day (21, 144). An alternative approach could have been to also consider Co-Amoxiclav and Amoxicillin prescriptions without Read codes, as these antibiotics are most commonly prescribed to treat RTIs; however, due to the possibility that such prescriptions were prophylactic or rescue prescriptions, this was not done (145).

5.4.2 Data Analyses

All data management and analysis was performed using STATA statistical software version 13 (146) and R version 3.2.3 (147) via the UCL Data Safe Haven (148).

5.4.2.1 Consultation, Hospitalisation and Prescription Rates

I used Poisson regression to calculate consultation, hospitalisation and prescription rates and rate ratios and their corresponding 95% confidence intervals. Within CALIBER, consultation and prescription rates were sourced from CPRD, and hospitalisation rates were sourced from HES. I computed rates by dividing the number of episodes during the active period in the database by the total number of active person years (pyr) for both the children with DS and the matched control groups. Persons who are active in the database are those who are alive and currently registered.

5.4.2.2 Hospital length of stay

For admissions lasting greater than one day, the length of stay was calculated as "discharge date – admission date". For admissions occurring solely over the course of one day, I calculated the length of stay as the "discharge date – admission date + 1 day" in order to avoid the implication that a zero-day admission meant children were not admitted to hospital at all. Since 2010, the numbers of zero day admissions have risen by over 90% so it was important to capture this group (149).

I reported the length of hospitalisation in both means and medians due to the highly skewed distribution of hospitalisation lengths. The Wilcoxon non-parametric test was

used to compare length of stay by RTI type due to the skewed distribution. This test determines if there is a difference in the variance (or location/central tendency of the data) in two groups – in this case the DS and control groups.

5.4.2.3 Subgroup Analyses – Year, Age Group, Gender, IMD quintile, RTI type,

I conducted analyses across years, age groups, gender, IMD quintile and by RTI type (i.e. URTI/LRTI/unclassified RTI, with the unclassified RTI label indicating uncertainty as to whether it was a URTI or LRTI). Since different distributions in co-morbidities that are part of DS could drive major differences in healthcare utilisation, the prevalence of co-morbidities was established using the code lists described in Chapter 3. This was done with the intention to analyse by co-morbidities which may influence RTI-related healthcare utilisation. Analyses by age and IMD quintile were undertaken between children with DS and controls in the same age group, and across ages and IMD quintiles within children with DS and controls.

5.4.2.4 Subgroup Analyses - Seasonality

I visualised the seasonal trend of RTIs in children with DS and controls through a week-by-week histogram graph.

In the UK, RSV season occurs during October (week 40) to March (week 19) each year (150). The influenza season typically lasts from November to March. I calculated the rate of RTI events during the Influenza/RSV season using RTIs events between the 40th week of the year and the 19th week of the subsequent year and compared this to the rate of RTI events occurring in the rest of the year.

5.4.2.5 Baseline risk of hospitalisation following a consultation

All GP consultations for RTIs, irrespective of type (i.e. URTI/LRTI/unclassified RTI), were defined as the exposure; whilst all RTI-related hospitalisations were considered as the outcome or complication.

A systematic review which determined the duration of symptoms of earache, sore throat, cough, bronchiolitis, croup and common cold in children was identified (151).

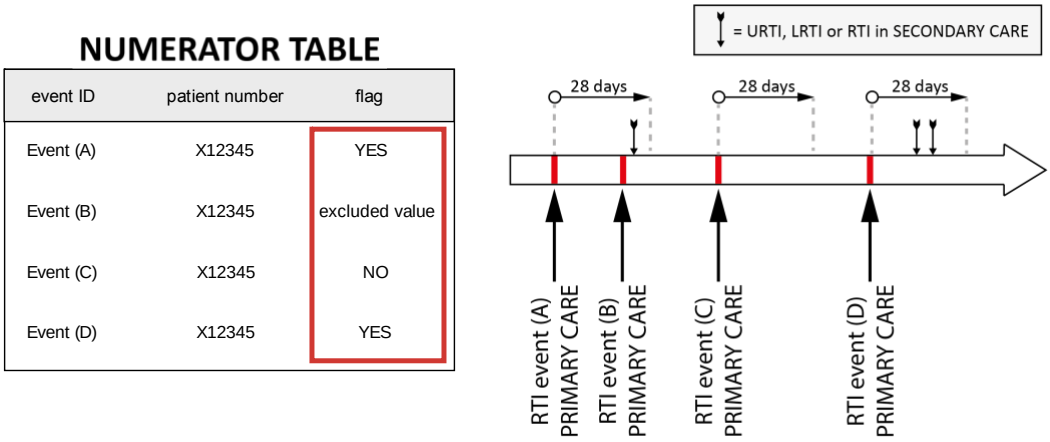
This review found that in 90% of children, earache was resolved by seven to eight days, sore throat between two and seven days, croup by two days, bronchiolitis by 21 days,

acute cough by 25 days, common cold by 15 days, and non-specific respiratory tract infections symptoms by 16 days.

A 28-day window was therefore utilised as the at-risk period for an RTI-related complication/hospitalisation. Each consultation for an RTI was followed up for up to 28 days or the first hospitalisation for an RTI within 28 days.

An illustration of this process is provided in **Figure 14.** Events (A) to (D) all are linked to the same patient, X12345.

Figure 14. Process for identifying RTI-related hospitalisations following RTI-related GP consultations.



A GP consultation for an RTI would be considered a new exposure if it occurred more than 28 days after the previous event. For example, Event (D) is considered a new event as it occurred after 28 days from Event (C). However, Event (B) is not considered a new event as it occurred less than 28 days after Event (A), and it is thus flagged as an excluded value.

A distribution of time-to-hospitalisation is displayed and compared using the Wilcoxon non-parametric test due to the highly-skewed distribution. By completing this analysis, hospitalisations linked to a prior GP consultation could be identified, which then allowed analysis in Chapter 6 of the effect of antibiotic prescriptions in primary care on the rate of subsequent hospitalisation.

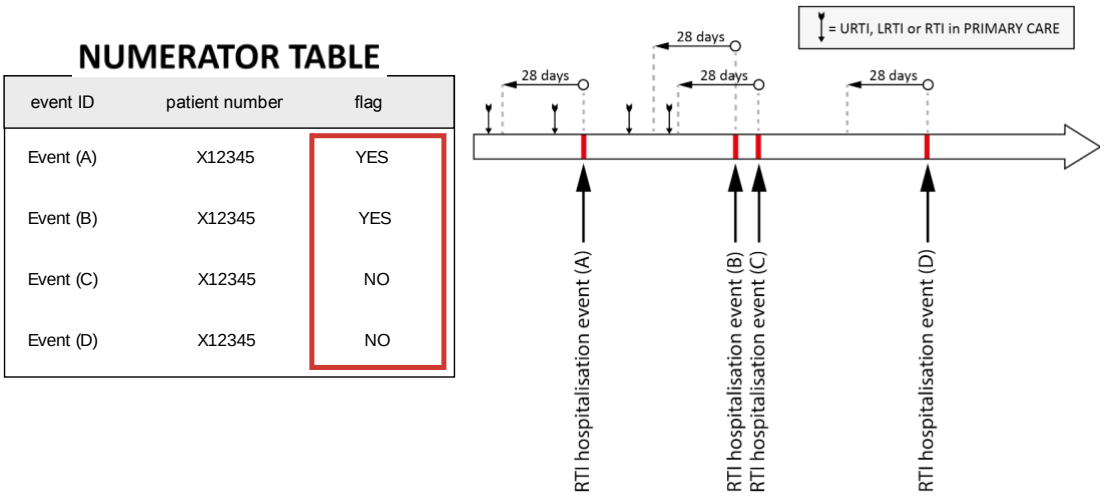
RTIs were given a hierarchical rank with secondary care superseding primary care irrespective of whether it involved an upper or lower respiratory tract infection (e.g.

Primary care consultation for LRTI on D1 followed by a URTI hospitalisation on day 4 was classified as a URTI). This strategy was chosen because it was assumed that diagnoses in secondary care would be more accurate, given the wider array of diagnostic tools available to clinicians in these settings. A systematic review comparing hospital discharge coding against medical records found that UK hospital diagnostic coding is 91% accurate (152).

5.4.2.6 Hospitalisations preceded by consultations

All RTI-related hospitalisations in the cohort were identified with a 28-day "look-back" undertaken to identify the proportion of hospitalisations preceded by a GP consultation for an RTI, shown in **Figure 15.** Events (A) to (D) all are linked to the same patient, X12345. Events (A) and (B) are flagged because in the 28-day "look back" period, a URTI, LRTI or unspecified RTI consultations in primary care was identified (denoted by an arrow). For Events (C) and (D), no RTI consultation was identified, so they are not flagged as hospitalisations preceded by consultations.

Figure 15. Process for identifying RTI-related consultations preceding RTI-related hospitalisations.



5.4.3 Scientific Approval

I obtained scientific approval for the study from the CPRD ISAC under the remit of ISAC protocol 15_041R: 'Respiratory tract infections in Down's Syndrome'.

5.5 RESULTS

5.5.1 Cohort size, demographics and co-morbidities

I identified 992 children with DS. They were followed up for a total of 4,681 person-years at risk, a mean of 4.72 years per child. Their 4,874 frequency controls were followed up for a total of 22,837 person-years at risk, a mean of 4.69 years per child. The demographics of the study populations are shown in **Table 8.**

The children were similarly distributed among the four age categories (25.6% infants, 23.2% toddlers, 21.3% juniors and 29.8% young persons). As ethnicity was not used in subsequent analyses, I did not seek to address missing data by use of methods such as multiple imputation.

The unadjusted prevalence of CHD and hypothyroidism were higher in children with DS compared with controls, whilst asthma was similarly common in both groups. CHD and asthma were both analysed in subgroup analyses.

Table 8. Demographic characteristics of the cohort.

	Control	Children with DS
Patient	4874 (100.0%)	992 (100.0%)
Gender		
Male	2626 (53.9%)	528 (53.2%)
Female	2248 (46.1%)	464 (46.8%)
Age at Entry into Cohort		
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%)
Co-morbidities		
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%)

5.5.2 Comparison with known prevalence rates for children with DS

The calculated prevalence of DS within the CALIBER cohort is 0.034%. This compares to an estimated prevalence of DS in England and Wales of 0.066% when a meta-analysis of papers assessing survival rates for DS was applied to data from the National Down Syndrome Cytogenetic Register, which produces annual reports on the number of babies born with DS each year (3).

When comparing the prevalence of comorbidities in DS, prevalence figures in this study are similar to those reported in existing literature. The calculated prevalence of CHD in DS of 39.6% compares to rates of 33.7% to 58.2% in other studies (153-156). A prevalence of 13.7% for asthma compares to rates of 3.1% to 19.4% (81, 157). Calculated prevalence figures of 1.1% for diabetes, 1.8% for epilepsy, and 10.4% for thyroid dysfunction in this study compare to prevalence figures of 0.3% (158), 1-13% (159), and 25-30% (160) reported by other studies and reviews.

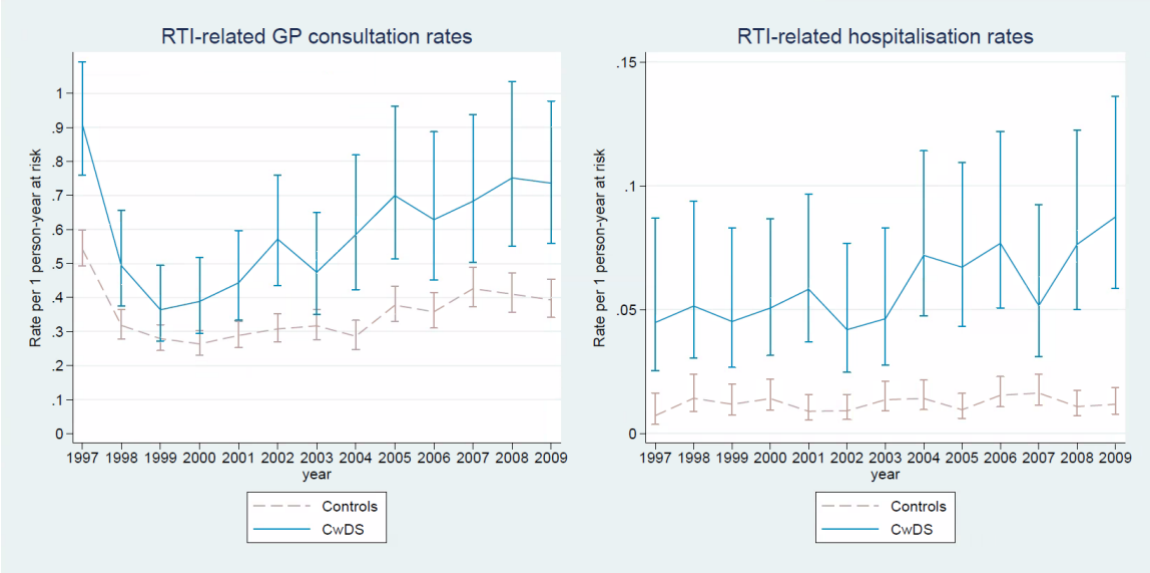
For the control group, the prevalence of comorbidities was mostly similar to other studies. A prevalence of CHD of 1.0% compares to a prevalence of 0.6-0.8% in other studies (161, 162). The prevalence of asthma of 12.7% was slightly higher than the reported prevalence of 9% from Asthma UK (163). Calculated prevalence figures of 0.4% for diabetes, 0.7% for epilepsy and 0.2% for thyroid dysfunction compare to prevalence figures of 0.2% (164), 0.5% (165), and 0.1% (166) reported elsewhere.

5.5.3 Consultation and hospitalisation rates

5.5.3.1 Across the cohort

Over the study period between 1997 and 2010, RTI-related GP consultation and hospitalisation rates were consistently higher in children with DS compared to controls. The disparities increased over time from a 0.1 rate difference in RTI-related consultations in 1999 to a 0.3 rate difference in 2009, and a 0.04 rate difference in RTI-related hospitalisations in 1997 to a 0.07 rate difference in RTI-related hospitalisations in 2009. This is illustrated in **Figure 16** below.

Figure 16. Annual RTI-related GP consultation and hospitalisation rates in children with DS compared to controls.



5.5.3.2 Differences between consultations and hospitalisations

Table 9 illustrates that across all RTI types (i.e. LRTI, URTI, and unclassified RTI), children with DS consistently experience consultations and hospitalisations for RTIs more frequently compared to controls.

When adjusted for age group, children with DS are nearly twice as likely (Adjusted RR 1.73; 95% CI 1.62-1.84) as matched controls to present to their GP with an RTI and six times more likely (Adjusted RR 5.70; 95% CI 4.82-6.71) to be admitted to hospital with an RTI.

The differences between children with DS and controls were most pronounced for LRTIs in GP consultations (RR 3.59; 95% CI 3.19-4.04) and hospitalisations (RR 11.30; 95% CI 8.45-15.10).

Table 9. RTI-related GP consultation (top) and hospitalisation (bottom) rates by RTI type in children with DS and controls.

RTI-related GP consultation rates

Classification	CwDS			Controls			CwDS vs controls		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
URTI	3442	2245	0.421 [0.385-0.460]	9093	14072	0.258 [0.247-0.270]	1.628 [1.514-1.750]	1.604 [1.493-1.723]	<0.0001
POSSIBLE	286	4250	0.044 [0.038-0.051]	952	21223	0.033 [0.031-0.036]	1.321 [1.118-1.554]	1.329 [1.131-1.561]	0.0005
PROBABLE	3156	2313	0.393 [0.359-0.430]	8141	14600	0.237 [0.227-0.247]	1.661 [1.543-1.788]	1.633 [1.518-1.757]	<0.0001
LRTI	874	3657	0.119 [0.107-0.134]	1039	21255	0.034 [0.031-0.037]	3.508 [3.108-3.955]	3.589 [3.188-4.041]	<0.0001
POSSIBLE	33	4627	0.006 [0.004-0.009]	80	22696	0.003 [0.002-0.004]	2.258 [1.402-3.558]	2.325 [1.499-3.606]	0.0003
PROBABLE	841	3686	0.115 [0.103-0.129]	959	21335	0.032 [0.030-0.035]	3.567 [3.153-4.031]	3.646 [3.231-4.114]	<0.0001
unclassified RTI	1697	3158	0.199 [0.179-0.220]	3825	18344	0.114 [0.109-0.120]	1.739 [1.588-1.902]	1.759 [1.609-1.923]	<0.0001
POSSIBLE	213	4313	0.037 [0.031-0.044]	628	21857	0.023 [0.021-0.025]	1.599 [1.330-1.914]	1.618 [1.355-1.933]	<0.0001
PROBABLE	1484	3280	0.177 [0.160-0.197]	3197	18902	0.097 [0.092-0.103]	1.825 [1.660-2.004]	1.865 [1.699-2.048]	<0.0001
ALL	6013	1770	0.638 [0.582-0.699]	13957	12161	0.363 [0.348-0.378]	1.760 [1.647-1.880]	1.726 [1.617-1.843]	<0.0001
POSSIBLE	532	3925	0.083 [0.074-0.094]	1660	20301	0.058 [0.054-0.061]	1.440 [1.270-1.629]	1.443 [1.276-1.631]	<0.0001
PROBABLE	5481	1854	0.588 [0.537-0.644]	12297	12800	0.327 [0.314-0.341]	1.799 [1.682-1.924]	1.761 [1.648-1.882]	<0.0001

RTI-related hospitalisation rates

Classification	CwDS			Controls			CwDS vs controls		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
URTI	205	4367	0.035 [0.030-0.043]	187	22513	0.007 [0.006-0.009]	4.814 [3.842-6.029]	4.989 [4.007-6.211]	<0.0001
POSSIBLE	5	4673	0.001 [0.000-0.004]	0	22829	-	-	-	-
PROBABLE	200	4371	0.035 [0.029-0.042]	187	22513	0.007 [0.006-0.009]	4.717 [3.760-5.913]	4.882 [3.917-6.085]	<0.0001
LRTI	213	4428	0.032 [0.026-0.038]	73	22704	0.003 [0.002-0.004]	10.557 [7.847-14.321]	11.295 [8.448-15.101]	<0.0001
POSSIBLE	0	4680	-	0	22829	-	-	-	-
PROBABLE	213	4428	0.032 [0.026-0.038]	73	22704	0.003 [0.002-0.004]	10.557 [7.847-14.321]	11.295 [8.448-15.101]	<0.0001
unclassified RTI	55	4603	0.010 [0.007-0.013]	67	22701	0.003 [0.002-0.004]	3.468 [2.314-5.158]	3.578 [2.444-5.239]	<0.0001
POSSIBLE	34	4629	0.006 [0.004-0.009]	52	22732	0.002 [0.002-0.003]	2.644 [1.608-4.264]	2.728 [1.723-4.319]	<0.0001
PROBABLE	21	4651	0.004 [0.003-0.007]	15	22795	0.001 [0.000-0.001]	6.651 [3.162-14.336]	6.785 [3.405-13.517]	<0.0001
ALL	473	4127	0.067 [0.058-0.077]	327	22283	0.013 [0.011-0.014]	5.342 [4.506-6.332]	5.693 [4.818-6.727]	<0.0001
POSSIBLE	39	4624	0.007 [0.005-0.010]	52	22732	0.002 [0.002-0.003]	3.025 [1.885-4.789]	3.126 [2.013-4.854]	<0.0001
PROBABLE	434	4162	0.062 [0.054-0.072]	275	22364	0.011 [0.009-0.012]	5.871 [4.905-7.029]	6.243 [5.233-7.447]	<0.0001

5.5.3.3 By age and gender

Across all age groups, children with DS consult with their GP and are hospitalised for RTIs more commonly than controls. This is illustrated in **Figure 17** below.

For example, across 100 infants with DS (0-1 years old), there will be 150 RTI-related GP consultations and 52 hospitalisations. This is in contrast to 124 GP consultations and 8 hospitalisations in matched controls.

The differences between children with DS and controls are more pronounced in RTI-related hospitalisations. For example, juniors with DS (5-10 years) are seven times more likely to be hospitalised compared to controls (Adjusted RR 7.33; 95% CI 5.08- 10.58). This is in contrast to RTI-related GP consultations where the rate ratio is 2.21 (95% CI 1.95-2.50).

Figure 17. RTI-related GP consultation and hospitalisation rates stratified by age group in children with DS and controls.

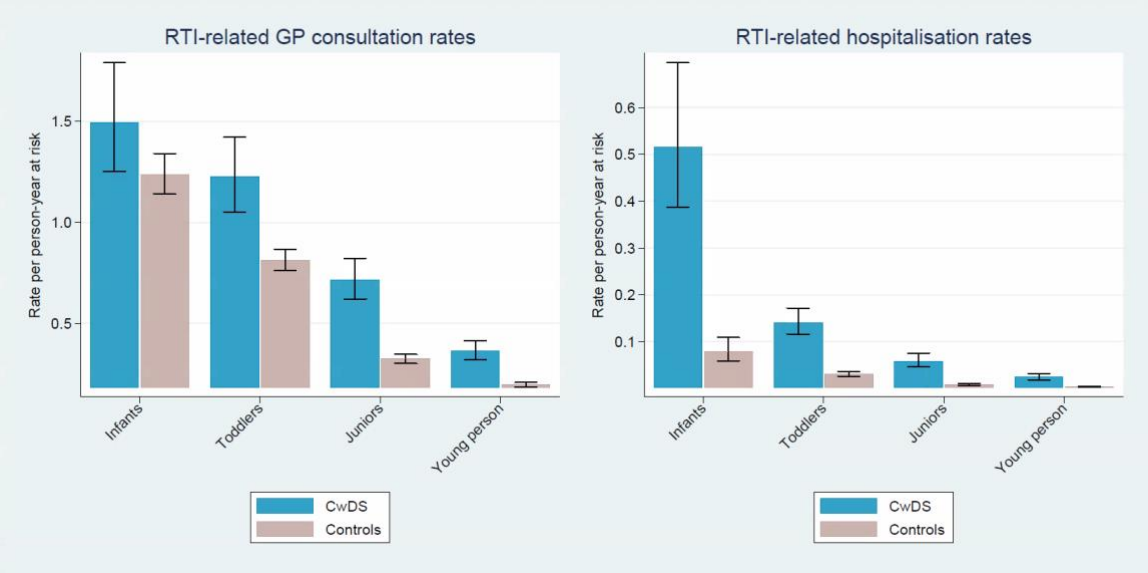


Table 10. RTI-related GP consultation (top) and hospitalisation (bottom) rates stratified by age groups and compared between children with DS and controls.

RTI-related GP consultation rates

Classification	CwDS			Controls			CwDS vs controls		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
Infants	270	74	1.495 [1.252-1.790]	961	411	1.236 [1.140-1.341]	1.210 [0.975-1.490]	1.210 [0.985-1.487]	0.0371
Toddlers	2387	286	1.225 [1.052-1.422]	6185	1873	0.813 [0.761-0.867]	1.508 [1.339-1.695]	1.508 [1.343-1.694]	<0.0001
Juniors	1727	445	0.715 [0.621-0.822]	3365	3514	0.324 [0.302-0.346]	2.211 [1.946-2.505]	2.211 [1.952-2.503]	<0.0001
Young person	1629	966	0.364 [0.319-0.414]	3446	6362	0.195 [0.184-0.208]	1.861 [1.648-2.096]	1.861 [1.653-2.095]	<0.0001

RTI-related hospitalisation rates

Classification	CwDS			Controls			CwDS vs controls		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
Infants	73	91	0.515 [0.388-0.695]	56	529	0.079 [0.059-0.109]	6.491 [4.190-10.087]	6.491 [4.282-9.842]	<0.0001
Toddlers	240	805	0.140 [0.116-0.171]	176	4831	0.031 [0.026-0.036]	4.582 [3.554-5.893]	4.582 [3.587-5.853]	<0.0001
Juniors	93	1114	0.058 [0.046-0.075]	56	6407	0.008 [0.006-0.011]	7.330 [5.002-10.792]	7.330 [5.080-10.576]	<0.0001
Young person	67	2116	0.024 [0.018-0.032]	39	10516	0.004 [0.003-0.005]	6.669 [4.296-10.432]	6.669 [4.382-10.150]	<0.0001

Similar to the pattern seen in **Table 10,** both children with DS and controls experience fewer consultations and hospitalisations due to RTIs as they get older. This is in keeping with existing literature that RTI healthcare utilisation is higher in infants compared to their older peers (167). This is illustrated in **Table 11** below. The relative risk was calculated separately for children with DS and controls by using the age band 'infants' as a comparator.

Table 11. RTI-related GP consultation (top) and hospitalisation (bottom) rates stratified by age group and compared within children with DS and controls.

RTI-related GP consultation rates

	CwDS		Controls	
Classification	**RR [95%CI]**	**p-value**	**RR [95%CI]**	**p-value**
Infants	1.000 [0.761-1.315]	0.5000	1.000 [0.883-1.133]	0.5000
Toddlers	0.819 [0.660-1.025]	0.0361	0.658 [0.594-0.728]	<0.0001
Juniors	0.478 [0.384-0.600]	<0.0001	0.262 [0.236-0.291]	<0.0001
Young person	0.243 [0.196-0.304]	<0.0001	0.158 [0.142-0.176]	<0.0001

RTI-related hospitalisation rates

	CwDS		Controls	
Classification	**RR [95%CI]**	**p-value**	**RR [95%CI]**	**p-value**
Infants	1.000 [0.653-1.531]	0.5000	1.000 [0.636-1.572]	0.5000
Toddlers	0.272 [0.192-0.391]	<0.0001	0.386 [0.272-0.558]	<0.0001
Juniors	0.113 [0.077-0.168]	<0.0001	0.100 [0.065-0.155]	<0.0001
Young person	0.047 [0.031-0.071]	<0.0001	0.046 [0.029-0.072]	<0.0001

As denoted in **Table 12**, females have lower RTI-related hospitalisation rates compared to males in both children with DS (Adjusted RR 0.70; 95% CI 0.55-0.89) and matched controls (Adjusted RR 0.69; 95% CI 0.54-0.88). There is no significant gender difference for RTI-related GP consultation rates for children with DS (Adjusted RR 1.08; 95% CI 0.96-1.21) and matched controls (Adjusted RR 0.99; 95% CI 0.93-1.05).

Table 12. RTI-related GP consultation (top) and hospitalisation (bottom) rates between gender stratified by children with DS and controls.

RTI-related GP consultation rates

	Female			Male			Female vs Male		
Classification	**# episodes**	**person-year**	**Rate per person-year [95%CI]**	**# episodes**	**person-year**	**Rate per person-year [95%CI]**	**RR [95%CI]**	**Adjusted RR [95%CI] for age group**	**p-value**
CwDS	2803	784	0.666 [0.585-0.757]	3210	987	0.616 [0.542-0.700]	1.081 [0.960-1.217]	1.075 [0.957-1.208]	0.0964
Controls	6657	5735	0.364 [0.342-0.386]	7300	6425	0.362 [0.341-0.383]	1.006 [0.947-1.067]	0.991 [0.934-1.051]	0.4261

RTI-related hospitalisation rates

	Female			Male			Female vs Male		
Classification	**# episodes**	**person-year**	**Rate per person-year [95%CI]**	**# episodes**	**person-year**	**Rate per person-year [95%CI]**	**RR [95%CI]**	**Adjusted RR [95%CI] for age group**	**p-value**
CwDS	184	1945	0.056 [0.045-0.069]	289	2182	0.077 [0.064-0.093]	0.721 [0.561-0.924]	0.696 [0.547-0.887]	0.0038
Controls	119	10720	0.010 [0.008-0.012]	208	11563	0.015 [0.013-0.017]	0.671 [0.522-0.859]	0.691 [0.543-0.879]	0.0005

5.5.3.4 By IMD

There was no significant difference in RTI-related GP consultation and hospitalisation rates when stratified by IMD quintile, as illustrated by **Table 13.** For children with DS, the rates of GP consultations and hospitalisations in the least deprived quintile (Quintile 1) was 0.642 and 0.051, lower than rates of 0.765 and 0.079 in the most deprived quintile (Quintile 5) but the confidence intervals overlapped. Across each quintile, there was a pattern of children with DS engaging in more healthcare utilisation than controls, as described elsewhere in the thesis.

Table 13. RTI-related GP consultation (top) and hospitalisation (bottom) rates stratified IMD quintile and compared between children with DS and controls.

RTI-related GP consultation rates

	CwDS			Controls			CwDS vs Controls		
Classification	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age	p-value
IMD Quintile									
1	1422	436	0.642 [0.534-0.770]	2998	2718	0.356 [0.326-0.389]	1.802 [1.572-2.060]	1.788 [1.566-2.042]	<0.0001
2	1205	374	0.609 [0.500-0.740]	2990	2469	0.358 [0.327-0.393]	1.699 [1.463-1.968]	1.581[1.367-1.828]	<0.0001
3	1182	355	0.597 [0.479-0.741]	2497	2462	0.342 [0.312-0.376]	1.744 [1.493-2.029]	1.890 [1.626-2.198]	<0.0001
4	1110	360	0.619 [0.503-0.758]	2138	2499	0.368 [0.335-0.404]	1.681 [1.446-1.948]	1.546 [1.336-1.788]	<0.0001
5	1094	245	0.765 [0.604-0.961]	2734	2012	0.394 [0.356-0.437]	1.940 [1.646-2.278]	1.854 [1.581-2.173]	<0.0001

RTI-related hospitalisation rates

	CwDS			Controls			CwDS vs Controls		
Classification	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age	p-value
IMD Quintile									
1	74	1074	0.051 [0.038-0.071]	50	4961	0.008 [0.006-0.011]	6.351 [4.150-9.796]	6.922 [4.597-10.422]	<0.0001
2	98	864	0.068 [0.050-0.095]	63	4613	0.012 [0.009-0.016]	5.830 [3.962-8.594]	6.058 [4.183-8.773]	<0.0001
3	104	792	0.080 [0.060-0.107]	64	4459	0.013 [0.010-0.017]	6.331 [4.347-9.242]	7.227 [5.036-10.372]	<0.0001
4	99	803	0.065 [0.048-0.089]	84	4529	0.015 [0.012-0.019]	4.250 [2.907-6.181]	4.222 [2.947-6.049]	<0.0001
5	98	593	0.079 [0.056-0.114]	66	3722	0.016 [0.012-0.021]	4.918 [3.284-7.326]	5.149 [3.515-7.543]	<0.0001

The relative risk was also calculated separately for children with DS and controls by using the IMD Quintile 1 as a comparator, shown in **Table 14**. This quintile reflects the least deprived quintile of individuals. When this analysis was done, a significantly greater relative risk of GP consultations and hospitalisations were evident in children with DS living in Quintile 5 compared to children with DS living in Quintile 1. This was also the case for controls living in Quintiles 5, 2 and 4 relative to Quintile 1.

Table 14. RTI-related GP consultation (top) and hospitalisation (bottom) rates stratified by IMD quintile and compared within children with DS and controls.

RTI-related GP consultation rates

	CwDS		Controls	
Classification	RR [95%CI]	p-value	RR {95%CI]	p-value
IMD Quintile				
1	1.000 [0.844-1.184]	0.5000	1.000 [0.914-1.094]	0.5000
2	0.948 [0.793-1.133]	0.2762	1.005 [0.917-1.102]	0.4536
3	0.930 [0.774-1.115]	0.2116	0.961 [0.875-1.055]	0.1973
4	0.964 [0.804-1.153]	0.3400	1.033 [0.943-1.131]	0.2417
5	1.191 [0.984-1.438]	0.0331	1.106 [1.005-1.216]	0.0181

RTI-related hospitalisation rates

	CwDS		Controls	
Classification	RR [95%CI]	p-value	RR {95%CI]	p-value
IMD Quintile				
1	1.000 [0.675-1.480]	0.5000	1.000 [0.629-1.590]	0.5000
2	1.333 [0.907-1.961]	0.0632	1.452 [0.947-2.243]	0.0368
3	1.553 [1.064-2.271]	0.0087	1.558 [1.020-2.399]	0.1590
4	1.265 [0.849-1.882]	0.1133	1.890 [1.262-2.864]	0.0006
5	1.548 [1.026-2.327]	0.0148	1.99 [1.318-3.062]	0.0003

5.5.3.5 By season

The incidence of RSV, influenza and other respiratory infections varies by season. This is likely to influence healthcare utilisation in both children with DS and controls (168).

I analysed the weekly trends of RTI-related consultation and hospitalisation rates in children with DS and controls. The relative risk of consultations and hospitals, adjusted for age group, in the RSV-influenza season (Autumn and Winter) was compared against the same adjusted risk for the summer season, with results denoted in **Figure 18** and **Table 15.**

A significant difference in consultations and hospitalisations (Adjusted RR 1.17; 95% CI 1.10-1.26) was noted in controls but not in children with DS.

Figure 18. RTI-related consultations and hospitalisations in children with DS and controls by week.

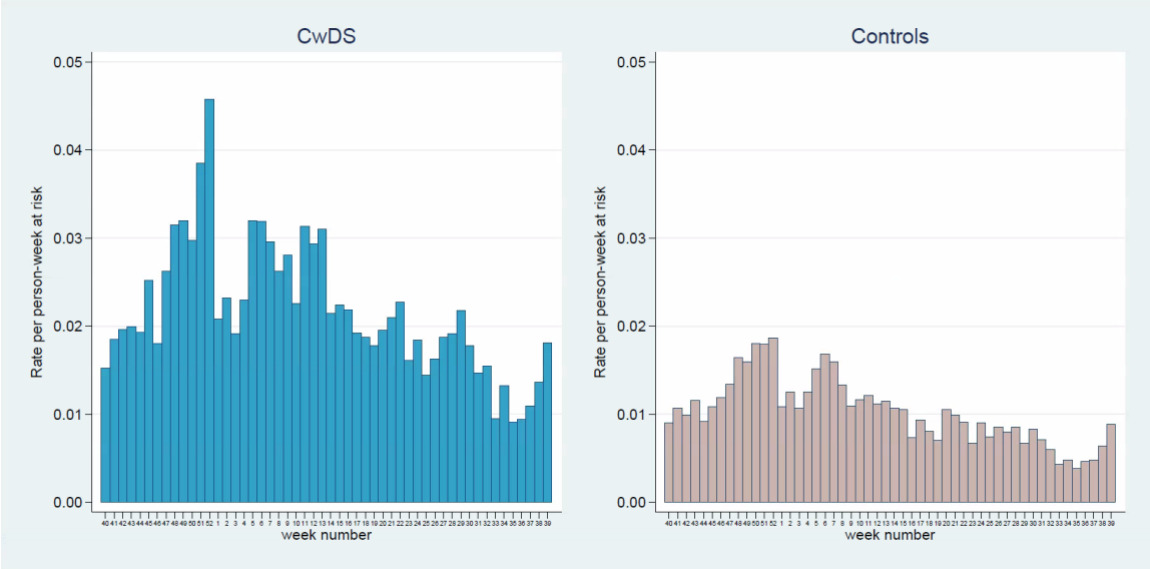


Table 15. RTI-related consultations and hospitalisations in children with DS and controls by season.

Classification	RSV-influenza season			Summer season			RSV-influenza season vs summer season		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
CwDS	4735	632	1.444 [1.310-1.588]	1751	181	1.423 [1.209-1.664]	1.015 [0.883-1.170]	1.029 [0.896-1.183]	0.4207
Controls	10548	3034	1.119 [1.067-1.173]	3736	1164	0.909 [0.846-0.975]	1.231 [1.149-1.321]	1.174 [1.096-1.258]	<0.0001

5.5.3.6 RTI-related consultations and hospitalisations by co-morbidities

Co-morbidities such as CHD and asthma may account for differences in healthcare utilisation between children with DS and controls. I therefore analysed RTI-related consultation and hospitalisation, first comparing those with DS and a particular comorbidity to those with DS who lack the comorbidity, and controls with to those without the comorbidity. Secondly, I compared children with DS and a comorbidity to

controls with same comorbidity, and then children with DS without the comorbidity to controls without the comorbidity.

Congenital Heart Disease

Children with DS and CHD have increased RTI-related consultation (Adjusted RR 1.21; 95% CI 1.04-1.40) and hospitalisation rates (Adjusted RR 3.07; 95% CI 2.38-3.95) compared to children with DS without CHD. A similar pattern is observed in controls. These are illustrated in **Figure 19** and **Table 16** below.

Figure 19. RTI-related consultations (left) and hospitalisations (right) in children with DS and controls with and without CHD.

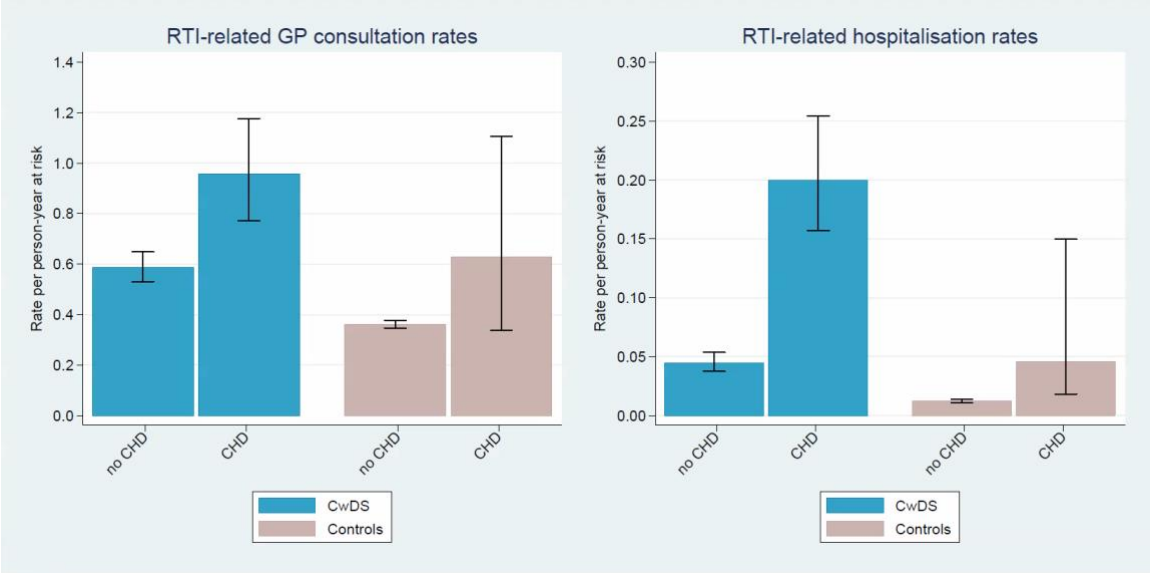


Table 16. RTI-related GP Consultation (top) and hospitalisation (bottom) rates between children with and without CHD stratified by DS.

RTI-related GP consultation rates

Classification	Children with CHD			Children without CHD			Children with CHD vs Children without CHD		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
CwDS	1351	247	0.956 [0.771-1.177]	4662	1523	0.587 [0.530-0.649]	1.629 [1.406-1.883]	1.206 [1.042-1.396]	<0.0001
Controls	57	25	0.629 [0.338-1.107]	13900	12135	0.362 [0.347-0.378]	1.737 [0.992-2.824]	1.633 [0.999-2.668]	0.0202

RTI-related hospitalisation rates

Classification	Children with CHD			Children without CHD			Children with CHD vs Children without CHD		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
CwDS	247	591	0.200 [0.157-0.254]	226	3536	0.045 [0.038-0.054]	4.469 [3.490-5.708]	3.065 [2.380-3.946]	<0.0001
Controls	3	66	0.046 [0.018-0.150]	324	22217	0.012 [0.011-0.014]	3.683 [0.755-10.877]	3.891 [1.250-12.114]	0.0300

In those with CHD, children with DS and CHD have higher rates of RTI-related hospitalisation (Adjusted RR 3.15; 95% CI 1.02-9.68) but similar RTI-related GP

consultations compared to controls with CHD. In those without CHD, children with DS have both higher RTI-related GP consultations (Adjusted RR 1.70; 95% CI 1.58-1.82) and hospitalisations (Adjusted RR 4.17; 95% CI 3.42-5.08) compared to controls. This is illustrated in **Table 17** below.

Table 17. RTI-related GP Consultation (top) and hospitalisation (bottom) rates between children with DS and controls stratified by CHD status.

RTI-related GP consultation rates

	CwDS vs controls		
Classification	**RR [95%CI]**	**Adjusted RR [95%CI] for age group**	**p-value**
Children without CHD	1.621 [1.507-1.742]	1.694 [1.576-1.820]	<0.0001
Children with CHD	1.520 [0.917-2.704]	1.260 [0.755-2.100]	0.0463

RTI-related hospitalisation rates

	CwDS vs controls		
Classification	**RR [95%CI]**	**Adjusted RR [95%CI] for age group**	**p-value**
Children without CHD	3.597 [2.939-4.390]	4.166 [3.417-5.079]	<0.0001
Children with CHD	4.364 [1.457-21.464]	3.145 [1.024-9.657]	0.0009

Asthma

Children with DS with asthma have increased RTI-related GP consultations (Adjusted RR 2.06; 95% CI 1.74-2.44) compared to those without asthma, but not increased RTI-related hospitalisations. Controls with asthma have increased RTI-related GP consultations (Adjusted RR 1.75; 95% CI 1.61-1.90) and also RTI-related hospitalisations (Adjusted RR 2.65; 95% CI 2.01-3.50) relative to controls without asthma. These results suggest that asthma may increase the risk of RTI-related healthcare utilisation for both groups. This is detailed in **Figure 20** and **Table 18** below.

Figure 20. RTI-related GP consultations and hospitalisations in children with DS (left) and controls (right) with and without asthma.

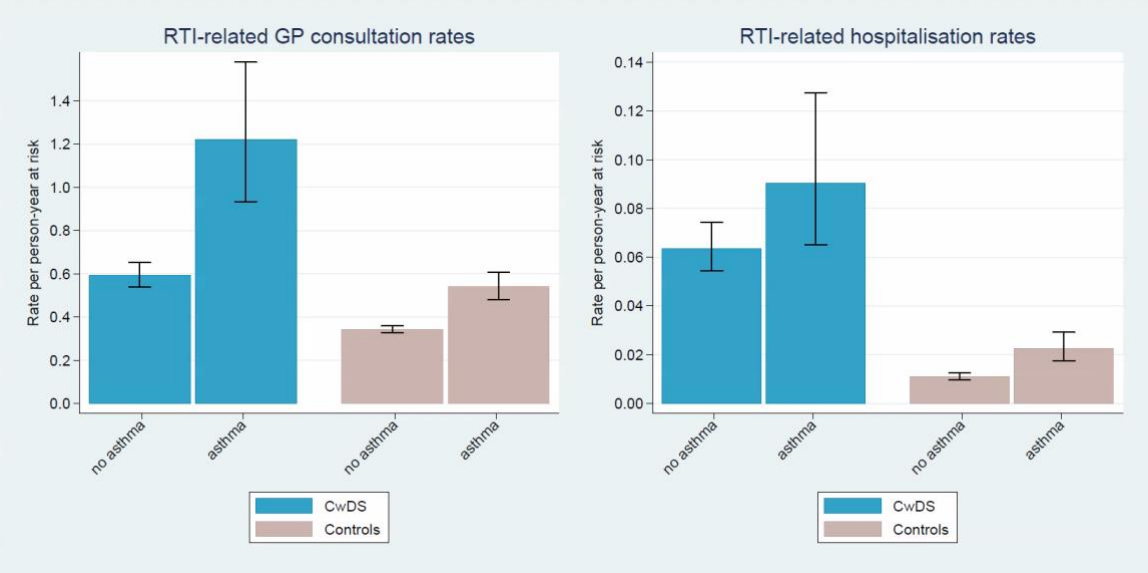


Table 18. RTI-related GP Consultation (top) and hospitalisation (bottom) rates between children with and without asthma stratified by DS.

RTI-related GP consultation rates

Classification	Children with asthma			Children without asthma			Children with asthma vs Children without asthma		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
CwDS	1516	129	1.220 [0.933-1.578]	4497	1641	0.592 [0.538-0.652]	2.060 [1.730-2.439]	2.059 [1.740-2.437]	<0.0001
Controls	2913	1200	0.540 [0.480-0.606]	11044	10960	0.343 [0.328-0.359]	1.573 [1.445-1.710]	1.752 [1.611-1.906]	<0.0001

RTI-related hospitalisation rates

Classification	Children with asthma			Children without asthma			Children with asthma vs Children without asthma		
	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
CwDS	85	532	0.090 [0.065-0.128]	388	3595	0.063 [0.054-0.074]	1.423 [1.020-1.950]	1.680 [1.229-2.297]	0.0158
Controls	82	2984	0.022 [0.018-0.029]	245	19299	0.011 [0.010-0.013]	2.044 [1.529-2.702]	2.649 [2.007-3.497]	<0.0001

Amongst children with asthma, children with DS and asthma have significantly more RTI-related GP consultations (Adjusted RR 2.11; 95% CI 1.78-2.51) and hospitalisations (Adjusted RR 4.03; 95% CI 2.79-5.83) compared to controls with asthma. Amongst children without asthma, children with DS still have higher RTI-related GP consultations (Adjusted RR 1.70; 95% CI 1.58-1.82) and hospitalisations (Adjusted RR 6.21; 95% CI 5.15-7.50) than controls. This is illustrated in **Table 19** below.

Table 19. RTI-related GP Consultation (top) and hospitalisation (bottom) rates between children with DS and controls stratified by presence of asthma.

RTI-related GP consultation rates

	CwDS vs controls		
Classification	**RR [95%CI]**	**Adjusted RR [95%CI] for age group**	**p-value**
Children without asthma	1.726 [1.607-1.853]	1.703 [1.588-1.828]	<0.0001
Children with asthma	2.260 [1.887-2.694]	2.116 [1.780-2.517]	<0.0001

RTI-related hospitalisation rates

	CwDS vs controls		
Classification	**RR [95%CI]**	**Adjusted RR [95%CI] for age group**	**p-value**
Children without asthma	5.774 [4.768-6.994]	6.215 [5.150-7.499]	<0.0001
Children with asthma	4.020 [2.715-5.910]	4.032 [2.790-5.827]	<0.0001

5.5.4 Length of stay in hospital

Overall, the length of stay in hospital due to RTIs is longer for children with DS (Mean 5.2; 95% CI 5.0-5.4 days per admission) compared to controls (Mean 2.4; 95% CI 2.2-2.6), as shown in **Table 20.**

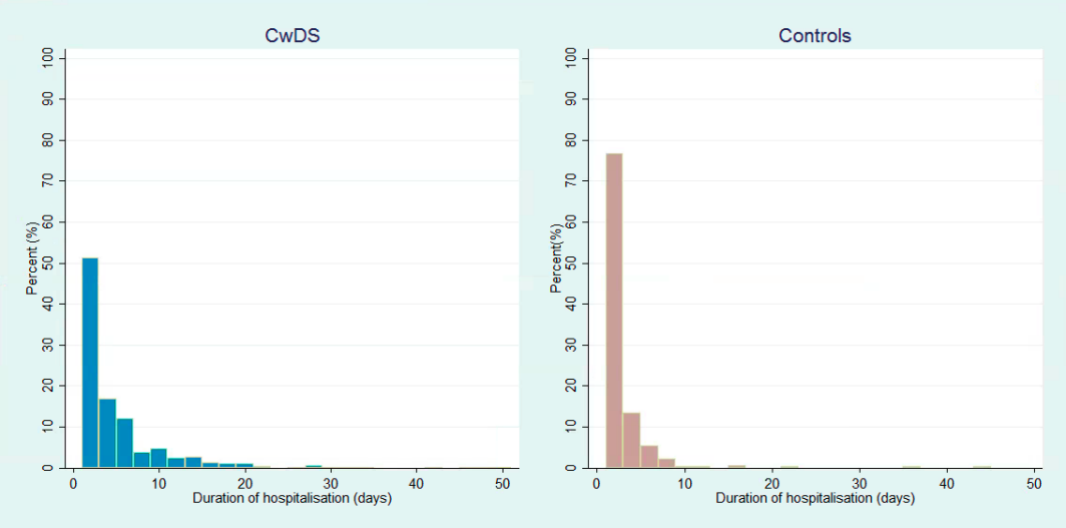
For each RTI type, a significantly longer hospitalisation stay was noted in children with DS compared to controls. In keeping with LRTIs being more severe than URTIs or unclassified RTIs, the longest hospitalisation time was noted in LRTI-related hospitalisations in both Children with DS and controls.

Table 20. Length of stay in hospital for LRTI, URTI, and unclassified RTI in days in children with DS and controls.

	CwDS		Controls		
Classification	**mean [95%CI]**	**median [IQR]**	**mean [95%CI]**	**median [IQR]**	**p-value**
URTI	2.4 [2.2-2.6]	2.0 [1.0-2.0]	1.9 [1.7-2.1]	1.0 [1.0-2.0]	0.0325
LRTI	7.8 [7.4-8.1]	5.0 [3.0-10.0]	4.2 [3.8-4.7]	3.0 [2.0-5.0]	<0.0001
unclassified RTI	5.6 [5.0-6.3]	2.0 [1.0-4.0]	1.9 [1.6-2.3]	1.0 [1.0-2.0]	0.0265
ALL	5.2 [5.0-5.4]	2.0 [1.0-5.0]	2.4 [2.2-2.6]	2.0 [1.0-2.0]	<0.0001

This is illustrated in **Figure 21** below, which consist of 473 hospitalisations (205 URTI, 213 LRTI, and 55 unclassified RTI) in 220 children with DS and 327 hospitalisations (187 URTI, 73 LRTI and 67 unclassified RTI) in 266 controls, respectively.

Figure 21. Distribution of RTI-related hospitalisation length of stay in children with DS and controls.



5.5.5 Baseline risk of RTI-related hospitalisation following a RTI-related GP consultation

Table 21 denotes the number and proportions of consultations for RTIs followed by a hospitalisation within 28 days. Across all RTI types (i.e. URTI, LRTI, or unclassified RTI), children with DS were three times (RR 3.15; 95% CI 2.35–4.24) more likely to be admitted for an RTI-related hospitalisation following a RTI-related GP consultation compared to controls.

With a baseline risk of 2.1% (95% CI 1.7-2.5%), this translates to two in 100 children with DS being admitted for an RTI-related hospitalisation following an RTI-related GP consultation compared to 0.7 controls.

Table 21. Risk of RTI-related hospitalisation following an RTI-related GP consultation within 28 days in children with DS and controls.

	CwDS			Controls			CwDS vs Controls	
Classification	# of consultations	# of hospitalisations	Risk [95%CI]	# of consultations	# of hospitalisations	Risk [95%CI]	Risk ratio [95%CI]	p-value
URTI	2769	42	0.015 [0.011-0.021]	7915	43	0.005 [0.004-0.007]	2.792 [1.829-4.262]	<0.0001
LRTI	621	15	0.024 [0.014-0.040]	838	7	0.008 [0.003-0.017]	2.892 [1.186-7.050]	0.0168
unclassified RTI	1295	40	0.031 [0.022-0.042]	3124	28	0.009 [0.006-0.013]	3.446 [2.135-5.561]	<0.0001
ALL	4685	97	0.021 [0.017-0.025]	11877	78	0.007 [0.005-0.008]	3.153 [2.345-4.239]	<0.0001

5.5.6 Time to RTI-related hospitalisation following a RTI-related GP consultation

It was hypothesised that, in addition to varying healthcare utilisation, children and families with DS may behave differently in the lead up to an episode of healthcare

utilisation, and may be more or less likely to seek help after the beginning of symptoms. Many factors can affect healthcare-seeking behaviour (169, 170). Building on the initial analyses undertaken above, **Figure 22** and **Table 22** denote the time-to-hospitalisation from an initial presentation to the GP for an RTI in children with DS and controls. The percentages indicate the percentage of consultations which are followed by a hospitalisation occurring at each time period out of all total consultations. No statistically significant differences were noted between both groups, with a median of 8.0 days (95% CI 3.0-19.0) in children with DS and 8.0 days (95% CI 2.0-18.0) in matched controls.

Figure 22. Time to hospitalisation in children with DS and controls following an RTI-related GP consultation.

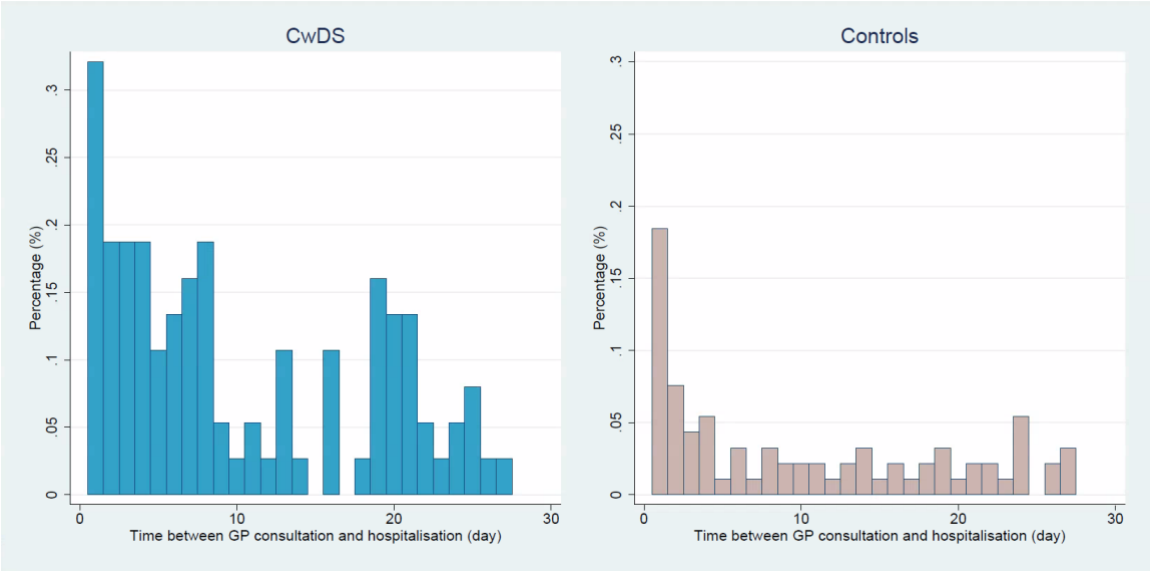


Table 22. Time to hospitalisation following an RTI-related GP consultation in children with DS and controls.

	CwDS		Controls		
Classification	**mean [95%CI]**	**median [IQR]**	**mean [95%CI]**	**median [IQR]**	**p-value**
URTI	13.0 [11.9-14.1]	11.5 [4.0-21.0]	12.4 [11.3-13.5]	11.0 [3.0-21.0]	0.6888
LRTI	7.9 [6.5-9.4]	5.0 [2.0-16.0]	7.1 [5.3-9.4]	6.0 [1.0-8.0]	0.9150
unclassified RTI	8.3 [7.5-9.3]	7.0 [2.5-13.0]	7.6 [6.7-8.7]	4.0 [1.0-15.0]	0.2867
ALL	10.3 [9.6-10.9]	8.0 [3.0-19.0]	10.2 [9.5-10.9]	8.0 [2.0-18.0]	0.6097

5.5.7 Re-consultation with a GP following an initial GP consultation for an RTI

Children with DS are more likely (OR 1.69; 95% CI 1.57-1.82) to re-consult with their GP for an RTI within 28 days of a prior RTI-related consultation compared to matched

controls, with a total of 24.3% children with DS re-consulting compared to 16.0% amongst matched controls. Full figures are available in **Table 23**.

Table 23. Re-consultation with GP following an initial RTI-related GP consultation in children with DS and controls.

	CwDS		Controls			
Classification	**n**	**%**	**n**	**%**	**odds ratio [95%CI]**	**p-value**
# of GP consultations					1.690 [1.569-1.820]	<0.0001
0	4549	75.7	11724	84.0		
1	1144	19.0	1882	13.5		
>1	320	5.3	351	2.5		
Total	6013	100.0	13957	100.0		

5.5.8 Hospitalisations preceded by consultations

Table 24 denotes the number and proportion of hospitalisations preceded by a RTI-related GP consultation. No significant differences were noted between children with DS and controls, with 74.1% and 73.4% of RTI-related hospitalisations occurring without any prior GP consultation in for children with DS and controls, respectively.

Table 24. RTI-related hospitalisations preceded by a RTI-related consultation in children with DS and controls.

	CwDS			Controls			CwDS vs Controls	
Classification	**# of hospitalisations**	**# of consultations**	**Risk [95%CI]**	**# of hospitalisations**	**# of consultations**	**Risk [95%CI]**	**Risk ratio [95%CI]**	**p-value**
URTI	201	32	0.159 [0.109-0.225]	179	42	0.235 [0.169-0.317]	0.679 [0.449-1.026]	0.0700
LRTI	201	73	0.363 [0.285-0.457]	68	26	0.382 [0.250-0.560]	0.950 [0.667-1.352]	0.7733
unclassified RTI	53	13	0.245 [0.131-0.419]	65	15	0.231 [0.129-0.381]	1.063 [0.556-2.032]	1.0000
ALL	455	118	0.259 [0.215-0.311]	312	83	0.266 [0.212-0.330]	0.975 [0.766-1.241]	0.8674

5.5.9 Antibiotic prescriptions

5.5.9.1 Prescribing Trends

The number of prescriptions for the whole study period varied considerably by antibacterial class, illustrated in **Figure 23** and **Table 25**.

Children with DS were prescribed at least twice as many antibiotics compared to matched controls over the entire study period, with a rate per person year (PPY) of 0.774 (95% CI 0.709-0.844), compared to 0.324 (95% CI 0.311-0.337) for controls (Adjusted RR 2.34; 95% CI 2.19-2.49). This relationship was consistent across all drug classes except for "Metronidazole and tinidazole" and "Tetracyclines", classes that are rarely prescribed for RTIs, where there was no significant difference.

Broad-spectrum penicillins were the most commonly prescribed drugs in both children with DS and controls.

Figure 23. Trends in antibiotic prescription rates by drug class in children with DS (left) and controls (right).

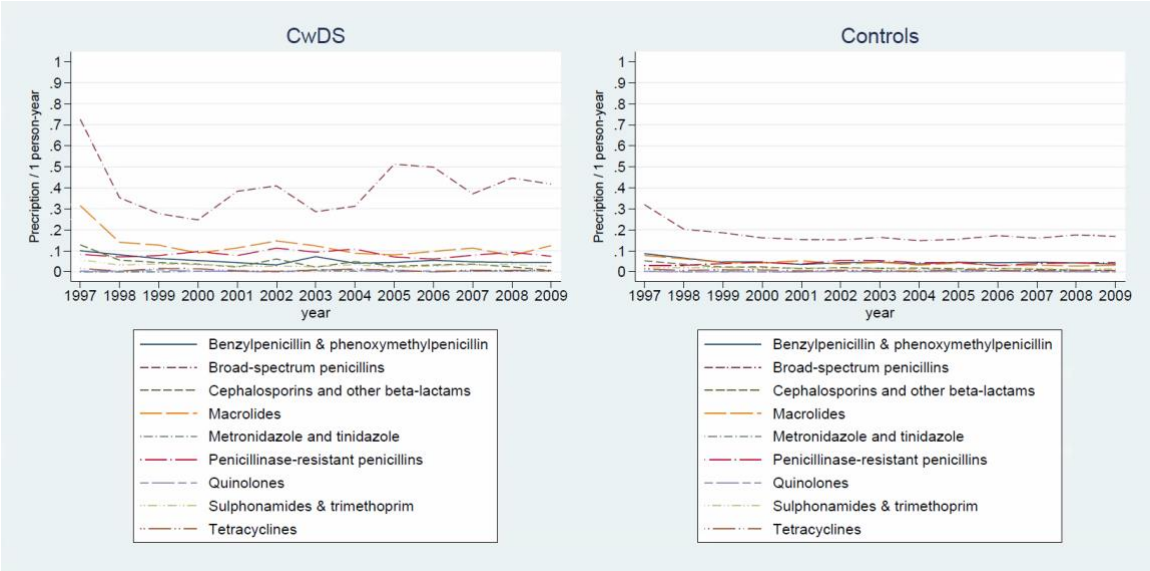
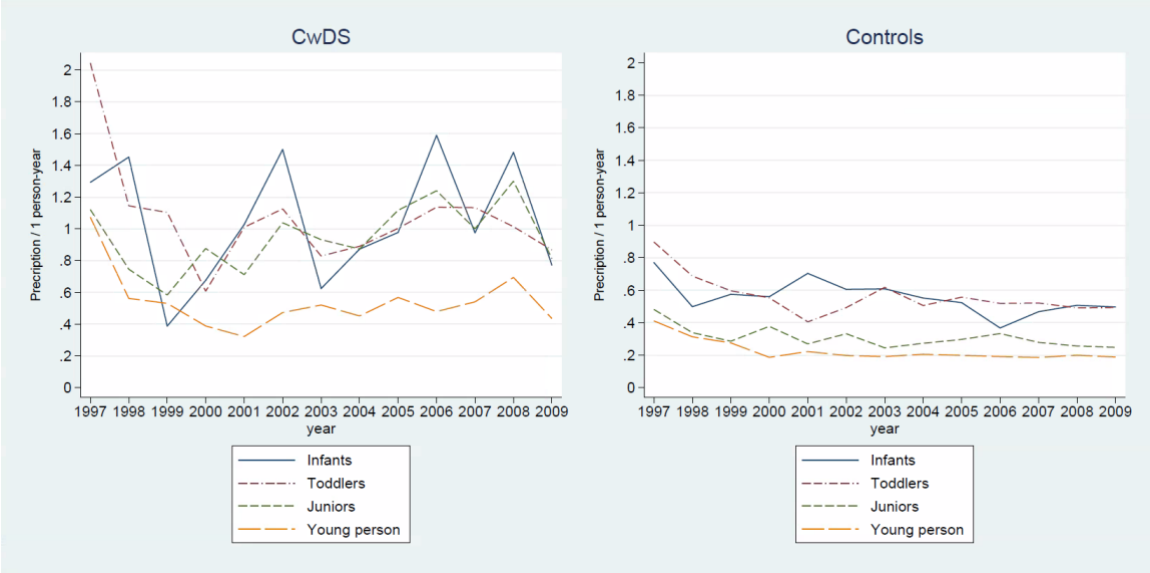


Table 25. Antibiotic prescriptions in children with DS compared to matched controls.

Classification	CwDS			Controls			CwDS vs Controls		
	# of prescriptions	person-year	Rate per person-year [95%CI]	# of prescriptions	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
Total	**7637**	**1506**	**0.774 [0.709-0.844]**	**12759**	**12476**	**0.324 [0.311-0.337]**	**2.393 [2.240-2.555]**	**2.337 [2.190-2.494]**	**<0.0001**
Benzylpenicillin & phenoxymethylpenicillin	447	4060	0.059 [0.052-0.068]	1580	20305	0.050 [0.047-0.054]	1.186 [1.027-1.366]	1.183 [1.028-1.362]	0.0094
Broad-spectrum penicillins	3659	2221	0.428 [0.390-0.469]	6005	15864	0.182 [0.174-0.190]	2.348 [2.180-2.528]	2.365 [2.198-2.545]	<0.0001
Cephalosporins and other beta-lactams	681	4124	0.046 [0.039-0.055]	805	21820	0.020 [0.018-0.022]	2.290 [1.921-2.721]	2.309 [1.948-2.737]	<0.0001
Macrolides	1418	3453	0.138 [0.123-0.154]	1647	20626	0.045 [0.042-0.048]	3.080 [2.752-3.445]	3.089 [2.766-3.451]	<0.0001
Metronidazole and tinidazole	14	4652	0.003 [0.002-0.006]	60	22739	0.002 [0.002-0.003]	1.488 [0.755-2.754]	1.466 [0.810-2.655]	0.1016
Penicillinase-resistant penicillins	609	3822	0.089 [0.080-0.100]	1249	20651	0.043 [0.041-0.046]	2.056 [1.810-2.332]	2.058 [1.817-2.332]	<0.0001
Quinolones	34	4625	0.005 [0.003-0.007]	36	22762	0.001 [0.001-0.002]	3.609 [1.984-6.470]	3.502 [2.026-6.055]	<0.0001
Sulphonamides & trimethoprim	634	4321	0.036 [0.030-0.043]	671	22041	0.017 [0.015-0.019]	2.157 [1.777-2.607]	2.181 [1.809-2.629]	<0.0001
Tetracyclines	137	4611	0.008 [0.006-0.011]	676	22530	0.007 [0.006-0.009]	1.096 [0.745-1.573]	1.052 [0.736-1.502]	0.3032

The highest rates of antibiotic prescribing were noted in infants and toddlers, with marked variations in antibiotic prescription rates by age groups. This trend is illustrated in **Figure 24**, where it is also notable that prescribing patterns in infants fluctuate by as much as 0.6 per person year on year, such as between 2002-2003 and 2008-2009.

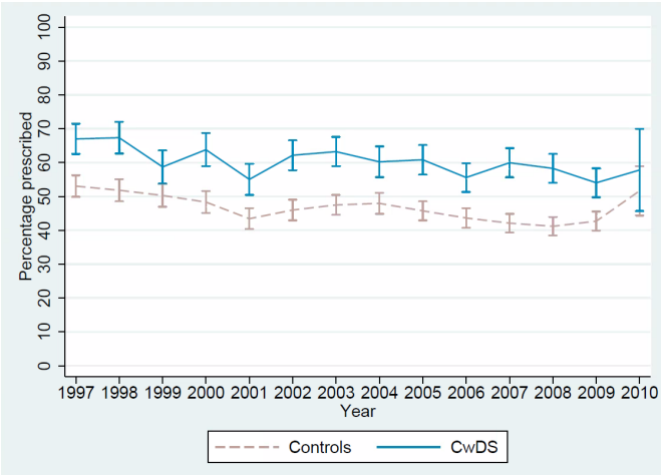
Figure 24. Trends in antibiotic prescription rates by age group in children with DS (left) and controls (right).



5.5.9.2 RTI-related GP consultations with antibiotics prescribed on the same day

Over the study period, a reduction in RTI-related GP consultations with antibiotics prescribed on the same day was noted in children with DS (67.0% in 1997 to 57.8% in 2010), shown in **Figure 25**. There was a slight reduction for controls (53.1% to 51.7%, respectively).

Figure 25. Trends in percent of RTI-related GP consultations with a same day antibiotic prescription.



Year	CwDS Percentage, mean [95%CI]	Controls Percentage, mean [95%CI]
1997	67.0 [62.5-71.4]	53.1 [49.9-56.2]
1998	67.4 [62.7-72.0]	51.8 [48.6-55.1]
1999	58.7 [53.8-63.6]	50.3 [46.9-53.6]
2000	63.8 [58.9-68.7]	48.3 [45.1-51.6]
2001	55.0 [50.4-59.6]	43.4 [40.4-46.5]
2002	62.2 [57.7-66.6]	46.0 [43.0-49.0]
2003	63.2 [58.9-67.6]	47.5 [44.6-50.4]
2004	60.2 [55.7-64.8]	48.0 [44.8-51.1]
2005	60.8 [56.5-65.2]	45.8 [42.9-48.6]
2006	55.6 [51.4-59.8]	43.6 [40.8-46.5]
2007	60.0 [55.7-64.2]	42.1 [39.4-44.8]
2008	58.3 [54.0-62.6]	41.2 [38.5-43.9]
2009	54.0 [49.8-58.3]	42.7 [39.9-45.5]
2010	57.8 [45.7-69.9]	51.7 [44.4-59.0]

When findings were stratified by RTI-type in **Table 26,** significant differences were observed in the percentage of RTI-related GP consultations with an antibiotic prescribed

on the same day, with more URTIs (57.0%; 95% CI 55.3-58.6% vs 47.9%; 95% CI 46.9-49.0%) and unclassified-RTIs (52.9%; 95% CI 50.5-55.3% vs 32.0%; 95% CI 30.5-33.5%) in children with DS being prescribed antibiotics compared to controls. There was no significant difference in the high proportion of LRTIs that were prescribed antibiotics in children with DS compared with controls (87.0% vs. 82.5%).

Table 26. Percentage of RTI-related GP consultations with an antibiotic prescribed on the same day, stratified by RTI type.

Classification	CwDS		Controls		
	n	Percentage, mean [95%CI]	n	Percentage, mean [95%CI]	p-value
URTI	3442	57.0 [55.3-58.6]	9093	47.9 [46.9-49.0]	<0.0001
LRTI	874	87.0 [84.7-89.2]	1039	82.5 [80.2-84.8]	0.2279
unclassified RTI	1697	52.9 [50.5-55.3]	3825	32.0 [30.5-33.5]	<0.0001
ALL	6013	60.2 [58.9-61.4]	13957	46.1 [45.3-47.0]	<0.0001

When stratified by age group in Error! Reference source not found., significant d ifferences were noted between all age-groups in the percentage of RTI-related GP consultations prescribed an antibiotic, with children with DS consistently prescribed more antibiotics for RTIs compared to controls.

Table 27. Percentage of RTI-related GP consultations prescribed an antibiotic on the same day, stratified by age.

Classification	CwDS		Controls		
	n	Percentage, mean [95%CI]	n	Percentage, mean [95%CI]	p-value
Infants	270	43.3 [37.4-49.2]	961	26.7 [23.9-29.5]	0.0002
Toddlers	2387	56.2 [54.2-58.2]	6185	42.6 [41.4-43.8]	<0.0001
Juniors	1727	63.1 [60.8-65.3]	3365	49.2 [47.5-50.9]	<0.0001
Young person	1629	65.7 [63.4-68.1]	3446	54.9 [53.3-56.6]	0.0001

Similar to findings described above (Chapter 5.5.9.1), when restricted to antibiotic prescriptions prescribed on the same day as an RTI-related GP consultation, children with DS were twice as likely to be prescribed an antibiotic for an RTI compared to matched controls (Adjusted RR 2.26; 95% CI 2.10–2.43), with a rate per person-year of 0.424 for children with DS compared to 0.188 for controls. This is shown in **Table 28.** The greatest Adjusted RR was for the Penicillinase-resistant penicillins, Quinolones, and Sulphonamides & trimethoprim, all of which had an Adjusted RR for children with DS compared to controls of greater than 5.

Table 28. RTI-related GP consultations with a same day antibiotic prescription sorted by antibiotic class in children with DS and controls.

Classification	CwDS			Controls			CwDS vs Controls		
	# of prescriptions	person-year	Rate per person-year [95%CI]	# of prescriptions	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
Total	**3664**	**2211**	**0.424 [0.386-0.465]**	**6486**	**15603**	**0.188 [0.180-0.197]**	**2.253 [2.091-2.426]**	**2.259 [2.099-2.432]**	**<0.0001**
Benzylpenicillin & phenoxymethylpenicillin	272	4209	0.045 [0.038-0.052]	1208	20821	0.039 [0.036-0.042]	1.138 [0.966-1.335]	1.134 [0.968-1.328]	0.0563
Broad-spectrum penicillins	2259	2688	0.297 [0.269-0.327]	4064	17486	0.129 [0.123-0.136]	2.291 [2.111-2.485]	2.338 [2.156-2.534]	<0.0001
Cephalosporins and other beta-lactams	255	4343	0.028 [0.022-0.034]	295	22312	0.010 [0.008-0.011]	2.867 [2.274-3.601]	2.898 [2.319-3.623]	<0.0001
Macrolides	764	3804	0.090 [0.079-0.103]	817	21585	0.025 [0.023-0.028]	3.584 [3.122-4.111]	3.625 [3.167-4.149]	<0.0001
Metronidazole and tinidazole	1	4678	0.000 [0.000-0.000]	1	22827	0.000 [0.000-0.000]	-	-	-
Penicillinase-resistant penicillins	30	4617	0.006 [0.004-0.009]	27	22769	0.001 [0.001-0.002]	5.114 [2.905-9.018]	5.154 [3.036-8.750]	<0.0001
Quinolones	11	4662	0.002 [0.001-0.004]	11	22811	0.000 [0.000-0.001]	5.592 [1.772-18.115]	5.513 [2.002-15.186]	0.0008
Sulphonamides & trimethoprim	65	4588	0.009 [0.007-0.012]	39	22745	0.002 [0.001-0.002]	5.807 [3.608-9.392]	5.902 [3.763-9.257]	<0.0001
Tetracyclines	7	4665	0.002 [0.001-0.004]	23	22789	0.001 [0.001-0.001]	1.710 [0.611-4.209]	1.642 [0.695-3.884]	0.1182

When antibiotic prescriptions issued on the same day as a RTI-related GP consultations were stratified by RTI type in **Table 29** below, antibiotic prescriptions for LRTIs were noted to be markedly higher in children with DS compared to matched controls (Adjusted RR 3.79; 95% CI 3.34-4.30), with a rate per person-year of 0.108 for children with DS compared to 0.029 for controls. Prescriptions for unclassified RTIs (Adjusted RR 2.90; 95% CI 2.59-3.25) and URTIs (Adjusted RR 1.99; 95% CI 1.83-2.16) were also significantly higher.

Table 29. Rate of RTI-related GP consultations with a same day antibiotic prescription by RTI type in children with DS and controls.

Classification	CwDS			Controls			CwDS vs Controls		
	# of prescriptions	person-year	Rate per person-year [95%CI]	# of prescriptions	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
URTI	1986	2772	0.262 [0.238-0.287]	4382	17208	0.132 [0.125-0.138]	1.988 [1.826-2.162]	1.990 [1.831-2.164]	<0.0001
LRTI	771	3729	0.108 [0.097-0.121]	872	21408	0.029 [0.027-0.032]	3.719 [3.273-4.223]	3.790 [3.344-4.295]	<0.0001
unclassified RTI	907	3594	0.122 [0.109-0.138]	1232	20947	0.044 [0.041-0.047]	2.812 [2.504-3.154]	2.901 [2.589-3.251]	<0.0001
ALL	3664	2211	0.424 [0.386-0.465]	6486	15603	0.188 [0.180-0.197]	2.253 [2.091-2.426]	2.259 [2.099-2.432]	<0.0001

When stratified by age group in **Table 30** below, it was noted that infants with DS had the highest rate of RTI-related antibiotic prescribing compared to all other groups including controls, with rates of 0.80 (95% CI 0.65-0.99) per person-year.

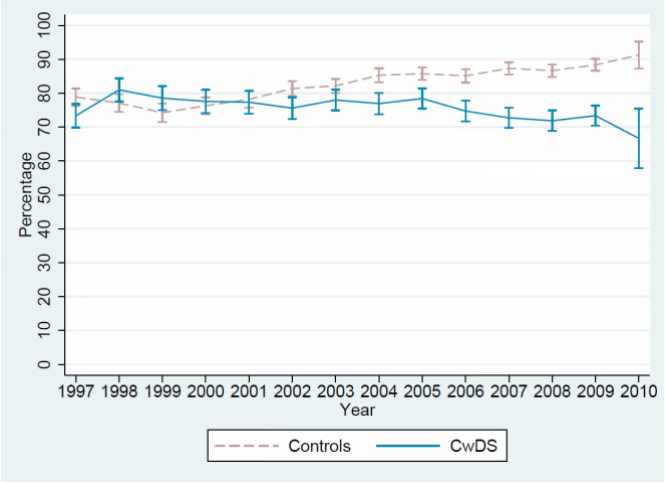
Table 30. Rate of RTI-related GP consultations with a same day antibiotic prescription by age group in children with DS and controls.

Classification	CwDS			Controls			CwDS vs Controls		
	# of prescriptions	person-year	Rate per person-year [95%CI]	# of prescriptions	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age group	p-value
Infants	117	88	0.795 [0.645-0.988]	258	502	0.392 [0.345-0.448]	2.026 [1.520-2.674]	2.026 [1.543-2.661]	<0.0001
Toddlers	1361	421	0.699 [0.605-0.807]	2653	3014	0.352 [0.329-0.376]	1.988 [1.741-2.264]	1.988 [1.747-2.262]	<0.0001
Juniors	1108	567	0.464 [0.399-0.538]	1670	4480	0.175 [0.162-0.189]	2.652 [2.298-3.054]	2.652 [2.307-3.050]	<0.0001
Young person	1078	1135	0.273 [0.239-0.312]	1905	7607	0.118 [0.110-0.126]	2.323 [2.035-2.647]	2.323 [2.042-2.644]	<0.0001

5.5.9.3 Antibiotic prescriptions linked with any (not restricted to RTI) same day consultation code

To assess whether these trends may be due to variation in consultation recording behaviour, an analysis of antibiotic prescriptions linked to any (not restricted to RTI) same day consultation codes was undertaken. **Figure 26** shows a high but increasing trend of antibiotics prescriptions recorded with consultation codes on the same day in controls but not children with DS. This factor may mean there is an underestimation of the difference in RTI-related antibiotic prescribing in children with DS compared to controls.

Figure 26. Percentages of antibiotics prescribed with any same day consultation code in children with DS and controls.



Year	CwDS Percentage, mean [95%CI]	Controls Percentage, mean [95%CI]
1997	73.3 [69.8-76.8]	78.9 [76.3-81.4]
1998	81.0 [77.6-84.4]	77.1 [74.5-79.7]
1999	78.5 [75.0-82.1]	74.2 [71.5-77.0]
2000	77.6 [74.2-81.0]	76.3 [73.8-78.8]
2001	77.3 [74.0-80.7]	78.2 [75.7-80.7]
2002	75.6 [72.4-78.8]	81.4 [79.1-83.6]
2003	78.0 [74.9-81.1]	82.2 [80.1-84.2]
2004	76.9 [73.7-80.1]	85.3 [83.3-87.3]
2005	78.4 [75.4-81.4]	85.7 [83.9-87.6]
2006	74.7 [71.7-77.8]	85.1 [83.1-87.1]
2007	72.7 [69.8-75.7]	87.3 [85.5-89.1]
2008	71.9 [68.8-74.9]	86.6 [84.8-88.5]
2009	73.4 [70.4-76.3]	88.4 [86.6-90.1]
2010	66.7 [57.9-75.4]	91.2 [87.3-95.2]

5.6 DISCUSSION

5.6.1 Summary of main results

The aim of this retrospective cohort study was to quantify RTI-related primary and secondary healthcare utilisation and antibiotic treatment in children with DS compared to age matched children without DS, and also to assess risk of RTI-related hospitalisation, time to RTI-related hospitalisation and re-consultation with their GP. I utilised a linked primary and secondary care longitudinal dataset which allowed the quantification of differences between RTI-related consultation, hospitalisation, and antibiotic prescribing rates in children with DS and controls for the first time.

This study demonstrated that children with DS attend GP consultations more often, are hospitalised more often, stay in hospital longer, and are prescribed antibiotics more frequently for RTIs compared to controls. These findings were shown to be individually independent of age, gender, and co-morbidities that may influence RTI-related healthcare utilisation, such as CHD and asthma. Among subgroups, male children with DS had higher RTI-related hospitalisation rates compared to females, with a rate of 7.7% for males compared to 5.6% for females. This relationship was also present in female controls. Children with DS and controls were hospitalised less often as they aged, and children with DS and CHD had RTI-related hospitalisations more often than controls with CHD and without DS.

Children with DS were three times more likely to be admitted to hospital for an RTI following an RTI-related GP consultation than controls, with a risk of 2.1%, compared to 0.7% amongst controls. However, it was also notable that a significant proportion of these RTI-related hospitalisations (74% in children with DS and 73% in controls) were not preceded by a recorded GP consultation.

In this study, children with DS were prescribed over twice as many antibiotics for RTIs (0.774 PPY) compared to controls (0.324 PPY). These differences were seen in all antibiotic classes commonly prescribed for RTIs.

Differences in prescribing were apparent when stratified by RTI-type, with the highest difference observed in prescribing for LRTIs, which was nearly four-fold greater for children with DS (0.108 PPY) compared to controls (0.029 PPY). Children with DS were also prescribed almost three times as many antibiotics for unclassified RTIs, and twice as

many for URTIs, compared to controls. Infants with DS (0-1 years) were prescribed the most antibiotics for RTIs compared to all other age groups (0.795 PPY).

Children with DS receive more antibiotics for RTIs; firstly, because they consult their GPs for RTIs more often, and secondly because they are more likely to be prescribed an antibiotic when they do so.

5.6.2 Comparison with existing literature

This is the largest study of RTI-related healthcare utilisation in children with DS worldwide (n=992). Additionally, this is the first study known to me which compares healthcare utilisation in children with DS with internal controls and the first to assess healthcare utilisation and antibiotic prescribing in primary care for children with DS.

The calculated prevalence of DS in the CALIBER cohort from this study is 0.034%, which compares to an estimated prevalence of DS in England and Wales of 0.066% using other methods (3). This may be due to a number of factors. The key reason for the reduced prevalence in this cohort may be because patients are simply not being identified in their GP patient records as having a DS diagnosis, which may lead to misclassification bias. The calculated prevalence of comorbidities within the DS cohort was consistent with existing studies, which implies that although the calculated prevalence was lower than other studies, our findings remain representative of the wider DS population.

In keeping with studies of hospitalisations in children with DS in Australia (n=405), the USA (n=217), and Spain (n=93), children with DS have more hospitalisations and longer hospital stays compared to the general population (71, 72, 76). These differences are more pronounced in LRTIs. To my knowledge, no studies have been conducted in developing countries.

Existing literature shows that younger children with DS have an increased risk of RTIs with markedly significant differences in infants compared to controls (167). In this study, I found that the risk of hospitalisations consistently decreased with age, and hence infants were at highest risk.

I found that male children with DS have higher RTI-related hospitalisation rates compared to matched controls. This is in keeping with a 2007 systematic review that identified 84 eligible studies describing differences in incidence of infections between genders and

discovered that males are more likely to develop LRTIs, an RTI-type more likely to predispose to RTI-related hospitalisation. However, the aetiology is not yet understood (171).

Existing literature on CHD and asthma notes that both CHD and asthma appear to be risk factors for increased RTI-related healthcare use (43, 172). In this study, increased RTI-related GP consultations were observed amongst children with DS and asthma, relative to children with DS without asthma (Adjusted RR 2.06). Amongst children with DS and CHD, there was an increased risk of RTI-related consultation (Adjusted RR 1.28) and hospitalisation (Adjusted RR 3.18) relative to those with DS without CHD. Asthma and CHD also increased the risk of RTI-related hospitalisation and consultation amongst controls.

The baseline risk of an RTI-related hospitalisation following an RTI-related GP consultation in our cohort was 0.7% in controls (95% CI 0.5-0.8%), a finding similar to a recent UK population based cohort study which noted a baseline risk of 0.9% (95% CI 0.7-1.2%) (173). The disparity relative to children with DS, where 2.1% are admitted, is disappointing, but it is both notable and encouraging that the absolute numbers for both groups are low.

5.6.3 Strengths and Weaknesses

5.6.3.1 Representativeness

As previous research has noted, the CALIBER database is broadly representative of the UK population as a whole. These study findings can therefore be considered nationally representative (98, 102, 130). Similar findings could also be expected in other industrialised countries with similarly structured healthcare systems.

5.6.3.2 Misclassification

As described in Chapter 3, by relying on READ and ICD-10 codes for diagnoses, this study may be subject to misclassification bias. In this study, its effects would be most pronounced in the selection of RTI-related consultations and hospitalisations.

It is known that considerable inter-practice variation exists in coding certain conditions such as RTIs (144, 174, 175). For example, READ or ICD-10 codes for “respiratory tract infection” could be either an URTI or LRTI. This may lead to either over or underestimation

of healthcare utilisation and/or the effects of antibiotics, depending on whether the consultation/hospitalisation is analysed as an exposure or outcome. I aimed to address this by separately considering unclassified RTI-types.

Furthermore, GPs may not use diagnostic codes to define every RTI episode, and may instead rely on symptom codes or free text entries (144, 174, 175). Whilst my developed codelists incorporated symptom codes, a proportion of RTIs are likely to be missed either due to free text entries or non-recording by GPs.

Whilst antibiotic prescriptions are well coded in CPRD, it's not possible to estimate whether prescriptions were dispensed, or whether a delayed prescribing strategy was intended. This is unlikely to be different between children with DS and controls, so it may lead to either over or underestimation of RTI-related antibiotic use in both groups. There may also be differences in the propensity of parents of children in each group to give antibiotics to their children. The analysis linking antibiotic prescriptions with any types of consultation codes noted high levels of prescribing with any code for both groups, and an increasing trend over time of antibiotics linked with same day consultation codes for controls, but not for children with DS. Children with DS seem to be receiving more prescriptions without consultation codes relative to controls, which may imply an analysis of rescue or prophylactic prescribing would be worthwhile, or that future analysis should consider prescriptions of relevant antibiotics without Read codes.

Whilst a longstanding link between viral RTIs and asthma is known (172), it is possible that episodes of asthma exacerbation may have been misclassified as RTIs due to overlapping symptoms (e.g. difficulty in breathing or cough). If GPs perceive children with DS to be at increased risk of RTIs, they may record RTIs more carefully and accurately for this group compared to controls. Consequentially, some RTI-related prescribing for controls could have been misattributed. This may mean that the difference in prescribing rates could be greater than was calculated. This is differential misclassification bias (e.g. consultation codes better recorded in children with DS compared to controls).

With regards to asthma, it is also important to note that formal diagnoses are not normally given until a child is aged over 5 years and can participate in objective testing, meaning information on healthcare utilisation relying on CPRD codes may be unreliable in the infant and toddler groups. Labels of 'asthma' in this group may actually relate to

viral induced wheeze, which is a more common symptom of a normal respiratory infection in younger age groups due to smaller airways (176). It is estimated that approximately 18-53% of infants who are hospitalised with wheezing symptoms subsequently have asthma when they reach preschool age (177). However, this misclassification most likely was not differential between the two groups. In general, asthma diagnoses made solely using specific asthma codes on CPRD were found to have a positive predictive value of 86.4% in a recent validation study (178). The approach in this study only used consultation codes, so future studies could consider incorporating information on steroid inhaler prescriptions. However, interestingly, the same validation study found that the addition of information on asthma-related prescribing and reversibility testing did not increase the positive predictive value (178).

Finally, amongst limitations related to misclassification, it is thought that linking antibiotic prescriptions to RTI-related GP consultations is a sensitive marker of RTI-related antimicrobial prescribing in EHR research. However, antibiotic drug classes, such as Benzylpenicillins and Macrolides (an alternative for penicillin allergic patients), are also commonly prescribed for skin and soft tissue infections, which children with DS may also be at risk of. These antibiotic groups may therefore not be as specific markers for RTI-related antibiotic prescribing.

5.6.3.3 Missing data

A proportion of medically attended RTIs in both children with DS and controls will be missed, as RTIs are seen not only by GPs but also at other ambulatory care centres (i.e. Urgent Care Centres, Out-of-Hours GP) and A&E (38). Whilst A&E attendances are recorded in a discharge summary, this is variably coded subsequently in the GP record with little information aside from recording of "OOH Visit" or "ED attendance" (38). Little recording of these Read codes were identified. If families of children with DS perceive an increased risk of severe RTIs and correspondingly attend A&E or ambulatory care centres, a larger proportion of RTIs will be missed in children with DS compared to controls. This will therefore lead to an underestimation of healthcare utilisation between children with DS compared to controls.

Research has noted that most RTIs do not lead to a GP consultation (179). There is little qualitative evidence on healthcare seeking behaviour in families of children with DS, and

whether this varies from other patient groups. The data may therefore reflect a difference in propensity to consult when children with DS and controls have RTIs, rather than a true difference in RTI incidence.

Whilst incomplete and/or poor recording of co-morbidities will be evident in CALIBER, it is not possible to address missingness when it is not clear whether data are missing or not. Amongst the included comorbidities, poor recording of asthma may be present particularly for under-5 year olds. The format is only to record chronic illnesses that do occur, not to record the fact that chronic illnesses do not occur. This is in contrast to other data types, such as age and gender, where it is clear whether or not data is missing. This can therefore lead to either an over or underestimation of the prevalence of co-morbidities in children with DS and/or controls.

5.6.4 Implications for practice

5.6.4.1 Primary and secondary care

This study demonstrates that children with DS are twice as likely to consult their GP for an RTI and six times more likely to be hospitalised due to RTIs compared to children without DS. When hospitalised, children with DS remain in hospital for twice the duration of controls.

Two in 100 children with DS who attend their GP for an RTI will later be hospitalised, a threefold increased risk compared to controls. They are similarly more likely to re-consult with their GP for an RTI compared to controls. This suggests that a review of the current management of children with DS presenting with RTIs in primary care would be beneficial. It will be important to identify whether the high rates of admission are related to severity of the infection, time at presentation, or time and type of antibiotics prescribed. Healthcare professionals in primary care should be vigilant when assessing children with DS with the knowledge that subsequent hospital admissions are more likely. The PPI panel felt that symptoms in children with DS were sometimes dismissed as merely being part of the disorder. For example, in one case of floppiness, this was presumed to represent normal hypotonia and was actually a sign of meningitis. Cases such as this could impede early intervention in acute illness. A focus group based study reported that parents feel the level of their child's functioning is sometimes related to the level of care that they receive (180).

One of the reasons for the higher rate of hospitalisation in children with DS could be increased uncertainty with regards to morbidity in this group, such as speed of deterioration or oxygen requirements, and many of the admissions may be precautionary rather than related to increased severity. In this context, parents have even reported that some doctors seem 'afraid' of children with DS (180). With this in mind, it is important to consider that an increased likelihood of hospitalisation may not be an appropriate proxy for an increased likelihood of severe infection. Even so, any hospitalisation can be a traumatic event for a child and their family, especially if such interruptions in their lives are common, and can be a risk in its own right for subsequent complications such as hospital acquired pneumonia.

Given that a significant proportion of RTI-related hospitalisations (74% in children with DS and 73% in controls) are not preceded by GP consultations, it is important to direct any education of professionals or other interventions towards multiple points along the patient pathway, and to include the diverse set of professionals with whom children with DS come into contact. A&E, community and other general or respiratory professionals should receive consistent guidance on how to assess and manage children with DS and RTIs. In addition, it may be useful to educate parents to help them understand when it is most appropriate to attend a GP, A&E, or ambulatory care centre. Such education could be delivered by healthcare professionals at routine appointments.

Finally, the relative difference in RTI-related healthcare utilisation was most prominent in infants with DS relative to controls. It could be argued that this is linked to immune system immaturity at this age, as discussed in Chapter 1 (181). A study of children aged 0-24 months found a rapid increase in respiratory infections in the first two months after the commencement of daycare, followed by a rapid fall sustained over the following nine months; first socialising with other young children may begin at this stage, increasing the risk of RTIs (182).

5.6.4.2 Antibiotic prescribing

Children with DS are twice as likely as controls to be prescribed antibiotics for RTIs overall (0.774 PPY vs 0.324 PPY), and three times more likely to be prescribed antibiotics for LRTIs (0.103 PPY vs 0.028 PPY). Infants with DS (<1 years) are prescribed the most antibiotics across all age groups (0.795 PPY) and significantly more than control infants (0.392 PPY).

All antibiotic classes in section 5.1 of the BNF were included, in line with the methodology of previous studies investigating RTI related antibiotic prescribing (21).

NICE do already recommend a lower threshold for prescribing antibiotics in children with comorbidities, which may account for the higher rates in antibiotic prescription rates (33). However, this study quantifies the baseline risk of RTIs in children with DS compared with controls and antibiotic prescribing patterns for the first time, and enables healthcare professionals to inform families and carers of the risks to their child accurately.

The greater rates of prescribing may mostly be attributed to greater clinical need, which could be due to a more complex individual problem or multiple simultaneous problems requiring attention. However, a number of other factors should be considered. As identified by the PPI panel, rescue pack prescriptions are common for children with DS. Various factors have been identified as being related to prescribing decisions, such as parental expectation, uncertainty, and pressure from employers (41, 42). Parental expectation may be greater due to experience with past admissions and frequent complications; uncertainty may be better due to clinicians infrequently encountering children with DS; and employer pressure may be exacerbated given that children with DS are otherwise more likely to need further interventions later on (71). As shown in **Figure 24**, there is a notable variation in prescribing rates year on year, especially for infants and the younger age categories, where uncertainty with regards to rapid deteriorations is likely to be more of a problem. The PPI panel also felt that children with DS "usually need stronger antibiotics" and may have to try several before one works, which may further exacerbate the higher prescribing rate.

It will also be important to emphasise to families that, although a significant difference in consultation and hospitalisation rates were noted, the absolute numbers mean that families can expect 0.638 RTI-related GP consultations per child per year, and 0.067 RTI-related hospitalisations per child per year. This can also be expressed by saying that the average child with DS can expect to have three RTI-related GP consultations every two years, and one RTI-related hospitalisation every 15 years, although this advice can be further refined by age and infants are noted to be at most risk. Regarding prescribing rates, this study found that children with DS are prescribed 0.774 antibiotics for RTIs per child per year. This means families can expect close to one episode of an RTI severe enough to justify receiving antibiotics in primary care, each year.

All children with DS should receive an annual review where health risks such as these are discussed (183). The RCPCH currently recommends that children with DS should be seen by a designated paediatrician at least yearly, so they could fulfil this role (6). Healthcare professionals can use the information on risk provided by this study to inform their management of reviews, consultations and decisions, especially considering the advantages and disadvantages related to antibiotic prescribing, different antibiotic prescribing strategies and also provision of 'safety netting' for the child.

The differences between children with DS and controls are more pronounced in children with DS and asthma or CHD, and younger children with DS. There are therefore specific at-risk groups and/or periods within the whole population of children with DS (who are already at higher risk of RTI) that both healthcare professionals and families must be aware of in order to guide appropriate antibiotic management.

5.6.5 Implications for research

The results from this chapter provide some initial insight into the RTI risks associated with children with DS, but separately there is a need to explore further what contributes to some of the findings. It will be important to identify; whether differences in RTI-related healthcare utilisation in children with DS and controls correspond to true differences in incidence or simply a difference in the propensity to seek healthcare; why children with DS and controls that are hospitalised for RTIs do not utilise primary care more often preceding their hospitalisation; what are the mechanisms for children with DS having increased RTI-related healthcare use independent of co-morbidities; and why are there differences between RTI-related healthcare use between males and females?

With regards to further variables, one rationale behind investigating healthcare utilisation in asthma and CHD was in order to separate out groups of patients who may be prescribed steroid inhalers or diuretics, which could affect the presentation or incidence of RTIs. In the case of reflux medication, there were only 10 prescriptions so the power was insufficient to conduct such an analysis, although this could be conducted in subsequent studies. Future research may also seek to analyse subgroups specifically with regards to these prescriptions as additional co-variates, ideally with a larger dataset. In addition, other studies have demonstrated a link between socioeconomic factors and incidence of RTIs (184, 185). Although I analysed by IMD quintile, it may have been useful

to analyse by some of the sub-components of the IMD score, such as Living Environment, or Education, skills and training.

Only inpatient admissions were examined, rather than A&E attendances. Admission routes were also not examined and may provide some useful information for the design of future interventions. Given that 74% of admissions in children with DS were not preceded by an RTI-related GP consultation, and any referrals for acute RTIs would likely be quick, it may be expected that more admissions were acute or emergency admissions.

Although not explored by this study, further research may also want to examine prescribing rates for antivirals for influenza in children with DS. These are rarely prescribed for children without DS, despite recommendations to do so (34, 186). It may be even more important to prescribe them in children with disorders such as DS which put them at greater risk. In the US, the Centers for Disease Control and Prevention recommend that all children with neurological disorders be treated with a neuraminidase inhibitor if they present with symptoms indicative of influenza, and DS is associated with many neurological complications (187). Examining rates of uptake of the influenza vaccine and other preventative methods will also be important; after the 2009 H1N1 pandemic adults and children with DS in Mexico were at higher risk of severe complications (188). The PPI panel felt that children with DS were sometimes too ill to receive vaccinations, so this should be explored.

In the next chapter, I will establish; (a) the risk of RTI-related hospitalisation following a RTI-related GP consultation, stratified by whether or not they were prescribed antibiotics, and (b) whether children with DS and controls are appropriately prescribed antibiotics in primary care, by assessing the impact of antibiotic prescribing on subsequent RTI-related hospitalisation.

Chapter 6: Effects of Antibiotics in Preventing Hospitalisations in Children with Down's Syndrome

ABSTRACT

Background

Children with DS have increased rates of consultations and hospitalisations due to RTIs compared to controls. Despite this, there is little evidence on interventions to prevent or treat RTIs in this at-risk population. This chapter aims to estimate the risk of hospitalisation following a GP consultation for an RTI and the effects of antibiotics in reducing this risk.

Methods

Described in the earlier chapters, the data source is the CALIBER programme and the study population are children aged 0-18 matched with five controls from the same GP, gender, birth year and date of entry into CALIBER.

Individuals were followed up with GP consultations for RTIs with a flag variable inserted if an antibiotic prescription was issued on the same day. Each RTI-related GP consultation was followed up for the first RTI-related hospitalisation or up to 28 days, whichever occurred sooner.

Univariate and multivariate logistic regression was undertaken to assess the effects of antibiotics on the risk of RTI-related hospitalisation in patients consulting for RTIs. These analyses were conducted separately in children with DS and children without DS so that the protective effects could be compared. Co-variates for the final model include; (1) age group, (2) gender, (3) CHD, (4) asthma, (5) number of prior RTI-related hospitalisations and (6) number of prior RTI-related GP consultations. Where significant protective effects were seen, the number needed to treat (NNT) to prevent one RTI-related hospitalisation were estimated.

In addition, an alternative analysis using inverse probability of treatment weighting (IPTW) using propensity scores was undertaken to estimate the effects of antibiotics in children with and without DS. Baseline characteristics between the weighted and unweighted samples were compared using standardised mean differences.

Results

1.8% (95% CI 1.3%-2.3%) of children with DS consulting with an RTI who are prescribed an antibiotic have an RTI-related hospitalisation compared to 2.5% of those not prescribed an antibiotic (95% CI 1.9%-3.4%). 0.6% (95% CI 0.4%-0.8%) of children without DS consulting with an RTI have an RTI-related hospitalisation compared to 0.7% (95% CI 0.5%-1.0%) of those not prescribed an antibiotic.

Multivariate analysis using adjusted logistic regression models found that antibiotics had a significant protective effect for infants (0-1 years) with DS (AOR 0.260; 95% CI 0.077-0.876) with an NNT of 11.9. However, analysis using IPTW concluded that the protective effect was not significant (AOR 0.919; 95% CI 0.845-1.000). In children without DS there was no significant protective effect within any age group or within any sub-classification of RTI.

Discussion

Treating children with DS older than one year with antibiotics appears to make no difference in preventing RTI-related hospitalisations. There is conflicting evidence from two separate analysis methods as to whether treating infants with DS with antibiotics prevents RTI-related hospitalisation, so further investigation is recommended to inform definitive recommendations

In children without DS, treating RTIs with antibiotics was found to have a minimal impact on the risk of subsequent hospital admission. This study could not provide information on other potential benefits of prescription such as reduced symptom duration and severity.

6.1 CHAPTER OUTLINE

This chapter aims to estimate the effects of prescribing antibiotics for an RTI in primary care on the risk of subsequent RTI-related hospitalisation.

Using the same cohort of children with DS and controls described previously, RTI-related GP consultations were identified and flagged if a same-day antibiotic prescription was issued. Each consultation is subsequently followed up to 28 days to ascertain if an RTI-related hospitalisation occurred.

6.2 BACKGROUND

With findings from the previous chapter, healthcare professionals are now able to quantify the risk of consultation and hospitalisation in children with DS compared to controls alongside identifying children with DS who are at higher risk. However, as highlighted from my systematic review, there remains little evidence to guide them in management of RTIs.

In a study on complications after common RTIs in the general UK population using the CPRD, the absolute risk of rare outcomes, effects of antibiotics on this risk and the number of antibiotic courses needed to prevent one complication was estimated (38). This study provided evidence on the usefulness of antibiotics to healthcare professionals, generalizable to UK primary care.

Building on this methodology, and with advances in data linkage in CALIBER, more accurate estimates of both the absolute risk of RTI-related hospitalisations and effects of antibiotics on this risk is calculated in this chapter for children with DS and controls.

6.3 AIMS & OBJECTIVES

6.3.1 Aims

To assess the effect of antibiotic prescriptions in RTI-related GP consultations for preventing RTI-related hospitalisations, in children with and without DS.

6.3.2 Objectives

1. To investigate if antibiotic prescription on the same day as a RTI-related GP consultation will reduce the risk of RTI-related hospitalisations in children with DS and controls;
2. To establish the Number of children with DS and matched controls Needed to Treat (NNT) with antibiotics to prevent a RTI-related hospitalisation;
3. To establish the type of antibiotics prescribed by GPs on the same day as an RTI-related consultation.

6.4 METHODS

6.4.1 Data Management

Building on data management steps described in Chapter 5, all GP consultations for RTIs irrespective of type (i.e. URTI, LRTI, unclassified RTI) were defined as the exposure; whilst all RTI-related hospitalisations were considered as the outcome/complication.

Each consultation for an RTI was followed up until an RTI-related hospitalisation occurred or for 28 days, whichever occurred sooner.

GP consultations by RTI type were subdivided into those with and without an antibiotic prescription on the same day as the RTI-related GP consultation.

Antibiotics prescribed on the same-day as an RTI-related GP consultation were then listed. There was no separate analysis of multiple prescriptions issued on the same day; the classification was binary as to whether a child received antibiotic, or whether they did not. However, if two or more were prescribed, then each antibiotic would be included in individual antibiotic-specific prescribing rate calculations.

In preparation for the analyses stage, several new co-variates were created. These were used to aid adjustment and provide more precise estimates of the effects of antibiotics.

Co-Variate 1: 6-months RTI-related hospitalisation

The frequency of RTI-related hospitalisations in the 6 months preceding a consultation could influence the frequency of later RTI-related hospitalisations. This co-variate was created by counting the number of RTI-related hospitalisations for each patient in the 6 months preceding a relevant RTI-related GP consultation. A unique count was therefore present for each relevant RTI-related GP consultation analysed. A distribution of this count is illustrated in **Table 31** below.

Table 31. Count of RTI-related hospitalisations 6 months preceding an analysed RTI-related consultation in children with DS and controls.

# of RTI hospitalisation	CwDS	Controls
0	5575	13657
1	352	280
2	73	19
3	12	0
4	0	1
5	1	0

Co-Variate 2: 6-months RTI-related GP consultations average

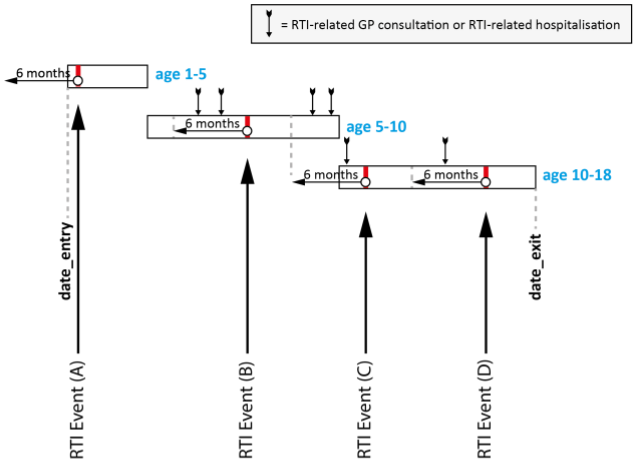
The frequency of RTI-related GP consultations in the 6 months preceding an individual consultation could influence the frequency of later RTI-related hospitalisations This co-variate was created by counting the number of RTI-related GP consultations for each patient in the 6 months preceding a relevant RTI-related GP consultation. A unique score was created for each relevant RTI. A distribution of this count is illustrated in **Table 32** below.

Table 32. Count of RTI-related GP consultations 6 months preceding an analysed RTI-related consultation in children with DS and controls.

# of RTI consultations	CwDS	Controls
0	2173	7349
1	1490	3557
2	914	1647
3	517	721
4	321	346
5	194	168
6	130	88
7	88	42
8	63	19
9	36	12
≥10	87	8

Figure 27 illustrates the process for creating both co-variates below. RTI events (A) to (D) are all linked to the same patient (71173) and occur across the age groups. For events (B) to (D), six months of data preceding each event is available, and for each of these at least one RTI-related GP consultation or hospitalisation was flagged, denoted by the small vertical arrows. For Event (B), there were two events; for Event (C), three events. For Event (A) less than six months of follow up was available because of the date the patient entered the dataset was less than six months before Event (A).

Figure 27. Process for creating Co-Variate 1 and Co-Variate 2.



NUMERATOR TABLE

event ID	patid2	patid	time window	score
RTI event (A)	**7117301**	**71173**	less than 6 months	1
RTI event (B)	**7117305**	**71173**	6 months	2
RTI event (C)	**7117310**	**71173**	6 months	3
RTI event (D)	**7117310**	**71173**	6 months	**1**

Two other additional co-variates were considered, but were ultimately not used because there was insufficient power to detect difference due to the ratio of co-variates to outcomes. These two co-variates were the 28-day RTI-related Consultation Average, and the 28-day RTI-related Hospitalisation Average. Details on the process to create these co-variates are included in the Appendix as **Figure A30** and **Figure A31.** The current Co-Variates were chosen over the alternatives after an academic consensus meeting, where it was decided that exposure to consultations or hospitalisations over 6 months were more clinically meaningful for the analysis.

6.4.2 Data Analysis

6.4.2.1 Adjusted logistic regression

Univariate analysis for each of the co-variates created above alongside age group, antibiotic treatment, CHD, asthma and gender were performed to assess whether these co-variates influenced RTI-related hospitalisation. All co-variates (i.e. gender, age group, hospitalisations 6-months before, consultation 6-months before, CHD and asthma) were included in the final regression model which was used to calculate adjusted odds ratios for the outcome of RTI-related hospitalisation following an RTI consultation comparing

treated and untreated patients. Separate models were calculated for children with DS and children without DS (Adjusted OR <1 suggests a protective effect of antibiotics after taking into account baseline differences in treated and untreated patients). Models initially examine the protective effect of antibiotics for all consultations in children with DS and in children without DS. Subsequent models are stratified according to age group and type of RTI.

Sensitivity analyses utilising 7, 14 and 21-day at-risk periods were also undertaken and detailed in Appendix **Table A 7** and **Table A 9**. Further sensitivity analyses adjusted for clustering, namely the effect posed by children with very high numbers of attendances which may skew the data, are included in **Table A 8** and **Table A 10.**

6.4.2.2 Number Needed to Treat (NNT)

The NNT was calculated following methods described in Laupacis *et al.* (189) and Newcombe's method 10 (Wilson scores), as described in Froud *et al.* (190), was used to estimate standard error, from which 95% Cis were derived for the absolute risk difference and inverted to obtain Cis for NNT point estimates. NNT calculation was only undertaken when there was evidence of a statistically significant independent protective effect of antibiotics. This was done to avoid the misleading conclusion that even when there is no significant protective effect, treating enough people may prevent a hospitalisation.

6.4.2.3 Inverse Probability of Treatment Weighting (IPTW) using propensity scores (PS)

As previously discussed, there are difficulties in utilising observational data to estimate causal treatment effects. There are several potential approaches to address this, such as IPTW using PS (135). The primary analysis was based on controlling for the effect of confounders but a secondary analysis was conducted to check the robustness of conclusions utilising IPTW.

The PS is defined as a subject's probability of treatment selection, conditional on observed baseline co-variates (191). Weighting subjects by the inverse probability of treatment received creates a synthetic sample in which treatment assignment is independent of measured baseline co-variates. As the goal of PS analyses should be to induce balance in measured and unmeasured baseline co-variates between treatment groups, IPTW using the PS will therefore allow one to obtain unbiased estimates of average treatment effects, assuming there is no unmeasured confounding (192).

There are various methods to utilise PS in reducing the effects of confounding, including PS matching, stratification on the PS, co-variate adjustment using PS, and IPTW. Several studies have proven PS matching to be more effective at inducing balance in baseline co-variates between treatment groups than stratification on the PS and co-variate adjustment using PS, while PS matching and IPTW have been comparable in reducing imbalances (135). However, PS matching requires new controls to be selected while IPTW does not require this step. Ultimately, IPTW using PS was chosen because of its strengths in utilising time-dependent co-variates and the ability to estimate a single overall treatment effect, and also because it was not necessary to produce a new control group with this analysis. It is important to note that adjustment using PS and IPTW may be sensitive to whether or not the PS was estimated appropriately (193).

It should be noted that PS tend to perform worse when there is confounding by indication, compared to multivariate outcome modelling (194). Confounding by indication occurs when a particular variable is both a risk factor for an outcome and is associated with the exposure of interest, while not acting as an intermediate step in the casual pathway between the exposure and outcome. Although PS is not the chief method to control for confounding, PS allows for special insights in nonexperimental studies since it places the focus on study design rather than analysis. PS allow for insights into the initiation of treatment and potential barriers to treatment while considering the timing of co-variates and treatment, giving depth to nonexperimental study designs.

For the purposes of this study, the other methods each had their own drawbacks. PS matching is effective in balancing known co-variates but may result in a loss of observations in the treatment group. Stratification separates subjects by PS to estimate treatment effects individually, however this can complicate interpretation and the stratification process may not produce results that are clinically relevant. Although co-variate adjustment is the simplest method to utilise PS, its accuracy relies on certain assumptions about the linear relationship of features distinguishing individual events (193).

Unlike analyses using adjusted logistic regression, no formal data-driven selection of co-variates was undertaken apart from *a priori* selection of variables into the PS model.

One reason for this is that the PS model is a multivariate model, in which relationships may be different than those found univariately. Stated differently, gender may appear to not be associated with the effects of antibiotics to prevent a RTI-related hospitalisation, but conditional on age groups, there may be a relationship with RTI-related hospitalisation.

With advice against selection of confounders in the PS model based on univariate p-values, all co-variates generated in Section 6.4.2.1 except for those included in the Appendix were utilised in the PS model to create a single propensity score from 0-1 that measures the propensity of a child with DS or matched controls to be treated with antibiotics or not for each exposure of "RTI-related GP consultation". The PS was created separately for children with DS, and for controls.

Each child was then weighted according to the inverse of the probability of being prescribed an antibiotic at an RTI-related consultation.

Baseline characteristics of the unweighted and weighted sample were then compared to assess whether the weighting process balanced measured baseline co-variates between treatment groups using standardised differences. Absolute standardised mean differences (SMDs) directly quantify balance in the means (or proportions) of co-variates across the groups and are expressed as percentages of pooled SDs. An absolute standardised difference of 0.00 on a co-variate indicates no between-group imbalance for that co-variate, and values <0.10 indicate negligible imbalance.

6.5 RESULTS

6.5.1 Risk of RTI-related hospitalisation following an RTI-related GP consultation categorised by antibiotic prescriptions

Building on initial analyses undertaken in Chapter 5, the risk of RTI-related hospitalisations following an RTI-related GP consultation categorised by antibiotic prescriptions was calculated. This is displayed in **Table 33**, with **Table 34** showing results stratified by RTI-type.

The risk of RTI-related hospitalisation following RTI consultation is higher in children with DS with and without antibiotic treatment compared to controls. In 1000 consultations for an RTI in children with DS who receive an antibiotic, 18 will subsequently be hospitalised for an RTI. In 1000 consultations for an RTI in children with DS who do not receive an antibiotic 25 will subsequently be hospitalised for an RTI. The figures for children without DS are 6 per 1000 consultations with antibiotics and 7 per 1000 consultations without antibiotics.

Table 33. Risk of RTI-related hospitalisation within 28 days in children with DS and controls who were/weren't prescribed antibiotics for an RTI-related GP consultation.

Classification	with antibiotics treatment			without antibiotics treatment			with vs without antibiotics	
	# of consultations	# of hospitalisations	Risk [95%CI]	# of consultations	# of hospitalisations	Risk [95%CI]	Risk ratio [95%CI]	p-value
CwDS	2874	51	0.018 [0.013-0.023]	1811	46	0.025 [0.019-0.034]	0.699 [0.471-1.036]	0.0913
Controls	5527	31	0.006 [0.004-0.008]	6350	47	0.007 [0.005-0.010]	0.758 [0.482-1.191]	0.2553

Table 34. Risk of RTI related hospitalisation within 28 days in children with DS and controls who were/weren't prescribed antibiotics for an RTI related GP consultation stratified by RTI type.

CwDS

Classification	with antibiotics treatment			without antibiotics treatment			with vs without antibiotics treatment	
	# of consultations	# of hospitalisations	Risk [95%CI]	# of consultations	# of hospitalisations	Risk [95%CI]	Risk ratio [95%CI]	p-value
URTI	1610	20	0.012 [0.008-0.019]	1159	22	0.019 [0.012-0.029]	0.654 [0.359-1.193]	0.2068
LRTI	566	12	0.021 [0.011-0.037]	55	3	0.055 [0.011-0.159]	0.389 [0.113-1.336]	0.1396
unclassified RTI	698	19	0.027 [0.016-0.043]	597	21	0.035 [0.022-0.054]	0.774 [0.420-1.425]	0.4249

Controls

Classification	with antibiotics treatment			without antibiotics treatment			with vs without antibiotics treatment	
	# of consultations	# of hospitalisations	Risk [95%CI]	# of consultations	# of hospitalisations	Risk [95%CI]	Risk ratio [95%CI]	p-value
URTI	3806	19	0.005 [0.003-0.008]	4109	24	0.006 [0.004-0.009]	0.855 [0.469-1.558]	0.6485
LRTI	724	5	0.007 [0.002-0.016]	114	2	0.018 [0.002-0.063]	0.394 [0.077-2.005]	0.2444
unclassified RTI	997	7	0.007 [0.003-0.014]	2127	21	0.010 [0.006-0.015]	0.711 [0.303-1.667]	0.5430

6.6.2 Effects of Antibiotics in preventing a RTI hospitalisation

6.6.2.1 Assessing independent effect of co-variates on the outcome of RTI-related hospitalisation

Table 35 denotes the univariate analyses of all the co-variates prepared. All the co-variates are incorporated into the final logistic regression model, whether or not they were significant. Small numbers prevented analyses in certain subgroups. The odds ratio represents the odds of hospitalisation in those who received an antibiotic prescription versus those who did not receive an antibiotic prescription for an RTI.

Table 35. Univariate analyses to assess which co-variates influenced the outcome: RTI-related hospitalisations.

	CwDS		Controls	
Factors	**odds ratio [95%CI]**	**p-value**	**odds ratio [95%CI]**	**p-value**
treatment	0.693 [0.463-1.037]	0.0747	0.756 [0.480-1.192]	0.2291
age group	0.827 [0.771-0.887]	<0.0001	0.733 [0.655-0.820]	<0.0001
gender	0.895 [0.597-1.342]	0.5915	0.507 [0.315-0.818]	0.0053
cardiac	3.141 [2.095-4.710]	<0.0001	-	-
asthma	1.171 [0.739-1.856]	0.5004	1.368 [0.821-2.278]	0.2292
RTI-consultation 6-months before	1.062 [0.967-1.166]	0.2053	1.248 [1.081-1.439]	0.0024
RTI-hospitalisation 6-months before	2.080 [1.377-3.141]	0.0005	2.695 [1.457-4.984]	0.0016

6.6.2.2 Effects of Antibiotics: Unadjusted using Logistic Regression

Table 36 presents the unadjusted effect of antibiotics in reducing the risk of hospitalisations following a RTI in primary care stratified by RTI type without incorporating any of the co-variates from **Table 35.** Unadjusted, antibiotics did not provide a significant protective effect for any individual subtype of RTI, either for children with DS or controls.

Table 36. Unadjusted protective effect of prescribing antibiotics for an RTI-related GP consultation to prevent a RTI-related hospitalisation in children with DS and controls stratified by RTI-type

	CwDS		Controls	
Classification	**odds ratio [95%CI]**	**p-value**	**odds ratio [95%CI]**	**p-value**
URTI	0.650 [0.353-1.197]	0.1667	0.854 [0.467-1.561]	0.6082
LRTI	0.375 [0.103-1.373]	0.1387	0.389 [0.075-2.032]	0.2632
unclassified RTI	0.768 [0.409-1.442]	0.4107	0.709 [0.300-1.674]	0.4327
ALL	0.693 [0.463-1.037]	0.0747	0.756 [0.480-1.192]	0.2291

Table 37 presents the unadjusted effect of antibiotics in reducing the risk of hospitalisations following an RTI in primary care stratified by age-group. This indicates that the protective effect of antibiotics was not significant across all age groups.

Table 37. Unadjusted protective effect of prescribing antibiotics for an RTI-related GP consultation to prevent a RTI-related hospitalisation in children with DS and controls stratified by age-group.

	CwDS		Controls	
Classification	**odds ratio [95%CI]**	**p-value**	**odds ratio [95%CI]**	**p-value**
Infants	0.319 [0.100-1.016]	0.0532	0.382 [0.086-1.684]	0.2034
Toddlers	0.862 [0.488-1.523]	0.6096	1.346 [0.762-2.376]	0.3058
Juniors	1.453 [0.560-3.768]	0.4425	0.858 [0.261-2.819]	0.8011
Young person	0.725 [0.204-2.584]	0.6204	-	-

Small number prevented analyses in certain subgroups

6.6.2.3 Effects of Antibiotics: Adjusted using Logistic Regression

All co-variates from 6.6.2.1 were incorporated into the final adjusted logistic regression models (i.e. age group, gender, cardiac, asthma, RTI-hospitalisation 6-months before and RTI-consultation 6-months before). When stratified by RTI-type, antibiotics had no impact on reducing RTI-related hospitalisation for any individual classification, shown in **Table 38**.

Table 38. Adjusted protective effect of prescribing antibiotics for an RTI-related GP consultation to prevent a RTI-related hospitalisation in children with DS and controls stratified by RTI-type (adjusted for all 7 identified co-variates).

	CwDS		Controls	
Classification	**odds ratio [95%CI]**	**p-value**	**odds ratio [95%CI]**	**p-value**
URTI	0.748 [0.403-1.390]	0.3587	1.033 [0.561-1.901]	0.9175
LRTI	0.470 [0.121-1.833]	0.2772	0.610 [0.114-3.270]	0.5644
unclassified RTI	0.784 [0.412-1.492]	0.4593	0.752 [0.318-1.781]	0.5175
ALL	0.769 [0.511-1.157]	0.2074	0.901 [0.569-1.426]	0.6554

When stratified by age group, shown in **Table 39,** antibiotics prescribed for an RTI-related GP consultation had a significant protective effect in preventing RTI-related hospitalisation for infants (0-1 years) with DS. The AOR was 0.260 (95% CI 0.077-0.876). The NNT was 11.9 (95% CI 6.0-1708.7). No significant protective effect at other ages or in controls was noted.

Table 39. Adjusted protective effect of prescribing antibiotics for an RTI-related GP consultation to prevent a RTI-related hospitalisation in children with DS and controls stratified by age-group (adjusted for all 7 identified co-variates).

	CwDS		Controls	
Classification	**odds ratio [95%CI]**	**p-value**	**odds ratio [95%CI]**	**p-value**
Infants	0.260 [0.077-0.876]	0.0297	0.409 [0.091-1.846]	0.2451
Toddlers	0.841 [0.472-1.497]	0.5557	1.316 [0.744-2.328]	0.3448
Juniors	1.422 [0.544-3.716]	0.4731	0.772 [0.232-2.571]	0.6739
Young person	0.705 [0.197-2.528]	0.5918	-	-

Small number prevented analyses in certain subgroups

6.6.2.4 Effects of Antibiotics: Adjusted using IPTW

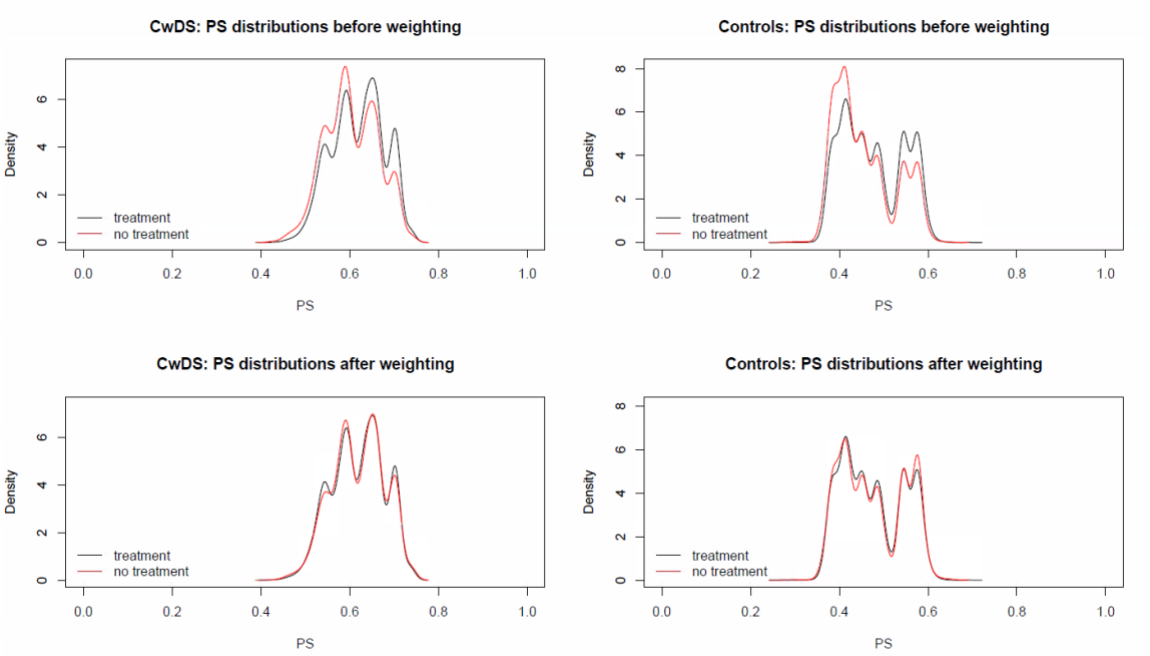
As described in Section 6.4.2.3, all co-variates identified in **Table 35**, whether or not they showed a significant effect on reducing RTI-related hospitalisations, were utilised in the PS model. These were age, gender, asthma co-morbidity, CHD comorbidity, and 6-month history of RTI-related consultations and hospitalisations. The PS model creates a single propensity score from 0-1 that measures the propensity of a child with DS, or matched controls, to be treated with antibiotics, or not, for each exposure of "RTI-related GP consultation".

Illustrative graphs in **Figure 28** denote the distribution of propensity scores in treated and untreated groups in children with DS and matched controls.

An inverse probability of treatment weighting was then calculated using the propensity score to weight a child with DS or matched control according to how likely at the time of exposure to an RTI-related GP consultation they were going to get an antibiotic prescription.

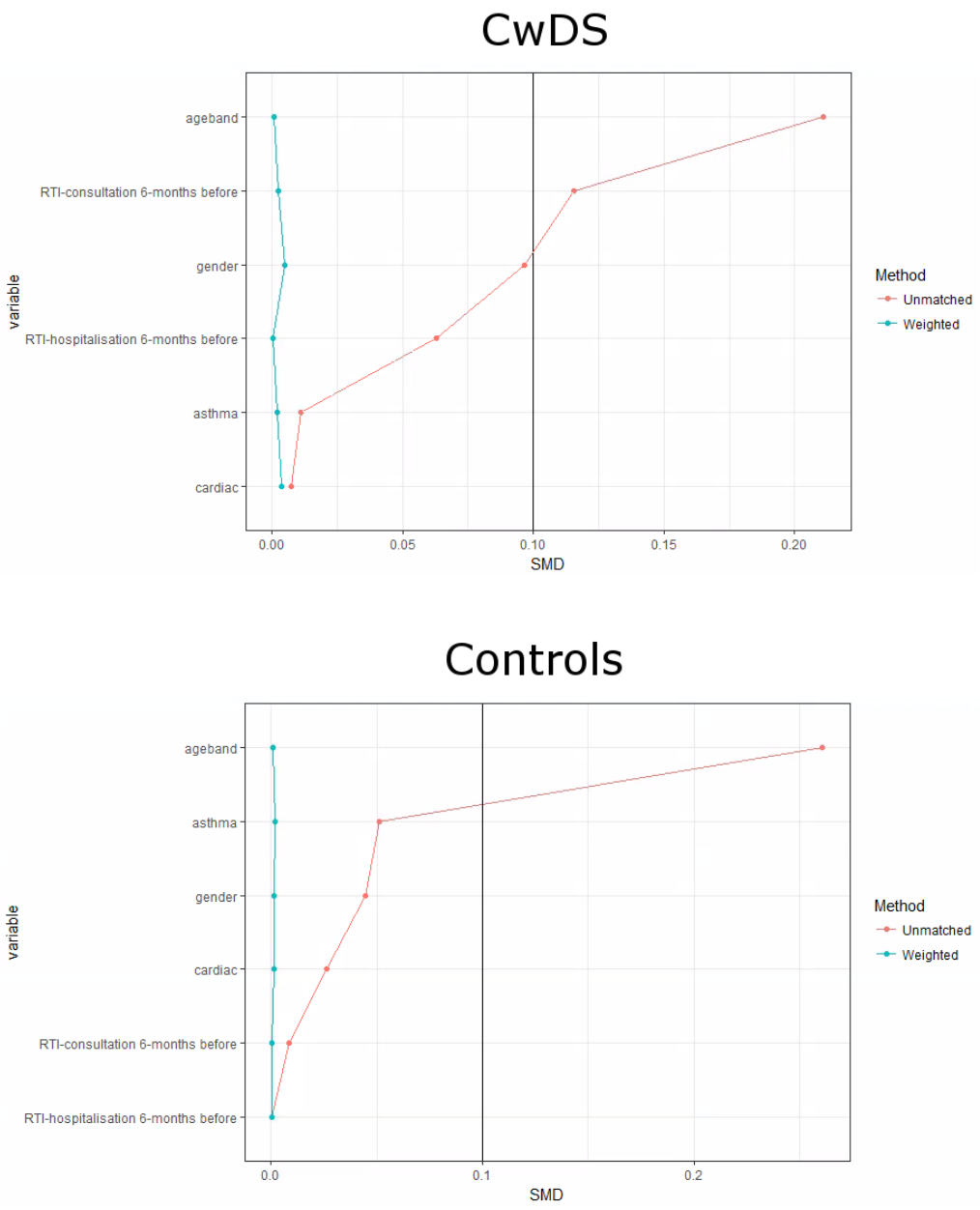
This therefore aimed to create a treated/untreated group that were balanced in terms of measured co-variates akin to a randomised controlled trial (that also balances for unmeasured co-variates). As can be seen, before weighting, the PS distributions for the treatment and no treatment groups were relatively well matched, but after weighting they matched more precisely. With more similarity in PS distributions for the treatment and no treatment groups, it will be more likely that the effects observed are due to the difference in treatment rather than due to differing measured or unmeasured co-variates.

Figure 28. Graph of distribution of propensity scores.



Before IPTW, the standardised mean difference (SMD) in co-variates in terms of age, gender, cardiac disease, asthma, gender, 6 months RTI-related hospitalisations and 6 months RTI-related GP consultations was noted below in **Figure 29**, both in the unmatched and the weighted sample**.** This quantifies balance in the means of co-variates across the groups and is expressed as percentages of pooled SMDs. An absolute standardised difference of 0.00 indicates no between-group imbalance for that co-variate, and values <0.10 indicate negligible imbalance. As can be seen, after weighting occurred, the SMD was below 0.01 for both children with DS and for controls across all variables, indicating negligible imbalance across all variables.

Figure 29. Standardised mean difference of co-variates between treated and untreated groups in children with DS and controls before and after matching and weighting.



The adjusted logistic regression model in **Table 38** and **Table 39** was re-run to produce **Table 40** and **Table 41** below. These were adjusted for: age, gender, asthma co-morbidity, CHD comorbidity, and 6-month history of RTI-related consultations and hospitalisations. For infants, the adjusted protective effect was not significant (AOR 0.919; 95% CI 0.845-1.000). Results at all other ages and for all types of RTI were also not significant.

Table 40. Adjusted protective effect of prescribing antibiotics for an RTI-related GP consultation to prevent a RTI-related hospitalisation in children with DS and controls stratified by age-group using IPTW.

	CwDS		Controls	
Classification	**odds ratio [95%CI]**	**p-value**	**odds ratio [95%CI]**	**p-value**
Infants	0.919 [0.845-1.000]	0.0506	0.983 [0.961-1.005]	0.1237
Toddlers	0.995 [0.980-1.011]	0.5343	1.002 [0.997-1.008]	0.4119
Juniors	1.004 [0.992-1.017]	0.5032	0.999 [0.995-1.004]	0.7878
Young person	0.998 [0.989-1.007]	0.6531	0.998 [0.997-1.000]	0.1259

Table 41. Adjusted protective effect of prescribing antibiotics for an RTI-related GP consultation to prevent a RTI-related hospitalisation in children with DS and controls stratified by RTI type using IPTW.

	CwDS		Controls	
Classification	**odds ratio [95%CI]**	**p-value**	**odds ratio [95%CI]**	**p-value**
URTI	0.992 [0.982-1.003]	0.1495	1.000 [0.997-1.004]	0.7875
LRTI	1.007 [0.987-1.027]	0.5155	0.991 [0.981-1.002]	0.0976
unclassified RTI	0.995 [0.979-1.010]	0.4969	0.998 [0.992-1.004]	0.4893
ALL	0.995 [0.987-1.003]	0.2238	0.999 [0.996-1.002]	0.5371

6.6.3 Antibiotics prescribed for an RTI-related GP consultation

Table 42 denotes the types of antibiotics prescribed on the same day as an RTI-related GP consultation in both children with DS and controls.

Similar proportions of Broad-spectrum penicillins were prescribed for RTIs in primary care in children with DS and controls (62.3% vs 63.0%).

In contrast, there are significant differences in the prescription of Macrolides, which were prescribed more often for children with DS (20.8% vs 12.5% in controls). Benzylpenicillins were prescribed less often for children with DS (7.4% in children with DS vs 18.7% in controls).

Table 42. Antibiotics prescribed on the same day as an RTI-related GP consultation in children with DS and controls stratified by drug class.

	# of prescription in CwDS		# of prescription in Controls		
Classification	**n**	**%**	**n**	**%**	**p-value**
Benzylpenicillin & phenoxymethylpenicillin	267	7.4	1199	18.7	<0.0001
Quinoles	11	0.3	11	0.2	0.1855
Broad-spectrum penicillins	2241	62.3	4039	63.0	0.4509
Cephalosprins and other beta-lactams	246	6.8	286	4.5	<0.0001
Macrolides	749	20.8	802	12.5	<0.0001
Metronidazole and tinidazole	0	0.0	1	0.0	1.0000
Penicillinase-resistant penicillins	28	0.8	24	0.4	0.0088
Sulphonamides & trimethoprim	50	1.4	29	0.5	<0.0001
Tetracyclines	7	0.2	17	0.3	0.5323

A further analysis in **Table 43** involves comparing and assessing whether the distribution of named antibiotics was different between children with DS and controls. Of particular relevance to RTIs, it is notable that Co-Amoxiclav (amoxicillin trihydrate/potassium clavulanate), Azithromycin (azithromycin dihydrate) and Clarithromycin are prescribed more frequently in children with DS compared to controls.

Table 43. Antibiotics prescribed on the same day as an RTI-related GP consultation in children with DS and controls stratified by drug class & antibiotic name.

	# of prescription in CwDS		# of prescription in Controls		
Classification	**n**	**%**	**n**	**%**	**p-value**
Benzylpenicillin & phenoxymethylpenicillin					**0.0872**
phenoxymethylpenicillin potassium	265	7.4	1198	18.7	
procaine benzylpenicillin/benzylpenicillin sodium	2	0.1	1	0.0	
Quinoles					-
ciprofloxacin	11	0.3	11	0.2	
Broad-spectrum penicillins					**<0.0001**
ampicillin trihydrate	0	0.0	4	0.1	
amoxicillin trihydrate/potassium clavulanate	200	5.6	146	2.3	
amoxicillin trihydrate	2038	56.6	3888	60.7	
benzylpenicillin sodium	2	0.1	0	0.0	
pivampicillin	1	0.0	1	0.0	
Cephalosprins and other beta-lactams					**<0.0001**
cefaclor	71	2.0	103	1.6	
cefadroxil monohydrate	2	0.1	10	0.2	
cefalexin	138	3.8	160	2.5	
cefixime	31	0.9	4	0.1	
cefradine	3	0.1	5	0.1	
cefuroxime axetil	1	0.0	4	0.1	
Macrolides					**<0.0001**
azithromycin dihydrate	48	1.3	18	0.3	
clarithromycin	98	2.7	92	1.4	
erythromycin	20	0.6	95	1.5	
erythromycin ethylsuccinate	579	16.1	591	9.2	
erythromycin stearate	4	0.1	6	0.1	
Metronidazole and tinidazole					-
metronidazole	0	0.0	1	0.0	
Penicillinase-resistant penicillins					**0.3533**
ampicillin trihydrate/flucloxacillin magnesium	5	0.1	1	0.0	
ampicillin trihydrate/flucloxacillin sodium	0	0.0	1	0.0	
flucloxacillin magnesium	10	0.3	10	0.2	
flucloxacillin sodium	13	0.4	12	0.2	
Sulphonamides & trimethoprim					**0.0802**
sulfamethoxazole/trimethoprim	6	0.2	0	0.0	
trimethoprim	44	1.2	29	0.5	
Tetracyclines					**0.2849**
doxycycline hyclate	2	0.1	8	0.1	
doxycycline monohydrate	1	0.0	0	0.0	
lymecycline	1	0.0	0	0.0	
minocycline hydrochloride	0	0.0	1	0.0	
oxytetracycline dihydrate	3	0.1	8	0.1	

6.7 DISCUSSION

6.7.1 Summary of main results

Children with DS are at higher risk of RTI-related hospitalisations than controls, with 13 of 1000 children with DS who are prescribed antibiotics after an RTI-related GP consultation being admitted to hospital, along with 23 of 1000 among those without prescriptions. This is in contrast to 4 and 6 per 1000 controls, respectively.

Despite current guidance that antibiotic prescriptions should be considered for 'at risk' children presenting with RTIs, which may include children with DS and comorbidities such as CHD, they appear to make no difference in preventing hospitalisations amongst older children with the DS, or when results were stratified by RTI type (33). For LRTIs it should be noted that the small number of subjects in this sample (15 hospitalisations in children with DS, and 7 in controls, shown in **Table 34**) may have led to the study being underpowered - the sample size calculation described in 5.4.1.2 advised that there should be at least 20 hospitalisations per group in order to detect a difference in hospitalisation rates. Given these results, caution is advised when prescribing; especially given concerns that overuse of antibiotics may lead to unnecessary side effects and promote antibiotic resistance.

There was some evidence to suggest that prescribing antibiotics to infants (0-1 years) may reduce the risk of RTI-related hospitalisations with an AOR of 0.260 (95% CI 0.077-0.876) and NNT of 11.9, although the NNT confidence interval was very large (95% CI 6.0-1708.7). However, in the IPTW model using propensity scoring which produces a result analogous to a randomised controlled trial, the protective effect for infants was not significant. The potential to reduce hospitalisations is notable given that infants with DS are the most hospitalised age group, hospitalised at a rate per person-year of 0.515.

It is also important to note that although the multivariate adjusted logistic regression analysis did show a significant effect for infants with DS, according to the sensitivity analysis in **Table A 9**, this only became significant after the 28-day at-risk period, rather than after the 7, 14, and 21 day risk periods. The adjusted odds ratio remained below 1 at each time period, and dropped as more time passed, but the 95% confidence interval crossed 1 in each instance until 28 full days had passed, and as the sample progressively increased in size. The 28-day risk period was chosen because a systematic review found

that the duration of RTI symptoms in children commonly lingered for up to 28 days, such as 25 days for acute cough and 21 days for bronchiolitis, so it may well be that deterioration linked to these specific symptoms underpinned the significant finding (151). Children continued to be admitted right up until the 28-day limit, as is shown in **Figure 22**.

6.7.2 Comparison with existing literature

Numerous high-quality studies and Cochrane reviews have concluded that antibiotics have little effect in reducing complications in children from the general population with RTIs in general, or URTIs (195-197). This study found that antibiotics are not justified in order to prevent admission in older children with DS, or when prescribed by RTI-type. A recent study found that treatment with early azithromycin prevented progression of RTI symptoms to severe LRTIs in toddler-age children suffering from recurrent RTIs, but did not report differences in hospitalisations, although the absolute number of hospitalisations was low (198).

A previously published CPRD based study identified 3.4 million episodes of RTIs and assessed the effects of antibiotics in preventing complications such as mastoiditis following otitis media, pneumonia following an URTI and quinsy following tonsillitis (38). In this previous study, the data were not linked to secondary care data, potentially leading to underestimation of complication rates and consequent overestimation of NNTs. This study successfully links to secondary care data, although the relatively small number of RTI episodes limits analysis by complications. Studies are needed using linked data to measure the impact of antibiotics utilising the entire data available through CPRD, expanding findings beyond the small number of controls used in this study.

My systematic review of interventions to treat RTIs in adults and children with DS identified few relevant studies, and those identified focused on uncommon treatments. This study is therefore the first to assess the efficacy of a common treatment option, namely antibiotics, for RTIs in this at-risk group.

6.7.3 Strengths and Weaknesses

This is the first study that I am aware of to assess the effects of antibiotics in primary care in children with DS. The strengths include the use of a large sample size of children with

DS, internally matched controls and collation of clinical data from primary and secondary care data sources within CALIBER.

There are several generic biases to observational evaluation of the effect of interventions using electronic health records that are described more fully in Chapters 3-5, such as missing data. A particular issue in the current analysis relates to the coding of RTIs. In particular, it may often be difficult to clinically distinguish LRTI from URTI. Consequently, many RTIs had nonspecific codes and there were relatively few patients with recorded LRTI. This limited the power to detect protective effects of antibiotics in LRTI in children with DS. This study aimed to address this problem by separately considering unclassified RTIs in its analysis.

There are also a number of limitations associated with the coding process. GPs are not coding predominantly to enable research, and data quality issues relating to matching presentations against codes may remain. Differential misclassification bias could have occurred if consultation codes are better recorded in patients who are prescribed antibiotics compared to those who are not. Separately, the nature of RTIs as predominantly clinical diagnoses may mean that distinctions between LRTIs and URTIs are unreliable. There are many factors that could influence the choice of certain coding labels and variation is likely to be present. By grouping symptoms and diagnoses under URTI/LRTI/unclassified RTI labels, I hoped to address variation in GPs' perceptions on what symptoms constitute each of these diagnoses, but the other factors cannot be addressed.

It is also possible that GPs may adjust their coding behaviours to justify their decision to prescribe; for example, simple sinusitis for 10 days or less should not be offered antibiotics, but patients with respiratory symptoms who meet three or more Centor criteria should be considered for immediate antibiotics (33, 199, 200). GPs who choose to prescribe if they perceive that a child is 'not quite right' but does not fit the clinical picture for immediate prescribing may reflexively emphasise Centor symptoms, namely absence of cough, fever, tonsillar exudate and enlarged anterior cervical nodes. Within my codelist, codes such as 'O/E ('On Examination') fever, Peritonsillar abscess, or Acute Bacterial Tonsillitis may have been chosen in such situations. In other cases, codes that include the label 'Bacterial' may have been chosen even if cultures had not been performed, for example if green sputum was present. The drive to prevent

overprescribing may mean GPs feel more under pressure to justify decision making even if some decisions are not quite in line with current guidelines.

The limitations of the NNT calculation for infants (0-1 years) of 11.9, 95% CI 6.0-1708.7, should also be stated. The NNT was only calculated in the event of significant results in the multivariate analyses, to avoid the implication that for non-significant results, treating a certain number of children would avert later infections. NNT values can be unreliable in observational studies, particularly due to confounding by indication, and indeed it is important to note that in the PS using IPTW analysis, the effect for infants was not significant (201). To minimise the impact of these limitations, the maximal number of co-variates should ideally be accounted for, but a lack of power impeded incorporation of further co-variates in this thesis (202).

All antibiotics were considered when analysing antibiotic prescriptions in primary care, following the approach taken by other respiratory research studies utilising CPRD and HES (21). An advantage of this approach is that it allows consideration of all possible prescribing behaviours, and there may be a minority of atypical prescribing behaviours if GPs are more uncertain particularly when treating children with DS. A disadvantage of this approach is that it does not capture the prescription of Co-Amoxiclav and Amoxicillin when no Read codes are used, even though these are likely to have been prescribed for RTIs; but since some could be rescue or prophylactic prescriptions, this may not have been a reliable approach (145). The PPI panel reported that their children tended to be prescribed Co-Amoxiclav more than Amoxicillin, the latter being the more common antibiotic for the general population (203). Whilst Co-Amoxiclav was not prescribed more commonly than Amoxicillin in this study, it was prescribed more commonly in children with DS than in controls.

Finally, a further limitation relates to the fact that, after their initial presentation to their GP for an RTI, some untreated children may ultimately have been prescribed antibiotics elsewhere (e.g. A&E, OOH). It is also not possible to tell whether prescribed antibiotics were ultimately taken.

6.7.4 Implications for practice

Healthcare professionals should be aware that prescribing antibiotics for RTIs in older children with DS appears to make minimal difference for the prevention of subsequent

RTI-related hospitalisation, irrespective of RTI type. This study was underpowered to detect differences for LRTIs, so antibiotic prescriptions should not be ruled out for these patients. However, these concerns will have to be balanced with the concern of overprescribing and resultant antibiotic resistance (204). The absolute risk of RTI-related hospitalisation for children with DS after a related GP consultation is 2.1%, which could be considered low given the complex medical needs of this group, although any hospitalisation, no matter how rare, is undesirable for the child and their family.

Regarding subgroups, there are conflicting results as to whether prescribing antibiotics for infants with DS presenting to primary care for RTIs averts subsequent hospitalisation. Consequently, no definitive recommendation can be given. Infants with DS have high overall RTI-related healthcare utilisation with a rate per person-year of 1.495 RTI-related GP consultation rates and 0.515 RTI-related hospitalisations. This are the highest rates amongst the age bands, although the role of GPs may be limited due to the high percentage (74%) of children with DS who present to hospital without a preceding RTI-related GP consultation.

In the absence of gold standard evidence such as a randomized controlled trial, a targeted approach in prescribing antibiotics in children with DS is recommended, balancing risks and potential benefits. Algorithms could be designed to support healthcare professionals in deciding when antibiotics should be prescribed for children with DS. One example algorithm is 'STARWAVe' which identifies children from the general population at risk of hospitalisations and informs decision making using factors such as short (≤3 days) illness; high temperature; age (<24 months); recession; wheeze; asthma; and vomiting (173). If a child has three or more of these symptoms, there is a higher risk they will be hospitalised for their RTI in the following 30 days (173). Such algorithms could be tailored for use in children with DS using data from this study, such as the indication that very young children may be more likely to benefit from antibiotic prescribing, and the finding in Chapter 5 that children with DS and asthma are more likely to be hospitalised than controls with asthma, but without DS.

Qualitative data has found that GPs sometimes experience diagnostic uncertainty and have varied prescribing strategies for at-risk children with influenza-like illnesses, and this study may offer guidance for prescribing strategies going forward (205). This is the case for middle-severity RTIs, where clinicians are more likely to err on the side of caution and

prescribe; however, this study found no particular benefit from prescribing for unclassified RTIs in either children with DS or controls (206).

6.7.5 Implications for research

It is recommended that further research is undertaken to quantify the benefit of antibiotic prescriptions for infants with DS in primary care to avert RTI-related hospitalisation. Ideally, this should be prospective research using a larger sample size. Further studies could also assess the benefit of antibiotics, particularly for LRTIs where this study was relatively underpowered.

There is also a need for research prospectively mapping the patient journey, experience, and interactions/interventions with the health service across the whole health system from primary to secondary and, where appropriate, tertiary care. More qualitative research with healthcare professionals and families is required to inform the co-design of future interventions, such as algorithms to support the management of an RTI, and to inform their implementation and evaluation in community and hospital settings. These interventions should support clarity and collaboration in prescribing decisions so that the use of antibiotics to manage RTIs in children with DS is optimised.

A prospective study with better data capture mechanisms on clinical presentations, risk factors, antibiotics received and pathogens responsible, such as a British Paediatric Surveillance Unit study, would be valuable to ascertain the impact of this increased antibiotic exposure on antimicrobial resistance in this at-risk group (207). A randomised trial, incorporating varied antibiotic prescribing strategies such as rescue treatment, prophylactic treatment, and the effects of delayed treatment, would be useful to further broaden the evidence base for treatment of children with DS.

Chapter 7: Key Findings, Discussion, Recommendations and Conclusions

7.1 DESCRIPTION OF CHAPTER CONTENTS

In this chapter, I summarise and draw together key findings from my thesis alongside the strengths and limitations of the methodology utilised. This is followed by a discussion of these findings placed in the context of previous literature and the implications for clinical and public health policy, practice and research.

For children with and without DS, this thesis aimed to use routinely collected data to identify RTI-related healthcare utilisation, those most at risk of RTI-related healthcare utilisation, and the effects of antibiotics in preventing RTI-related hospitalisation.

The objectives were:

1. To undertake a systematic review of the literature on the effectiveness of preventative and therapeutic interventions for RTIs in adults and children with DS (**Chapter 2**)
2. To quantify NHS healthcare utilisation attributable to RTIs in children with and without DS from 1997 to 2010 (**Chapter 5**)
3. To ascertain which children, with and without DS, are most at risk of increased RTI-related NHS healthcare utilisation (**Chapter 5**)
4. To assess the effect of antibiotic prescriptions in RTI-related GP consultations for preventing RTI-related hospitalisations, in children with and without DS (**Chapter 6**)

7.2 KEY FINDINGS

7.2.1 Limited evidence on interventions to prevent or treat RTIs in children with DS

In my systematic review of the literature (Chapter 2) in 2015, I reviewed a total of 13,575 records of which I identified three studies on preventative interventions for RTIs in children with DS that fulfilled the inclusion, exclusion and quality criteria. No RCTs, CBAs or cohort studies on therapeutic interventions in this field were found in the literature.

Of the three studies, one RCT of moderate risk of bias compared prophylactic zinc therapy with placebo for 62 children with DS, and noted no benefit on URTI episodes, doctor visits, antibiotic use, and school absence (92).

One non-RCT, with serious risk of bias, had a population of 26 children and compared prophylactic treatment with pidotimod (an immunostimulant) against no treatment and noted fewer parent-reported URTI recurrences (mean 2.7, S.D. 1.1 vs mean 6.8, S.D. 1.3) and days with fever (mean 4.5, S.D. 3.5 vs mean 16.9, S.D. 6.7) (91).

A prospective cohort study with serious risk of bias compared a cohort of 532 Canadian children with DS, treated prophylactically with palivizumab, with a cohort of 233 Dutch children with DS who did not receive palivizumab. It noted that the treated cohort had fewer RSV-related hospitalisations (23 untreated, 8 treated) but the same number of overall RTI-related hospitalisations (73 untreated, 74 treated) in the first two years of life (90).

Two further studies, one on a school based infection control programme and one on prophylactic zinc therapy were subsequently excluded due to critical risk of bias (93, 94).

After the 2017 update of the systematic review which identified a further 3,302 abstracts, I shortlisted two additional studies investigating treatment with prophylactic palivizumab. Both of these were also subsequently excluded due to critical risk of bias (76, 95).

My systematic review was based on a very broad search strategy that included DS-related co-morbidities such as CHD and adults with DS to ensure a thorough and comprehensive search of all relevant studies for RTIs in DS. By restricting the inclusion criteria to high quality study designs (e.g. randomised controlled trials, controlled before-after studies and cohort studies) I excluded case reviews and case series that may be more commonly published on DS but are less likely to inform routine clinical practice.

7.2.2 Children with DS have increased RTI-related healthcare utilisation compared to controls

Using the CALIBER dataset, I undertook a retrospective cohort study of 992 children with DS and 4,874 controls matched for birth year (±5y), starting date of follow-up, gender and general practice.

Children with DS consult their GP at a rate of 0.64 per person per year (PPY) in contrast to controls at 0.36 PPY (Adjusted RR 1.73; 95% CI 1.62-1.84). Children with DS are hospitalised for all RTIs at a rate of 0.067 PPY compared to controls at 0.013 PPY (Adjusted RR 5.69; 95% CI 4.82-6.73).

The differences between children with DS and controls were most pronounced for LRTIs (in contrast to URTIs and unclassified RTIs) with an Adjusted RR of 3.59 for LRTI-related GP consultations (95% CI 3.19-4.04) and 11.30 for LRTI-related hospitalisations (95% CI 8.45- 15.10).

Additionally, children with DS are admitted for a longer period of time in hospital due to RTIs (Mean 5.2 days; 95% CI 5.0-5.4) compared to controls (Mean 2.4 days; 95% CI 2.2-2.6).

7.2.3 Children with DS (in particular infants) are prescribed more antibiotics in primary care for RTIs compared to controls

Children with DS are prescribed more antibiotics than controls, at a rate of 0.774 PPY compared to 0.324 for controls (Adjusted RR 2.34; 95% CI 2.19-2.49). These differences were significant across all antibiotic drug classes that are routinely used for RTIs. These prescriptions were made in consultations that were coded as being RTI-related, although it is conceivable that a minority were prescribed for other reasons.

Differences in RTI-related antibiotic prescription on the same day as RTI-related consultations were most apparent in LRTIs (Adjusted RR 3.79; 95% CI 3.34-4.30).

Infants with DS (0-1 years) were prescribed the most antibiotics for RTIs compared to all other age groups at a rate of 0.795 PPY (95% CI 0.65-0.99).

7.2.4 Children with DS have an increased risk of hospitalisation following an RTI-related GP consultation

Children with DS have an increased risk of RTI-related hospitalisation following a RTI-related GP consultation (RR 3.15; 95% CI 2.35–4.24) compared to controls. In those hospitalised, the time to hospitalisation was similar with a median of 8.0 days (95% CI 3.0-19.0) in children with DS and 8.0 days (95% CI 2.0-18.0) in matched controls.

The odds of re-consultation with a GP for an RTI following an initial RTI-related GP consultation was higher in children with DS compared to matched controls (OR 1.69; 95% CI 1.57-1.82). This was unrelated to any subsequent hospitalisation episodes.

A high proportion of RTI-related hospitalisations are not preceded by a RTI-related GP consultation in both children with DS (74.1%; 95% CI 68.9-78.5%) and matched controls (73.4%; 95% CI 67.0-78.8%).

Stratified by antibiotic prescriptions, the baseline risk of RTI-related hospitalisation in children with DS is significantly higher compared to matched controls with 1.8% of children with DS (95% CI 1.3-2.3%) prescribed antibiotics being admitted compared to 0.6% of controls (95% CI 0.4%-0.8%).

In those not prescribed antibiotics, the baseline risk was 2.5% in children with DS (95% CI 1.9%-3.4%) and 0.7% in controls (95% CI 0.5-1.0%).

7.2.5 There are conflicting results as to whether prescribing antibiotics for all RTI-types in primary care reduces the risk of RTI-related hospitalisation in infants with DS (0-1 year)

When antibiotics are prescribed for all RTI types in primary care, adjusting for CHD, asthma, gender, and number of RTI hospitalisations and consultations preceding a RTI-related consultation using adjusted logistic regression, the risk of RTI-related hospitalisation is reduced in infants with DS (0-1 years) with an adjusted odds ratio of 0.260 (95% CI 0.077 to 0.876, p=0.297) and an NNT of 11.9 (95% CI 6.0- 1,708.7). This was not significant for infant controls with an AOR of 0.409 (95% CI 0.091- 1.846).

However, when using inverse probability of treatment weighting to calculate the propensity score, aiming to create treated/untreated groups that are balanced in measured co-variates akin to a randomised controlled trial, the effect for infants was not significant (AOR 0.919; 95% CI 0.845-1.000, p=0.0506). The effect for infant controls was also not significant (AOR 0.983; 95% CI 0.961-1.005, p=0.1237).

7.2.6 Prescribing antibiotics by type of RTI does not reduce the risk of RTI-related hospitalisation

Looking at specific RTI-types (i.e. URTI, unclassified RTI, LRTI), prescribing antibiotics had no significant effect for URTIs, unclassified RTIs and LRTIs in children with DS and controls.

However, the absolute number of LRTIs in both were small and the CIs relatively wide, so the study was underpowered to assess any impact in this domain.

7.2.7 Strengths and limitations of my CALIBER dataset work

Strengths

To date, this is first study to quantify objectively RTI-related healthcare utilisation using routinely collected data from both primary and secondary care datasets with matched controls, and the first to assess the effects of antibiotics for RTIs in children with DS. As the CALIBER database is broadly representative of the UK population as a whole, and the prevalence of comorbidities in the CALIBER cohort matched those from other studies of children with DS, these study findings can therefore be considered both nationally and internationally representative. To my knowledge it is also the largest study of RTI-related healthcare utilisation in children with DS worldwide.

Limitations

Considerable inter-practice variation exists in coding certain conditions such as RTIs (144, 174, 175). For example, READ or ICD-10 codes for "respiratory tract infection" may potentially mean that it could be either an URTI or LRTI. This may lead to either over or underestimation of healthcare utilisation. Separate consideration of 'unclassified RTIs' was incorporated in order to address this limitation. It could be argued that, with regards to subtypes of RTIs, misclassification in this domain is unimportant, because what the thesis is describing is whether prescribing antibiotics, when clinicians are presented with certain sorts of symptoms, averts subsequent hospitalisation. Whether these combinations neatly fit the URTI or LRTI labels may be unimportant.

Despite the extensive effort undertaken to code for co-morbidities such as asthma and congenital heart disease, due to the known variation in GP coding behaviour and HES coding of co-morbidities, it is likely that children with DS and matched controls may be misclassified as either having or not having CHD/asthma. This may lead to either an overestimation or underestimation of healthcare utilisation in comparison between these groups.

Selective recording of consultations codes by GPs when an antibiotic prescription is issued may lead to differential misclassification bias (e.g. consultation codes better recorded in children with DS compared to controls, or in treated vs untreated subjects).

It is also not possible to deduce whether prescriptions were ultimately dispensed, or dispensed but not taken.

Despite the extensive lists of co-variates generated to capture the baseline health and the risk of hospitalisations in the children under study, unmeasured confounding is likely to remain in the analyses. A large number of other relevant factors affecting RTI risk have been identified by other studies; atopy status, smoking status, presence at daycare, sharing a bedroom with adults, sharing a bedroom with young children, and exposure to damp or mould have been found to increase risk, and breastfeeding status has been found to decrease risk (14, 208, 209). Adjustment for these factors in subsequent studies may be difficult, because with the exception of atopy status, smoking status and in some cases breastfeeding status, this information will not be routinely collected or recorded. Smaller survey-based studies could collect this information, but there would consequently be an effect on sample size, and most likely a reduction in power would restrict any attempt to adjust for the additional co-variates.

Importantly, in the absence of data to assess RTI severity during consultation (e.g. clinical observations), confounding by indication is likely to persist in these analyses. This is likely to lead to an underestimation of the effects of antibiotics in both groups.

It has been noted anecdotally that prescribing rescue courses of antibiotics (i.e. antibiotics to be kept at home and taken when an RTI is worsening) is common in children with DS, as it is in other patients with chronic respiratory problems (210). The PPI panel observed that it was not uncommon for parents to phone their GP, request antibiotic prescriptions, and collect them without consultations. These children may present to their GP for a worsening RTI after having started their antibiotic course at home and subsequently be admitted to hospital for a severe RTI. As these children would be classified as not receiving antibiotics, (i.e. no same day antibiotic prescription recorded with a Read code for a RTI-related GP consultation), this could have had a role in minimising any difference in effect of antibiotics in the analyses.

Finally, it should be noted that the dataset for this thesis runs from 1997-2010. Over this time period, and indeed in the seven years since 2010, there has been an increased focus on antimicrobial resistance with various publicity campaigns designed to reduce prescribing rates. For example, in 2014 the UK Antibiotic Guardian Campaign was

launched, encouraging the public and clinicians to make pledges designed to reduce the use of antibiotics; in 2017 the Keep Antibiotics Working campaign aimed to encourage the public not to request antibiotics when visiting their GP (211, 212). Such campaigns could have reduced prescribing rates in children with DS, if families or clinicians are more concerned given their already higher prescribing rates; or they could have differentially affected the healthy matched controls, if they are perceived to be less in need of antibiotics. In the context of increasing antibiotic resistance, there will need to be a wider consideration of how to optimise prescribing for all children and adults in future, which could involve a greater use of algorithms to encourage targeted prescribing.

I am aiming to undertake further analysis incorporating 2010-2015 after the completion of this thesis, which hopefully could shed some light on any effect that has occurred to this end. Other new analyses which I aim to complete in this work will include analysis of multiple prescriptions and prescription combinations on the same day; and analysing prescriptions commonly prescribed for RTIs but prescribed without a Read code.

7.3 DISCUSSION

7.3.1 Implications for clinical and public health practice

The key message from this thesis is that parents and carers of children with DS should be made aware that the risk of RTIs-related healthcare in children with DS is elevated relative to children without DS. The average child with DS can expect to have three RTI-related GP consultations every two years, and one episode of an RTI severe enough to justify receiving antibiotics in primary care every year. The overall risk of hospitalisation is low; the average child with DS will have one RTI-related hospitalisation every 15 years, which is most likely to occur in infancy. Antibiotics prescribed in primary are not effective for averting subsequent hospitalisation for older children with DS. The risk of hospitalisation is higher in LRTIs compared to URTI and unclassified RTIs. Children with DS with concomitant asthma or CHD have also been identified as a high-risk population for increased RTI-related healthcare utilisation relative to those with DS but without asthma or CHD.

This thesis has also found that research into respiratory tract infections typically excludes children with DS. A systematic review in 2006 found there was no published evidence on the use of antibiotics for children with DS, and my systematic review likewise found no

such studies (77). Healthcare professionals are therefore currently lacking in guidance in how best to manage children with DS presenting on RTIs.

Work from this thesis has therefore contributed substantially towards addressing this problem by assessing the current literature on interventions to prevent or treat RTIs in children with DS, healthcare utilisation of children with DS, and the effects of antibiotics in reducing the risk of RTI-related hospitalisation in children with DS.

From the treatments identified in the systematic review, I found some evidence for the use of palivizumab in preventing RSV-related hospitalisations in a population of children with DS under two years (90). Pidotimod reduced parent-reported URTI recurrences and days with fever (91), and zinc had no effect on URTI episodes (92). It is clear that current guidelines have little to rely on in the way of evidence, and as such clinicians need more support in decision making. In the two years since my initial search took place, no new high-quality studies were identified, and going forward more would be welcomed.

When a child develops symptoms of a RTI, there are a number of options a parent or carer can take - either to watch and wait, access treatment in primary care or secondary care, or to start treatment themselves. The decision taken can be directed by a number of factors such as severity of symptoms, co morbidities, parents' capacity to manage their child's illness and also to recognise when further treatment is required. Other identified factors from a cross-study analysis include perceived child vulnerability, combatting uncertainty, and combatting social disapproval, all factors that may be felt more acutely in the parents of children with complex needs (169). Children who are at higher risk of deterioration are more likely to require prompt recognition of symptoms and access to primary and secondary care for assessment and effective management. The difficulty for health professionals is often how to identify the high-risk populations who require targeted, prompt assessment and treatment, which can be better achieved by building good relationships with parents and carers.

Whilst GP consultations and antibiotic prescribing may be a function of health-seeking behaviour by parents or carers and risk-aversion by GPs who do not wish to under-treat children with DS, the differences in hospitalisations together with the prolonged length of stay observed are a sensitive marker of illness severity and provide evidence that future public health campaigns or education strategies to increase symptom recognition

for children with DS may be valuable. This will endeavour to ensure that children receive timely assessment and an effective management plan, whether this be antibiotic treatment, watch and wait policy with safety netting or referral for more intense intervention. Parents and carers should be informed of the high risk of RTI, but they should also be educated about signs and symptoms to alert them to a possible RTI, and provided with information on where and how to access support from the health service. Although the outright frequency of RTI-related hospitalisation is low, it should not be forgotten that families and children may experience other hospitalisation events related to other comorbidities, such as CHD, which may be traumatic if they involve surgery. Any individual hospitalisation puts a child at risk of infections such as hospital acquired pneumonia, and can have an effect on development, schooling and mood. Therefore, it cannot be said that even if the frequency of RTI-related hospitalisations is low, that it is acceptable.

Regarding antibiotics, current NICE recommendations state that antibiotics should be prescribed immediately if the child is (1) systemically unwell or (2) at high risk of serious complications due to pre-existing co-morbidities such as CHD (33). Findings from my thesis indicate that children with DS in particular could benefit from a more targeted antibiotic prescribing strategy for RTIs in primary care. This is more vital for children with DS at high risk such as infants with DS (0-1 years), although this study provided conflicting results about the benefits of prescribing for this group. The existing NICE guidelines could be more specific as to how to manage children with DS. In addition, national best practice guidance disseminated by the Down Syndrome Medical Interest Group could also include guidance on this issue, alongside consideration of what factors can help parents (213).

However, it should not be forgotten that there are legitimate concerns about the overuse of antibiotics in primary care and the development of antimicrobial resistance (214, 215). For example, a recent randomised controlled trial has clearly shown increased carriage in resistant organisms after macrolide administration but not after placebo (216). Children with DS may be more at risk given possible immune system immaturity (50-53) as discussed in Chapter 1.

Finally, with 74% of children with DS being admitted for an RTI-related hospitalisation without presenting to their GP and hence accessing primary care, the impact of prompt antibiotic prescribing in primary care have a limited impact on overall RTI-related

hospitalisation rates across the cohort. The reasons why parents and carers do not readily access their GP remains unclear, and needs to be explored. Parents and carers of children with DS may have different health seeking behaviour either due to personal preferences, differing advice to utilise secondary care, because the child's symptoms have deteriorated enough to warrant direct access to secondary care, or because of direct or indirect discrimination (217). Healthcare professionals should consider all these possibilities when treating children with DS in the context of RTI-related hospitalisations, and adjust their behaviour accordingly.

As discussed in Chapter 1, children with DS often come under the care of a multidisciplinary team and the RCPCH recommends that children with DS should primarily be cared for by paediatricians with particular expertise in DS (6). It is recommended that they are reviewed once every three months up to the age of one, and subsequently yearly where an annual review could take place. At such an annual review, families and children could be examined and assessed as to their general health, as well as for identified at-risk comorbidities; families could be given the opportunity to consider what adaptations could be made to their care to improve the fluidity of their experiences through the NHS; and paediatricians could answer questions that families may have about events during the year, such as hospitalisations.

A possible reason for the lack of presentation to primary care prior to hospitalisations may be that families of children with DS are more familiar with their paediatrician and the paediatrician is also relatively accessible. Of course, it is not known to what extent the RCPCH guidance is followed in practice. However, any intervention should certainly be directed towards paediatricians, especially for younger children with DS. According to the RCPCH guidance, children with DS should also be reviewed by at least four other specialists and then up to six more services; in this context, it is conceivable that families of children with DS experience healthcare provider 'fatigue' and therefore, to some degree, may want to minimise the number of services they see unless necessary. They may also be more aware about when it is appropriate to present to A&E as opposed to seeing a General Practitioner, given their greater experience of the NHS compared to families of children without DS.

7.3.2 Implications for research

The overall evidence base for management of RTIs in children with DS is low. It is clear that research is necessary in many areas in order to optimise care. These research areas are as follows: a) An accurate map of the patient journey; b) Development of an algorithm to guide prescribing strategies; c) Examination of strategies to prevent RTIs beyond antibiotic prescription; d) A more detailed analysis of sub-populations of children with DS who are at greater risk; e) Use of laboratory data to identify certain bacteria or viruses, and hence certain antibiotics, linked to healthcare utilisation behaviours; f) An RCT to further quantify the benefit of antibiotic prescribing for RTIs in children with DS. Each of these research recommendations is explained in the subsequent paragraphs.

First, this thesis has quantified RTI-related healthcare utilisation at GPs and hospitals, but there is now a need for a more detailed map of current services that deliver care. This should encompass A&E and walk-in centres, as well as social care and other potential contact points; the large number of comorbidities means children with DS will encounter a variety of specialists in different settings (141). As a result, there is a need to prospectively follow the patient journey when and how critical decisions are made with regards to management of RTIs. This could run alongside qualitative research exploring the patient and family experience and decision making in relation to accessing health services and antibiotic prescribing.

Second, research is required to establish and co-design an algorithm to better target antibiotics in children with DS for RTIs. This study found that certain groups, namely infants, those with CHD, and with asthma, are at greater risk of hospitalisation. It may be that those at risk of RTI-related hospitalisation could be defined in greater detail, thus enabling the development of a symptoms-based scoring algorithm could optimise prescribing, modelled on algorithms those that already exist for many other conditions (173, 218, 219).

Third, research should examine other RTI treatment strategies beyond antibiotics. Qualitative work and/or a scoping survey of prescribers is necessary to clarify the extent of rescue antibiotic prescribing which is not quantifiable in my thesis due to the absence of Read codes for “rescue prescribing”. Prophylactic antibiotic usage is another strategy to explore, as it has been successful in reducing exacerbations in chronic respiratory

diseases (220). The efficacy of antivirals should be quantified, which is already recommended for children at high risk of RTI-related complications (34). Finally, vaccine uptake was not assessed in this thesis and research into methods to ensure uptake remains high in children with DS should be encouraged. As discussed in Chapter 1, poor responses to certain vaccines have been noted in children with DS (79, 80) and it would be interesting to see whether this has resulted in a perception amongst families that vaccines are not always worthwhile, which could be assessed in a qualitative study alongside outright assessment of uptake of vaccinations such as the flu vaccine. The degree to which families would be supportive of children with DS undergoing regular serological testing to assess vaccine responses (*e.g.*, antibody functionality) and repeat vaccinations could also be assessed (81).

Fourth, while studies in this thesis have identified children with DS as an at-risk group for increased healthcare utilisation and hospitalisation following an RTI, the magnitude of increased risk in children with DS with certain other relevant co-morbidities (e.g. chronic lung disease or immunosuppression due to cancer therapy) could not be assessed due to the small numbers identified. Adequately powered stratified analyses using larger datasets of children with DS (e.g. CALIBER dataset with data from more recent years) will be necessary to quantify this risk.

Fifth, linking laboratory data (e.g. from the PHE's 'Lab base') on positive specimens to general practice datasets would allow assessment of the relative effects of influenza versus other respiratory infections on RTI-related healthcare utilisation. The effects of specific antibiotics in reducing RTI-related hospitalisations linked to specific pathogens could also be better delineated.

Finally, more evidence is needed, ideally from RCTs, on the effect, risks, benefits and impact on antimicrobial resistance of using antibiotics to treat RTIs in children with DS, particularly for infants with DS.

7.4 CONCLUSION

Work from this thesis has contributed substantially to understanding the relationship between respiratory tract infections and the effects of treatments such as antibiotics in children with and without DS with important research, clinical and public health implications.

Overall, there was good evidence suggesting a higher healthcare utilisation in both primary and secondary care in children with DS for RTIs compared to controls. This is further increased in infants (0-1 year olds) and children with asthma and CHD.

My systematic review found that there is little existing evidence on interventions to prevent and treat RTIs in children with DS, and I was then able to quantify the benefit provided by the prescription of antibiotics in primary care for RTIs in children with DS. Based upon my results I recommend that prioritisation of further research into antibiotic treatment for infants with DS presenting to primary care with any RTI.

For children with DS at other ages presenting with RTIs, I would not recommend antibiotic treatment; for lower RTIs, further investigation is recommended with a larger sample size. Other prescribing strategies should be explored to broaden the evidence base for this at-risk group.

Appendix

Table A 1. Condition and co-morbidities searched using the RCALIBERcodelists package

Sub-Category	Conditions Searched	Conditions Not Searched	Codes Searched
Conditions Associated with Breathing Difficulties in Down's Syndrome			
Respiratory	Obstructive sleep apnoea		Sleep|Apnoe*
	Chronic lung disease		Lung
	Tracheostomy		Trache*
		Subpleural cysts	
Cardiovascular	Congenital heart disease		Congenital|Heart
	Atrioventricular canal defect		Atri*
	Atrial & ventricular septal defects		Atri*|Ventric*
	Aortic regurgitation		Regurg*
	Patent ductus arteriosus		Duct*
	Tetralogy of Fallot		Fallot
	Double outlet right ventricle		Ventric*
	Mitral valve prolapse		Valve
	Acquired valve disease		Valve
Gastrointestinal	Gastroesophageal reflux disease		Reflux*
	Swallowing dysfunction		Swallow*
	Oesophageal atresia repair		Oesophag*
	Tracheo-oesophageal fistula		Trache*
Anatomical	Tracheal bronchus		Trache*
	Tracheomalacia		Trache*
		Small jaw	
		Macroglossia	
		Narrow nasopharynx	
		Adenotonsillar hypertrophy	
		Choanal stenosis	
		Laryngomalacia	
		Narrow trachea	
		Mid-face hypoplasia	
		Subglottic stenosis	
		Small upper airway	
Contributory factors		Obesity	
		Hypotonia	
Conditions Associated with Infections in Down's Syndrome			
Cancer	Acute Leukaemia		Acute|Leukaemi*
	Myeloproliferative disease		Myeloproliferative
Misc		Increased mucus secretions	
		Reduced ciliary beat frequency	
		B-cell function abnormality	
		Decreased neutrophil chemotaxis	
		Thymic abnormalities	
		Alteration of levels of immunoglobulin subclasses	

		Alterations in response to vaccinations	
		Reduced T and B lymphocyte subpopulations	
		Ciliary dysfunction	
Population: Down's Syndrome			
Down's Syndrome	Down's Syndrome		Down|Trisomy|Mongol
Infections			
URTI	Common Cold		Common|upper|infection
	Rhinitis		Acute|rhinitis
	Sinusitis		Sinusit*|rhinosinusitis
		Nasopharyngitis	
		Pharyngitis	
	Epiglottits		Epiglot*
		Laryngitis	
		Laryngotracheitis	
	Tracheitis		Trache*
		Tonsillitis	
		Otitis Media	
LRTI	Chest infection		Chest|Lower resp*
	Bronchitis		Bronchi*
	Bronchiolitis		Bronchi*
	Croup |Laryngotracheobronchitis		Croup |Laryngotracheo
	Pneumonia		Pneumon*
SBIs	Meningitis		Mening*
	Septicaemia		Sepsis |Septic*
	Endocarditis		Endocard*
	Abscess		Abscess
Other Infections	Skin and soft tissue		Infect*
	Urinary		Infect*
	Gastro		Infect*
	TB (All subtypes)		Infect*| Lung
	Named organism infections w/out site		Infect*
	Otitis externa		Infect*
	Bone		Infect*

Table A 2. List of Read codes

Down's Syndrome			
	Q909		Down's Syndrome, unspecified
	1543		Down's Syndrome- trisomy 21
	10759		Down's Syndrome NOS
	19062		Partial Trisomy Syndromes
	18415		Trisomy 21
	Q929		Trisomy and partial trisomy of autosomes, unspecified
	Q901		Trisomy 21, mosaicism (mitotic nondisjunction)
	Q900		Trisomy 21, meiotic nondisjunction
LRTI			
	22448	POSSIBLE	O/E - intercostal recession
	25722	POSSIBLE	O/E - subcostal recession
	7092	POSSIBLE	Recurrent wheezy bronchitis
	152	POSSIBLE	Wheezy bronchitis
	8582	POSSIBLE	O/E - chest findings
	5978	PROBABLE	Acute wheezy bronchitis
	13573	PROBABLE	Influenza with bronchopneumonia
	8539	POSSIBLE	O/E - shallow breathing
	14976	PROBABLE	Viral pneumonia NOS
	5202	PROBABLE	Viral pneumonia
	44425	PROBABLE	Pleural empyema
	7000	POSSIBLE	O/E - dyspnoea
	1934	PROBABLE	Laryngotracheobronchitis
	18451	PROBABLE	Acute bronchiolitis due to respiratory syncytial virus
	17359	PROBABLE	Chest infection - unspecified bronchitis
	10321	POSSIBLE	O/E - consolidation
	41137	PROBABLE	Acute bronchitis or bronchiolitis NOS
	8318	PROBABLE	Lung consolidation
	22795	PROBABLE	Chest infection - other bacterial pneumonia
	3683	PROBABLE	Basal pneumonia due to unspecified organism
	23095	PROBABLE	Bacterial pneumonia NOS
	25694	PROBABLE	Pneumonia due to other specified organisms

1576	PROBABLE	Pneumonia due to mycoplasma pneumoniae
3480	PROBABLE	Bronchitis NOS
3163	PROBABLE	Tracheobronchitis NOS
10114	POSSIBLE	O/E - tachypnoea
9639	PROBABLE	Lobar pneumonia due to unspecified organism
5324	PROBABLE	Atypical pneumonia
25571	POSSIBLE	O/E - coarse crepitations
1382	PROBABLE	Acute viral bronchitis unspecified
10086	PROBABLE	Pneumonia and influenza
11101	PROBABLE	Acute tracheobronchitis
9062	POSSIBLE	O/E - crepitations
4626	POSSIBLE	O/E - rhonchi present
29669	PROBABLE	Acute bronchitis and bronchiolitis
1849	PROBABLE	Lobar (pneumococcal) pneumonia
6094	PROBABLE	Pneumonia or influenza NOS
37447	PROBABLE	Acute lower respiratory tract infection
886	PROBABLE	Bronchopneumonia due to unspecified organism
4899	PROBABLE	Recurrent chest infection
978	PROBABLE	Pleurisy
572	PROBABLE	Pneumonia due to unspecified organism
148	PROBABLE	Bronchitis unspecified
6124	PROBABLE	Acute lower respiratory tract infection
1019	PROBABLE	Acute bronchiolitis
3358	PROBABLE	Lower resp tract infection
312	PROBABLE	Acute bronchitis
2581	PROBABLE	Chest infection NOS
68	PROBABLE	Chest infection
2375	PROBABLE	Empyema

RTI

6475	POSSIBLE	[D]Respiratory system and chest symptoms
7118	POSSIBLE	O/E - pyrexia - ? cause
5892	POSSIBLE	O/E - fever
16660	POSSIBLE	O/E - nose crusting
4519	POSSIBLE	H/O: bronchitis

1740	POSSIBLE	Night sweats
2389	POSSIBLE	[D]Pyrexia of unknown origin
6086	POSSIBLE	Pyrexia symptoms
6484	POSSIBLE	Temperature symptoms
6065	POSSIBLE	Fever symptoms
5859	POSSIBLE	Feels hot/feverish
1020	POSSIBLE	[D]Fever NOS
24181	POSSIBLE	Sputum: mucopurulent
15430	POSSIBLE	[D]Sputum abnormal - colour
14804	POSSIBLE	Sputum appears infected
1025	POSSIBLE	Bronchial cough
735	POSSIBLE	[D]Breathlessness
7707	POSSIBLE	Cough symptom NOS
21113	PROBABLE	Acute respiratory infection NOS
9807	POSSIBLE	Sputum - symptom
7708	POSSIBLE	Productive cough-yellow sputum
550	POSSIBLE	Rhinorrhoea
7074	PROBABLE	Respiratory infection NOS
5896	POSSIBLE	Dyspnoea - symptom
5175	POSSIBLE	Breathlessness symptom
7773	POSSIBLE	Productive cough -green sputum
2931	POSSIBLE	Difficulty breathing
3628	POSSIBLE	Persistent cough
1234	POSSIBLE	Productive cough NOS
4931	POSSIBLE	Dry cough
1429	POSSIBLE	Breathlessness
1160	POSSIBLE	[D]Cough
4822	POSSIBLE	Shortness of breath
293	PROBABLE	Respiratory tract infection
292	POSSIBLE	Chesty cough
1273	POSSIBLE	C/O - cough
92	POSSIBLE	Cough

URTI

32802	POSSIBLE	Other upper respiratory tract diseases
2097	PROBABLE	Nasal cavity and sinus disease NOS
16986	POSSIBLE	Nose running
8975	POSSIBLE	Catarrh unspecified
11139	POSSIBLE	Blocked nose
1309	PROBABLE	Nasal infection
9483	POSSIBLE	Sinus congestion
1401	POSSIBLE	Nasal obstruction
7479	POSSIBLE	Catarrh - eustachian
3821	POSSIBLE	Rhinitis - acute
3110	POSSIBLE	Nasal congestion
6481	POSSIBLE	Nasal symptoms
5765	POSSIBLE	C/O - catarrh
1513	PROBABLE	Infection ear
5577	PROBABLE	Nonsuppurative otitis media + eustachian tube disorders
731	POSSIBLE	Otalgia
5813	POSSIBLE	Earache symptoms
10781	PROBABLE	Acute suppurative otitis media tympanic membrane intact
15774	PROBABLE	Influenza with laryngitis
16184	PROBABLE	Streptococcal sore throat with scarlatina NOS
16147	POSSIBLE	O/E - purulent ear discharge
22131	POSSIBLE	O/E - tonsils hyperaemic
20372	PROBABLE	Acute suppurative otitis media NOS
97279	PROBABLE	[X]Influenza+other manifestations, virus not identified
21012	PROBABLE	Acute mucoid otitis media
20669	PROBABLE	Acute suppurative otitis media tympanic membrane ruptured
10641	PROBABLE	Acute epiglottitis (non strep)
17899	PROBABLE	Acute bacterial pharyngitis
20618	POSSIBLE	O/E - nose discharge
7266	PROBABLE	O/E - follicular tonsillitis
14791	PROBABLE	Influenza with gastrointestinal tract involvement
4718	PROBABLE	Pharyngolaryngitis
8570	POSSIBLE	O/E - rhinorrhoea
3605	PROBABLE	Peritonsillar abscess - quinsy

10087	PROBABLE	Acute laryngotracheitis
9973	PROBABLE	Recurrent acute otitis media
15287	POSSIBLE	Sore throat symptom NOS
4902	PROBABLE	Streptococcal pharyngitis
6958	POSSIBLE	Otorrhagia
6620	PROBABLE	Febrile cold
6498	POSSIBLE	O/E - tonsils mod. enlarged
16388	PROBABLE	Influenza NOS
18363	POSSIBLE	O/E - tympanic membrane red
5115	PROBABLE	Acute viral laryngitis unspecified
5102	PROBABLE	Serous otitis media NOS
19431	PROBABLE	Croup
15410	POSSIBLE	Throat symptom NOS
10156	PROBABLE	Acute bacterial tonsillitis
18371	PROBABLE	Acute otitis media with effusion
3260	PROBABLE	Acute nasopharyngitis
4221	PROBABLE	Recurrent upper respiratory tract infection
26010	PROBABLE	Other acute upper respiratory infections
7021	PROBABLE	Acute maxillary sinusitis
20104	PROBABLE	Acute tonsillitis NOS
9357	PROBABLE	Acute viral tonsillitis
8950	PROBABLE	Feverish cold
20374	PROBABLE	Acute nonsuppurative otitis media NOS
1285	PROBABLE	Laryngotracheitis
2984	PROBABLE	Frontal sinusitis
2476	PROBABLE	Chest cold
5148	PROBABLE	Acute secretory otitis media
5947	PROBABLE	Influenza like illness
911	PROBABLE	Quinsy
1765	PROBABLE	Streptococcal sore throat
1747	PROBABLE	Recurrent acute tonsillitis
9093	PROBABLE	Pyrexial cold
3624	PROBABLE	Maxillary sinusitis
4061	PROBABLE	Acute follicular tonsillitis

8496	PROBABLE	Streptococcal tonsillitis
7730	PROBABLE	Acute serous otitis media
386	POSSIBLE	Throat pain
11499	PROBABLE	Throat infection - tonsillitis
5935	POSSIBLE	O/E - nasal discharge
6466	PROBABLE	Viral sore throat NOS
5390	PROBABLE	Catarrhal otitis media NOS
4868	PROBABLE	Acute viral pharyngitis
8980	POSSIBLE	Influenza-like symptoms
5553	POSSIBLE	Has a sore throat
14931	POSSIBLE	Inflamed throat
1134	PROBABLE	Acute bilateral otitis media
1390	POSSIBLE	Snuffles
6014	POSSIBLE	Sore throat NOS
5806	POSSIBLE	O/E - painful ear
407	PROBABLE	Acute pharyngitis NOS
556	PROBABLE	Influenza
896	PROBABLE	Nasal catarrh - acute
2137	PROBABLE	Acute suppurative otitis media
638	POSSIBLE	Otorrhoea
3694	PROBABLE	Acute left otitis media
4348	PROBABLE	Acute right otitis media
2125	PROBABLE	Tonsillitis
1257	PROBABLE	Acute tracheitis
6421	PROBABLE	Viral upper respiratory tract infection NOS
1142	PROBABLE	Croup
310	PROBABLE	Throat infection - pharyngitis
368	PROBABLE	Common cold
5887	PROBABLE	Acute non suppurative otitis media
1246	PROBABLE	Coryza - acute
142	PROBABLE	Acute laryngitis
1474	PROBABLE	Suppurative and unspecified otitis media
243	PROBABLE	Sinusitis
2157	PROBABLE	Flu like illness

893	PROBABLE	Acute pharyngitis
6294	PROBABLE	Acute upper respiratory tract infection
980	PROBABLE	Acute sinusitis
267	PROBABLE	Otitis media NOS
404	POSSIBLE	Throat soreness
5755	POSSIBLE	Sore throat symptom
138	PROBABLE	Acute tonsillitis
2637	PROBABLE	Upper respiratory tract infection NOS
76	PROBABLE	Upper respiratory infection NOS

asthma

39570	Asthma causes night symptoms 1 to 2 times per month
38145	Asthma limits walking on the flat
13175	Asthma disturbs sleep frequently
11370	Asthma confirmed
1555	Bronchial asthma
7191	Asthma limiting activities
3018	Mild asthma
4442	Asthma unspecified
13065	Moderate asthma
24884	Asthma causes daytime symptoms 1 to 2 times per week
7416	Asthma disturbing sleep
31225	Asthma causes daytime symptoms 1 to 2 times per month
13066	Asthma - currently dormant
233	Severe asthma attack
26504	Asthma never restricts exercise
16655	Asthma monitoring admin.
19520	Asthma treatment compliance satisfactory
232	Asthma attack
38143	Asthma never disturbs sleep
10274	Asthma medication review
19539	Asthma monitoring check done
5515	Seen in asthma clinic
13064	Asthma severity

	7378	Asthma management plan given
	185	Acute exacerbation of asthma
	25707	Asthma monitor 1st letter
	13176	Asthma follow-up
	10043	Asthma annual review
	81	Asthma monitoring
	78	Asthma
cardiac		
	8464	Acute cor pulmonale
	39885	Revision of closure of defect of atrioventricular septum
	50626	Close defect interventricular septum using pericardial patch
	12889	Percut transluminal prosth occlusion patent ductus arterios
	12312	Pulmonary valve disorders
	5058	Mitral incompetence, non-rheumatic
	49551	Tricuspid stenosis and regurgitation, cause unspecified
	3810	Complete atrioventricular block
	35372	Tricuspid regurgitation, non-rheumatic
	41569	Other specified catheterisation of heart
	3169	Heart valve and adjacent structures operations NOS
	36668	Closure of patent ductus arteriosus NEC
	42132	Ventricular septal defect, unspecified
	48207	Other operations on heart
	54772	Other specified ventricular septal defect
	89256	Congenital heart disease
	30443	Mitral valve disease NOS
	12844	Repair of tetralogy of Fallot
	48331	Primary closure of defect of atrioventricular septum NEC
	4939	Bacterial endocarditis
	20940	Repair of subaortic stenosis
	19188	Percut translum prosth occlus patent ductus arteriosus (PDA)
	63046	Tetralogy of Fallot NOS
	1267	Mitral valve diseases
	30725	Aortic arch anomalies

84407	Other operations on ventricles of heart
34902	Closure of defect of interatrial septum
10078	Diseases of mitral and aortic valves
1007	Aortic incompetence alone, cause unspecified
48205	Congenital malforms of cardiac chambers+connections unsp
6886	Congenital aortic valve stenosis
39810	Heart wall, septum and chamber operations
3301	Coarctation of aorta
73602	Repair of atrium NEC
16191	Closure of defect of interatrial septum NOS
9573	Ligation of patent ductus arteriosus
3300	Bicuspid aortic valve
16539	Subaortic stenosis
2977	Mitral valve incompetence
30173	Valves of heart and adjacent structures operations
3863	Cyanotic congenital heart disease NOS
12775	Acute and subacute endocarditis
15133	Replacement of aortic valve NEC
17088	H/O: cardiac surgery
10079	Right heart failure
11878	Mitral and aortic regurgitation
5621	Other congenital heart anomalies
30340	Closure of defect of unspecified septum of heart
17328	Aorta operations
38436	Closure of defect of atrioventricular septum NOS
36575	Closure of defect of interventricular septum
19019	Aortic valve disorders NOS
18820	H/O: cardiac anomaly
7342	Open correction of patent ductus arteriosus (PDA)
5743	Valvular heart disease
18785	Heart septal defects
7894	Plastic repair of mitral valve
9498	Plastic repair of aortic valve
4548	Aortic valve disorders

	22003	Regurgitation of unspecified heart valve
	3418	Paroxysmal ventricular tachycardia
	73476	Repair of defect of the atrioventricular septum
	1005	Aortic regurgitation alone, cause unspecified
	5477	Correction of tetralogy of Fallot
	9450	Mitral valve regurgitation
	2343	Aortic stenosis alone, cause unspecified
	247	Congenital heart anomaly NOS
	32163	Closure of defect of atrioventricular septum
	2841	Implantation of intravenous cardiac pacemaker system
	1294	Mitral valve prolapse
	6401	H/O: heart disorder
	18395	Other specified atrial septal defect
	9286	Tricuspid regurgitation, cause unspecified
	10187	Aortic regurgitation, non-rheumatic
	1735	Aortic aneurysm
	3520	Catheterisation of heart NOS
	7474	Ostium secundum atrial septal defect
	3625	Patent foramen ovale
	2427	Catheterisation of heart
	44896	Common atrioventricular-type ventricular septal defect
	9011	Eisenmenger's complex
	1536	Supraventricular tachycardia NOS
	2727	Patent ductus arteriosus
	561	Mitral regurgitation
	3255	Atrial septal defect NOS
	246	Ventricular septal defect

diabetes		
	14803	Diabetes mellitus, adult onset, no mention of complication
	85660	Diabetes type 1 review
	8403	Non-insulin dependent diabetes mellitus - poor control
	30323	Type 1 diabetes mellitus with persistent proteinuria
	30294	Type 1 diabetes mellitus with persistent microalbuminuria
	32359	Perceived control of insulin-dependent diabetes

11626	Diabetic retinopathy NOS
26054	Type 2 diabetes mellitus with persistent proteinuria
2342	Diabetic neuropathy
5884	NIDDM - Non-insulin dependent diabetes mellitus
1682	Diabetes mellitus with ketoacidosis
55239	Type 1 diabetes mellitus with gastroparesis
18219	Type II diabetes mellitus
18390	Type 2 diabetes mellitus with persistent microalbuminuria
18824	Diabetic foot examination declined
16230	Diabetes mellitus with neurological manifestation
10692	Type 1 diabetes mellitus with ketoacidosis
18278	Insulin treated Type 2 diabetes mellitus
1407	Insulin treated Type 2 diabetes mellitus
35383	Diabetic patient unsuitable for digital retinal photography
17858	Type 1 diabetes mellitus
11047	Conversion to insulin
83532	Diabetes type 2 review
18505	IDDM-Insulin dependent diabetes mellitus
28769	Diabetic on insulin and oral treatment
22823	Diabetic foot examination
17859	Type 2 diabetes mellitus
13074	Diabetic diet
11471	Diabetes medication review
1038	Insulin dependent diabetes mellitus
22130	Diabetes monitoring default
1647	Insulin dependent diabetes mellitus
95994	Diabetic foot screen
9974	Seen in diabetic eye clinic
1323	Diabetic retinopathy
506	Non-insulin dependent diabetes mellitus
12675	Diabetes: shared care programme
7563	Diabetic on diet only
1549	Type 1 diabetes mellitus
8836	Diabetes management plan given

	4513	Non-insulin dependent diabetes mellitus
	7069	Background diabetic retinopathy
	13067	Diabetic monitoring NOS
	1684	Diabetic on oral treatment
	2378	Diabetic - poor control
	12506	Diabetes: practice programme
	608	Follow-up diabetic assessment
	758	Type 2 diabetes mellitus
	711	Diabetes mellitus
	2379	Seen in diabetic clinic
	6125	Diabetic annual review
	3550	Diabetic monitoring
	9897	Diabetes monitoring admin.

epilepsy

	9747	Epilepsy NOS
	4093	Status epilepticus
	5117	Grand mal status
	46603	Emergency epilepsy treatment since last appointment
	4801	Epileptic seizures - myoclonic
	22341	Epilepsy confirmed
	18471	Epileptic seizures - clonic
	1715	Epileptic absences
	8187	Tonic-clonic epilepsy
	6271	Status epilepticus, unspecified
	19550	Epilepsy control good
	8487	Myoclonic seizure
	5152	Epileptic seizures - tonic
	36696	Epilepsy monitoring NOS
	2907	Petit mal (minor) epilepsy
	3607	Fit (in known epileptic) NOS
	11752	Patient on maximal tolerated anticonvulsant therapy
	6983	Epilepsy monitoring
	9326	Epilepsy medication review
	11015	Seizure free >12 months

	573	Epilepsy

thyroid

	11146	TSH - thyroid-stimulating hormone deficiency
	95885	Hypothyroidism annual review
	718	Subclinical iodine-deficiency hypothyroidism
	51481	Congenital hypothyroidism NOS
	24681	Thyroid dis.treatment changed
	10097	Congenital hypothyroidism
	28735	Hypothyroidism monitoring administration
	46630	Hypothyroidism monitoring second letter
	3941	Hypothyroidism NOS
	46057	Hypothyroidism monitoring first letter
	14704	Thyroid deficiency
	3290	Acquired hypothyroidism
	8268	Thyroid disease monitoring
	273	Hypothyroidism

Table A 3. List of ICD-10 codes

LRTI

	B953	PROBABLE	Streptococcus pneumoniae as the cause of diseases classified to other chapters
	J154	PROBABLE	Pneumonia due to other streptococci
	J121	PROBABLE	Respiratory syncytial virus pneumonia
	J152	PROBABLE	Pneumonia due to staphylococcus
	J851	PROBABLE	Abscess of lung with pneumonia
	J14X	PROBABLE	Pneumonia due to Haemophilus influenzae
	J153	PROBABLE	Pneumonia due to streptococcus, group B
	J852	PROBABLE	Abscess of lung without pneumonia
	J158	PROBABLE	Other bacterial pneumonia
	J168	PROBABLE	Pneumonia due to other specified infectious organisms
	J218	PROBABLE	Acute bronchiolitis due to other specified organisms
	J159	PROBABLE	Bacterial pneumonia, unspecified
	J188	PROBABLE	Other pneumonia, organism unspecified
	J151	PROBABLE	Pneumonia due to Pseudomonas
	J129	PROBABLE	Viral pneumonia, unspecified

	J209	PROBABLE	Acute bronchitis, unspecified
	B961	PROBABLE	Klebsiella pneumoniae [K. pneumoniae] as the cause of diseases classified to other chapters
	J157	PROBABLE	Pneumonia due to Mycoplasma pneumoniae
	J13X	PROBABLE	Pneumonia due to Streptococcus pneumoniae
	J210	PROBABLE	Acute bronchiolitis due to respiratory syncytial virus
	J180	PROBABLE	Bronchopneumonia, unspecified
	J219	PROBABLE	Acute bronchiolitis, unspecified
	J189	PROBABLE	Pneumonia, unspecified
	J181	PROBABLE	Lobar pneumonia, unspecified
	J22X	PROBABLE	Unspecified acute lower respiratory infection

RTI

	B349	PROBABLE	Viral infection, unspecified
	R05X	POSSIBLE	Cough
	R060	POSSIBLE	Dyspnoea

URTI

	J398	PROBABLE	Other specified diseases of upper respiratory tract
	J038	PROBABLE	Acute tonsillitis due to other specified organisms
	J019	PROBABLE	Acute sinusitis, unspecified
	J041	PROBABLE	Acute tracheitis
	J040	PROBABLE	Acute laryngitis
	J020	PROBABLE	Streptococcal pharyngitis
	H660	PROBABLE	Acute suppurative otitis media
	J208	PROBABLE	Acute bronchitis due to other specified organisms
	J030	PROBABLE	Streptococcal tonsillitis
	H709	PROBABLE	Mastoiditis, unspecified
	J028	PROBABLE	Acute pharyngitis due to other specified organisms
	J101	PROBABLE	Influenza with other respiratory manifestations, other influenza virus identified
	H650	PROBABLE	Acute serous otitis media
	H651	PROBABLE	Other acute nonsuppurative otitis media
	H920	POSSIBLE	Otalgia
	J00X	PROBABLE	Acute nasopharyngitis [common cold]
	J029	PROBABLE	Acute pharyngitis, unspecified
	H921	POSSIBLE	Otorrhoea

H659	PROBABLE	Nonsuppurative otitis media, unspecified
H669	PROBABLE	Otitis media, unspecified
J050	PROBABLE	Acute obstructive laryngitis [croup]
J039	PROBABLE	Acute tonsillitis, unspecified
J069	PROBABLE	Acute upper respiratory infection, unspecified

asthma

J458	Mixed asthma
J46X	Status asthmaticus
J450	Predominantly allergic asthma
J459	Asthma, unspecified

cardiac

Q232	Congenital mitral stenosis
Q264	Anomalous pulmonary venous connection, unspecified
Q238	Other congenital malformations of aortic and mitral valves
Q228	Other congenital malformations of tricuspid valve
Q201	Double outlet right ventricle
Q262	Total anomalous pulmonary venous connection
Q258	Other congenital malformations of great arteries
Q268	Other congenital malformations of great veins
I052	Mitral stenosis with insufficiency
Q282	Arteriovenous malformation of cerebral vessels
I510	Cardiac septal defect, acquired
Q254	Other congenital malformations of aorta
I059	Mitral valve disease, unspecified
I080	Disorders of both mitral and aortic valves
I083	Combined disorders of mitral, aortic and tricuspid valves
I081	Disorders of both mitral and tricuspid valves
Q208	Other congenital malformations of cardiac chambers and connections
I330	Acute and subacute infective endocarditis
Q251	Coarctation of aorta
I071	Tricuspid insufficiency
Q230	Congenital stenosis of aortic valve

I361	Nonrheumatic tricuspid (valve) insufficiency
I441	Atrioventricular block, second degree
Q244	Congenital subaortic stenosis
Q231	Congenital insufficiency of aortic valve
Q221	Congenital pulmonary valve stenosis
I341	Mitral (valve) prolapse
I440	Atrioventricular block, first degree
Q256	Stenosis of pulmonary artery
Q213	Tetralogy of Fallot
T825	Mechanical complication of other cardiac and vascular devices and implants
Z954	Presence of other heart-valve replacement
Q233	Congenital mitral insufficiency
I38X	Endocarditis, valve unspecified
I350	Aortic (valve) stenosis
Q219	Congenital malformation of cardiac septum, unspecified
T828	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts
Q249	Congenital malformation of heart, unspecified
Q257	Other congenital malformations of pulmonary artery
T827	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts
I351	Aortic (valve) insufficiency
I517	Cardiomegaly
I340	Mitral (valve) insufficiency
Z952	Presence of prosthetic heart valve
Q250	Patent ductus arteriosus
I420	Dilated cardiomyopathy
Q218	Other congenital malformations of cardiac septa
Q211	Atrial septal defect
Q210	Ventricular septal defect
I270	Primary pulmonary hypertension
Q212	Atrioventricular septal defect
Z867	Personal history of diseases of the circulatory system

diabetes

	E100	Insulin-dependent diabetes mellitus
	E105	Insulin-dependent diabetes mellitus
	E115	Non-insulin-dependent diabetes mellitus
	E106	Insulin-dependent diabetes mellitus
	E143	Unspecified diabetes mellitus
	Y423	Insulin and oral hypoglycaemic [antidiabetic] drugs
	E116	Non-insulin-dependent diabetes mellitus
	E112	Non-insulin-dependent diabetes mellitus
	E114	Non-insulin-dependent diabetes mellitus
	E111	Non-insulin-dependent diabetes mellitus
	E113	Non-insulin-dependent diabetes mellitus
	E108	Insulin-dependent diabetes mellitus
	O240	Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, insulin-dependent
	E139	Other specified diabetes mellitus
	E101	Insulin-dependent diabetes mellitus
	E109	Insulin-dependent diabetes mellitus
	E119	Non-insulin-dependent diabetes mellitus
epilepsy		
	Y466	Other and unspecified antiepileptics
	G408	Other epilepsy
	G419	Status epilepticus, unspecified
	G406	Grand mal seizures, unspecified (with or without petit mal)
	G403	Generalized idiopathic epilepsy and epileptic syndromes
	G409	Epilepsy, unspecified
thyroid		
	E02X	Subclinical iodine-deficiency hypothyroidism
	E038	Other specified hypothyroidism
	E890	Postprocedural hypothyroidism
	E031	Congenital hypothyroidism without goitre
	E039	Hypothyroidism, unspecified

Table A 4. Selection process of ethnicity codes from the CALIBER dataset

medid	readoricd10code	term	ethnicity
24690	9S7..00	Pakistani	Asian_or_Asian_British
12460	9i8..00	Pakistani or British Pakistani - ethnic category 2001 census	Asian_or_Asian_British
24740	9S8..00	Bangladeshi	Asian_or_Asian_British
28888	9i9..00	Bangladeshi or British Bangladeshi - ethn categ 2001 census	Asian_or_Asian_British
47997	9S42.12	Black West Indian	Asian_or_Asian_British
12482	9S6..00	Indian	Asian_or_Asian_British
12414	9i7..00	Indian or British Indian - ethnic category 2001 census	Asian_or_Asian_British
25937	9iFD.00	Iranian - ethnic category 2001 census	Asian_or_Asian_British
12653	9iA8.00	British Asian - ethnic category 2001 census	Asian_or_Asian_British
12420	9iF2.00	Filipino - ethnic category 2001 census	Asian_or_Asian_British
56127	9iF5.00	Hindu - ethnic category 2001 census	Asian_or_Asian_British
12473	9iF1.00	Japanese - ethnic category 2001 census	Asian_or_Asian_British
64133	9iA2.00	Kashmiri - ethnic category 2001 census	Asian_or_Asian_British
12730	9iF3.00	Malaysian - ethnic category 2001 census	Asian_or_Asian_British
26379	9SA8.00	Other Asian (NMO)	Asian_or_Asian_British
12513	9iA..00	Other Asian background - ethnic category 2001 census	Asian_or_Asian_British
12668	9SH..00	Other Asian ethnic group	Asian_or_Asian_British
28935	9iAA.00	Other Asian or Asian unspecified ethnic category 2001 census	Asian_or_Asian_British
12608	9iA4.00	Sri Lankan - ethnic category 2001 census	Asian_or_Asian_British
25411	9SC..00	Vietnamese	Asian_or_Asian_British
47950	9S42.11	Black Caribbean	Black_or_Black_British
12432	9iB..00	Caribbean - ethnic category 2001 census	Black_or_Black_British
12350	9iC..00	African - ethnic category 2001 census	Black_or_Black_British
35412	9S44.00	Black - other African country	Black_or_Black_British
12778	9S3..00	Black African	Black_or_Black_British
46812	9S43.11	Black North African	Black_or_Black_British
25451	9iFF.00	Moroccan - ethnic category 2001 census	Black_or_Black_British
32886	9iD1.00	Nigerian - ethnic category 2001 census	Black_or_Black_British
47028	9iFA.00	North African - ethnic category 2001 census	Black_or_Black_British
12443	9iD0.00	Somali - ethnic category 2001 census	Black_or_Black_British
12452	9S41.00	Black British	Black_or_Black_British
40097	9iD2.00	Black British - ethnic category 2001 census	Black_or_Black_British
57753	9S45.11	Black East African Asian	Black_or_Black_British
24339	9S4..00	Black, other, non-mixed origin	Black_or_Black_British
47969	9SA5.00	Other African countries (NMO)	Black_or_Black_British
32165	9S52.00	Other Black - Black/Asian orig	Black_or_Black_British
32389	9iD..00	Other Black background - ethnic category 2001 census	Black_or_Black_British
46047	9iD4.00	Other Black or Black unspecified ethnic category 2001 census	Black_or_Black_British
32136	9SG..00	Other black ethnic group	Black_or_Black_British
24962	9SA4.00	N African Arab/Iranian (NMO)	Black_or_Black_British
35350	9S47.00	Black - other Asian	Black_or_Black_British
24272	9S9..00	Chinese	Chinese_or_Other_Group
12468	9iE..00	Chinese - ethnic category 2001 census	Chinese_or_Other_Group
42290	9i2E.00	Gypsy/Romany - ethnic category 2001 census	Chinese_or_Other_Group
12434	9iF..00	Other - ethnic category 2001 census	Chinese_or_Other_Group
41214	9SAD.00	Other ethnic NEC (NMO)	Chinese_or_Other_Group
12757	9SJ..00	Other ethnic group	Chinese_or_Other_Group
30280	9SA..00	Other ethnic non-mixed (NMO)	Chinese_or_Other_Group
32126	9SAB.11	Turkish (NMO)	Chinese_or_Other_Group
12746	9i29.00	Turkish - ethnic category 2001 census	Chinese_or_Other_Group
32066	9SAB.00	Turkish/Turkish Cypriot (NMO)	Chinese_or_Other_Group
25676	9S5..00	Black - other, mixed	Mixed
32443	9SB6.00	Black African and White	Mixed
32425	9SB5.00	Black Caribbean and White	Mixed
12351	9i0..00	British or mixed British - ethnic category 2001 census	Mixed
12706	9i63.00	Chinese and White - ethnic category 2001 census	Mixed
47077	9iA3.00	East African Asian - ethnic category 2001 census	Mixed
46056	9iA9.00	Mixed Asian - ethnic category 2001 census	Mixed
25623	9S51.00	Other Black - Black/White orig	Mixed
12873	9i6..00	Other Mixed background - ethnic category 2001 census	Mixed
12591	9i2T.00	Other White or White unspecified ethnic category 2001 census	Mixed
32401	9SB2.00	Other ethnic, Asian/White orig	Mixed
12696	9SB..00	Other ethnic, mixed origin	Mixed
32420	9SB4.00	Other ethnic, other mixed orig	Mixed
12638	9i5..00	White and Asian - ethnic category 2001 census	Mixed
12437	9i4..00	White and Black African - ethnic category 2001 census	Mixed
12742	9i3..00	White and Black Caribbean - ethnic category 2001 census	Mixed
46059	9iF9.00	Arab - ethnic category 2001 census	Mixed
26246	9iFG.00	Latin American - ethnic category 2001 census	Mixed
12756	9iFH.00	South and Central American - ethnic category 2001 census	Mixed
26310	9S14.00	Other white British ethnic group	White
12681	9i22.00	Welsh - ethnic category 2001 census	White
12446	9S10.00	White British	White
98111	9i00.00	White British - ethnic category 2001 census	White
98111	9i00.00	White British - ethnic category 2001 census	White
26467	9S13.00	White Scottish	White
26391	9i2Q.00	Mixed Irish and other White - ethnic category 2001 census	White
24837	9S11.00	White Irish	White
12402	9i2R.00	Oth White European/European unsp/Mixed European 2001 census	White
12633	9SAC.00	Other European (NMO)	White
12421	9i2..00	Other White background - ethnic category 2001 census	White
12433	9i2G.00	Baltic Estonian/Latvian/Lithuanian - ethn categ 2001 census	White
28973	9i2H.00	Commonwealth (Russian) Indep States - ethn categ 2001 census	White
28866	9i2M.00	Croatian - ethnic category 2001 census	White
12355	9i27.00	Greek - ethnic category 2001 census	White
12769	9i28.00	Greek Cypriot - ethnic category 2001 census	White
46964	9iFC.00	Israeli - ethnic category 2001 census	White
12412	9i2B.00	Italian - ethnic category 2001 census	White
26341	9i2J.00	Kosovan - ethnic category 2001 census	White
12467	9i2F.00	Polish - ethnic category 2001 census	White
24270	9SA9.00	Irish (NMO)	White
12532	9i1..00	Irish - ethnic category 2001 census	White
12444	9S12.00	Other white ethnic group	White
22467	9S1..00	White	White

Table A 5. RTI-related GP consultation (top) and hospitalisation (bottom) rates between gender stratified by children with DS and controls – adjusted by cardiac co-morbidities

RTI-related GP consultation rates

	Female			Male			Female versus Male		
Classification	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age	p-value
CwDS	2803	784	0.666 [0.585-0.757]	3210	987	0.616 [0.542-0.700]	1.081 [0.960-1.217]	1.094 [0.973-1.229]	0.0964
Controls	6657	5735	0.364 [0.342-0.386]	7300	6425	0.362 [0.341-0.383]	1.006 [0.947-1.067]	1.005 [0.947-1.066]	0.4261

RTI-related hospitalisation rates

	Female			Male			Female versus Male		
Classification	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age	p-value
CwDS	184	1945	0.056 [0.045-0.069]	289	2182	0.077 [0.064-0.093]	0.721 [0.561-0.924]	0.716 [0.562-0.912]	0.0038
Controls	119	10720	0.010 [0.008-0.012]	208	11563	0.015 [0.013-0.017]	0.671 [0.552-0.859]	0.668 [0.525-0.850]	0.0005

Table A 6. RTI-related GP consultation (top) and hospitalisation (bottom) rates between gender stratified by children with DS and controls – adjusted by asthma co-morbidities

RTI-related GP consultation rates

	Female			Male			Female versus Male		
Classification	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age	p-value
CwDS	2803	784	0.666 [0.585-0.757]	3210	987	0.616 [0.542-0.700]	1.081 [0.960-1.217]	1.094 [0.973-1.229]	0.0964
Controls	6657	5735	0.364 [0.342-0.386]	7300	6425	0.362 [0.341-0.383]	1.006 [0.947-1.067]	1.018 [0.960-1.080]	0.4261

RTI-related hospitalisation rates

	Female			Male			Female versus Male		
Classification	# episodes	person-year	Rate per person-year [95%CI]	# episodes	person-year	Rate per person-year [95%CI]	RR [95%CI]	Adjusted RR [95%CI] for age	p-value
CwDS	184	1945	0.056 [0.045-0.069]	289	2182	0.077 [0.064-0.093]	0.721 [0.561-0.924]	0.724 [0.569-0.922]	0.0038
Controls	119	10720	0.010 [0.008-0.012]	208	11563	0.015 [0.013-0.017]	0.671 [0.552-0.859]	0.681 [0.535-0.867]	0.0005

Table A 7. Sensitivity analyses: Adjusted effects of antibiotics stratified by RTI-type using 7, 14, 21 and 28 day at-risk periods for RTI-related hospitalisation (adjusted by the 7 identified co-variates)

Classification	adjusted odds ratio [95%CI]	p-value	adjusted odds ratio [95%CI]	p-value
Complication in 7 days				
URTI	0.936 [0.385-2.276]	0.8835	0.766 [0.295-1.993]	0.5855
LRTI	0.460 [0.120-1.763]	0.2572	0.332 [0.070-1.587]	0.1672
unclassified RTI	1.592 [0.710-3.568]	0.2588	0.403 [0.117-1.384]	0.1488
ALL	1.161 [0.683-1.973]	0.5813	0.613 [0.324-1.160]	0.1328
Complication in 14 days				
URTI	0.658 [0.307-1.412]	0.2828	0.979 [0.440-2.177]	0.9587
LRTI	0.401 [0.104-1.555]	0.1865	0.374 [0.084-1.665]	0.1968
unclassified RTI	1.079 [0.564-2.062]	0.8190	0.493 [0.167-1.460]	0.2018
ALL	0.834 [0.533-1.305]	0.4261	0.759 [0.437-1.320]	0.3290
Complication in 21 days				
URTI	0.731 [0.367-1.456]	0.3728	0.968 [0.481-1.947]	0.9264
LRTI	0.506 [0.133-1.929]	0.3185	0.490 [0.086-2.786]	0.4212
unclassified RTI	0.988 [0.520-1.875]	0.9698	0.508 [0.191-1.349]	0.1739
ALL	0.878 [0.574-1.343]	0.5479	0.728 [0.436-1.214]	0.2234
Complication in 28 days				
URTI	0.748 [0.403-1.390]	0.3587	1.033 [0.561-1.901]	0.9175
LRTI	0.470 [0.121-1.833]	0.2772	0.610 [0.114-3.270]	0.5644
unclassified RTI	0.784 [0.412-1.492]	0.4593	0.752 [0.318-1.781]	0.5175
ALL	0.769 [0.511-1.157]	0.2074	0.901 [0.569-1.426]	0.6554

Table A 8. Sensitivity analyses: Adjusted effects of antibiotics stratified by RTI-type using 7, 14, 21 and 28 day at-risk periods for RTI-related hospitalisation (adjusted for clustering and by the 7 identified co-variates)

Classification	adjusted odds ratio [95%CI]	p-value	adjusted odds ratio [95%CI]	p-value
Complication in 7 days				
URTI	-0.038 [-0.905-0.829]	0.9316	-0.223 [-1.206-0.760]	0.6565
LRTI	-0.934 [-2.418-0.551]	0.2176	-1.102 [-2.721-0.517]	0.1823
unclassified RTI	0.465 [-0.303-1.233]	0.2353	-0.909 [-2.135-0.316]	0.1458
ALL	0.155 [-0.358-0.668]	0.5535	-0.511 [-1.147-0.126]	0.1159
Complication in 14 days				
URTI	-0.408 [-1.154-0.337]	0.2832	0.015 [-0.805-0.835]	0.9710
LRTI	-1.218 [-2.934-0.499]	0.1644	-0.983 [-2.431-0.465]	0.1832
unclassified RTI	0.076 [-0.557-0.709]	0.8149	-0.707 [-1.790-0.377]	0.2011
ALL	-0.182 [-0.628-0.264]	0.4240	-0.283 [-0.831-0.266]	0.3125
Complication in 21 days				
URTI	-0.299 [-1.024-0.426]	0.4191	-0.020 [-0.728-0.688]	0.9556
LRTI	-0.681 [-2.153-0.791]	0.3645	-0.713 [-2.476-1.050]	0.4279
unclassified RTI	-0.012 [-0.647-0.622]	0.9695	-0.678 [-1.649-0.293]	0.1712
ALL	-0.130 [-0.551-0.290]	0.5438	-0.322 [-0.836-0.191]	0.2181
Complication in 28 days				
URTI	-0.290 [-0.882-0.303]	0.3384	0.037 [-0.589-0.662]	0.9080
LRTI	-0.754 [-2.250-0.742]	0.3232	-0.494 [-2.196-1.209]	0.5699
unclassified RTI	-0.232 [-0.904-0.440]	0.4991	-0.285 [-1.154-0.584]	0.5208
ALL	-0.263 [-0.657-0.131]	0.1915	-0.105 [-0.569-0.359]	0.6576

Table A 9. Sensitivity analyses: Adjusted effects of antibiotics stratified by age-group using 7, 14, 21 and 28 day at-risk periods for RTI-related hospitalisation (adjusted by the 7 identified co-variates)

Classification	adjusted odds ratio [95%CI]	p-value	adjusted odds ratio [95%CI]	p-value
Complication in 7 days				
Infants	0.762 [0.202-2.877]	0.688	0.403 [0.049-3.295]	0.3963
Toddlers	1.502 [0.718-3.140]	0.2799	0.861 [0.401-1.846]	0.7003
Juniors	0.767 [0.240-2.447]	0.6541	-	-
Young person	2.091 [0.205-21.360]	0.5339	1.851 [0.164-20.849]	0.6182
Complication in 14 days				
Infants	0.480 [0.139-1.653]	0.2446	0.373 [0.046-3.002]	0.3538
Toddlers	0.875 [0.475-1.610]	0.6674	0.890 [0.451-1.757]	0.7378
Juniors	1.238 [0.425-3.606]	0.6952	0.629 [0.134-2.956]	0.5574
Young person	0.795 [0.188-3.367]	0.7551	1.682 [0.149-18.922]	0.6738
Complication in 21 days				
Infants	0.411 [0.121-1.394]	0.1536	0.517 [0.112-2.379]	0.3968
Toddlers	1.023 [0.567-1.847]	0.9398	0.882 [0.467-1.667]	0.6986
Juniors	1.258 [0.471-3.357]	0.6470	0.873 [0.210-3.620]	0.8513
Young person	0.722 [0.201-2.588]	0.6166	0.444 [0.039-5.010]	0.5113
Complication in 28 days				
Infants	0.260 [0.077-0.876]	0.0297	0.409 [0.091-1.846]	0.2451
Toddlers	0.841 [0.472-1.497]	0.5557	1.316 [0.744-2.328]	0.3448
Juniors	1.422 [0.544-3.716]	0.4731	0.772 [0.232-2.571]	0.6739
Young person	0.705 [0.197-2.528]	0.5918	-	-

Table A 10. Sensitivity analyses: Adjusted effects of antibiotics stratified by age-group using 7, 14, 21 and 28 day at-risk periods for RTI-related hospitalisation (adjusted for clustering and the 7 identified co-variates)

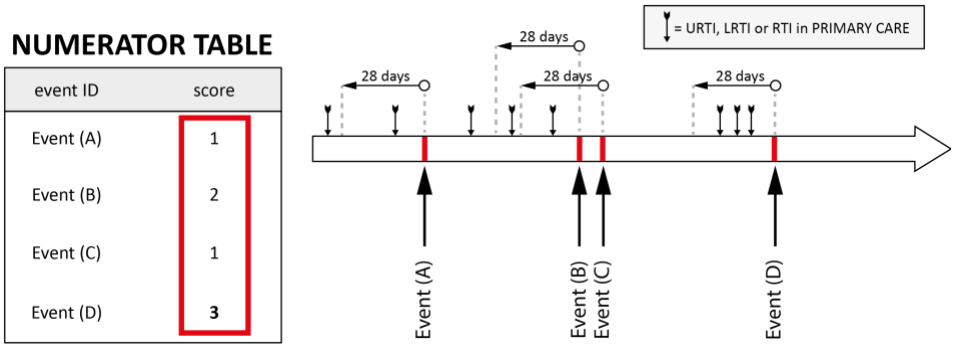
Classification	adjusted odds ratio [95%CI]	p-value	adjusted odds ratio [95%CI]	p-value
Complication in 7 days				
Infants	-0.309 [-1.542-0.924]	0.6234	-0.929 [-3.129-1.271]	0.4079
Toddlers	0.428 [-0.287-1.144]	0.2405	-0.154 [-0.900-0.592]	0.6861
Juniors	-0.330 [-1.520-0.859]	0.5861	-	-
Young person	0.738 [-1.791-3.266]	0.5675	0.616 [-1.896-3.128]	0.6308
Complication in 14 days				
Infants	-0.735 [-1.865-0.395]	0.2025	-0.987 [-3.144-1.169]	0.3696
Toddlers	-0.134 [-0.766-0.499]	0.6784	-0.116 [-0.784-0.552]	0.7331
Juniors	0.206 [-0.857-1.269]	0.7037	-0.463 [-1.937-1.011]	0.5381
Young person	-0.230 [-1.640-1.181]	0.7495	0.520 [-1.870-2.909]	0.6698
Complication in 21 days				
Infants	-0.890 [-2.031-0.251]	0.1264	-0.672 [-2.490-1.146]	0.4687
Toddlers	0.023 [-0.561-0.607]	0.9390	-0.126 [-0.754-0.502]	0.6947
Juniors	0.229 [-0.902-1.361]	0.6912	-0.136 [-1.511-1.239]	0.8462
Young person	-0.326 [-1.808-1.156]	0.6661	-0.793 [-3.146-1.559]	0.5087
Complication in 28 days				
Infants	-1.346 [-2.589--0.103]	0.0338	-0.908 [-2.564-0.748]	0.2827
Toddlers	-0.173 [-0.716-0.369]	0.5311	0.275 [-0.291-0.841]	0.3410
Juniors	0.347 [-0.760-1.455]	0.5389	-0.258 [-1.446-0.930]	0.6701
Young person	-0.349 [-1.587-0.889]	0.5803	-	-

Additional Co-Variates – Figures A30 and A31

RTI Level Co-Variate 3: 28-day RTI Consultation Average

This co-variate was created by counting the number of RTI related GP consultations for each virtual patient in the 28 days preceding a relevant RTI-related GP consultation. A unique score was created for each relevant RTI. No score was generated if less than 28 days follow up time present.

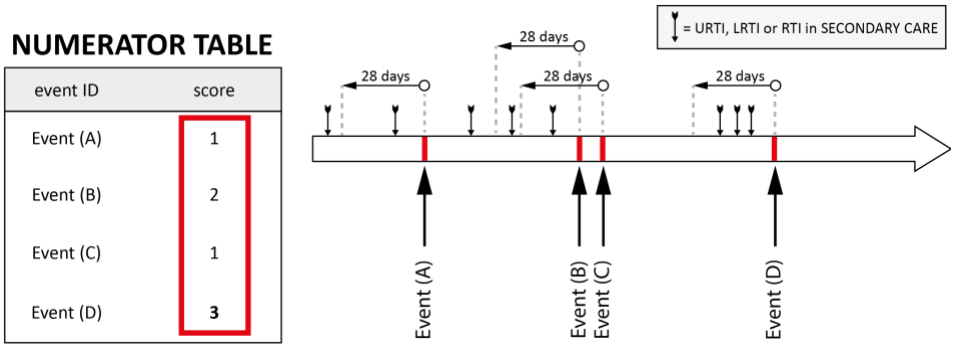
Figure A30. Process for creating RTI Level Co-Variate 3.



RTI Level Co-Variate 4: 28-day RTI Hospitalisation Average

This co-variate was created by counting the number of RTI related hospitalisations for each virtual patient in the 28 days preceding a relevant RTI-related GP consultation. A unique score was created for each relevant RTI. No score was generated if less than 28 days follow up time present.

Figure A31. Process for creating RTI Level Co-Variate 4.



References

1. Hickey F, Hivkey E, Summar, K.L. Medical update for children with Down syndrome for the pediatrician and family practitioner. Advances in pediatrics 2012;59(1):137-57.
2. Morris JK, Alberman E. Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register. British Medical Journal 2009:339.
3. Wu J, Morris JK. The population prevalence of Down's syndrome in England and Wales in 2011. European Journal of Human Genetics. 2013;21(9):1016-9.
4. Esbensen AJ. Health conditions associated with aging and end of life of adults with Down syndrome. International review of research in mental retardation. 2010;39(C):107-26.
5. Glasson EJ SS, Hussain R, Petterson B A, Montgomery PD, Bittles AH. The changing survival profile of people with Down's syndrome: implications for genetic counselling. Clinical Genetics. 2002;62(5):390-3.
6. RCPCH. Paediatric service specification 2015 [Available from: http://www.dsmig.org.uk/wp-content/uploads/2015/09/Draft-servcei-spec.pdf.
7. Witham L. Health care needs for pre-school children with Down syndrome – audit and evaluation of a regional UK service. 2012.
8. Jensen KM, Taylor LC, Davis MM. Primary care for adults with Down syndrome: adherence to preventive healthcare recommendations. Journal of intellectual disability research : JIDR. 2013;57(5):409-21.
9. Henderson A, Lynch SA, Wilkinson S, Hunter M. Adults with Down's syndrome: the prevalence of complications and health care in the community. British journal of general practice. 2007;57:50-5.
10. Murch H, Panjwani D, Williams B, Woolley C, Northey M. G154(P) Heath Surveillance for children with Down Syndrome. Archives of Disease in Childhood. 2014;99(Suppl 1):A68-A.
11. Murdoch JC. Comparison of the care of children with Down's syndrome with the care of matched controls. Journal of the Royal College of General Practitioners. 1984;34(261):205-9.
12. Perkin RM, Newton DA, Swift JD. Pediatric hospital medicine: textbook of inpatient management: Lippincott Williams & Wilkins; 2008.
13. Kenny T. Common Cold (and Other Upper Respiratory Tract Infections) 2016 [Available from: https://patient.info/pdf/4459.pdf.
14. van Gageldonk-Lafeber AB, van der Sande MA, Heijnen ML, Peeters MF, Bartelds AI, Wilbrink B. Risk factors for acute respiratory tract infections in general practitioner patients in The Netherlands: a case-control study. BMC infectious diseases. 2007;7:35.
15. Rovers MM, Schilder AG, Zielhuis GA, Rosenfeld RM. Otitis media. Lancet. 2004;363(9407):465-73.
16. Monto AS. Epidemiology of Viral Respiratory Infections. The American Journal of Medicine. 2002;112(6A):4S-12S.
17. Korppi M, Heiskanen-Kosma T, Jalonen E, Saikku P, Leinonen M, Halonen P, et al. Aetiology of community-acquired pneumonia in children treated in hospital. European journal of pediatrics. 1993;152(1):24-30.

18. Whittaker R, Economopoulou A, Dias JG, Bancroft E, Ramliden M, Celentano LP, et al. Epidemiology of Invasive Haemophilus influenzae Disease, Europe, 2007-2014. Emerg Infect Dis. 2017;23(3):396-404.
19. Lamagni TL, Darenberg J, Luca-Harari B, Siljander T, Efstratiou A, Henriques-Normark B, et al. Epidemiology of severe Streptococcus pyogenes disease in Europe. J Clin Microbiol. 2008;46(7):2359-67.
20. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax. 2011;66 Suppl 2:ii1-23.
21. Gulliford MC, Dregan A, Moore MV, Ashworth M, Staa T, McCann G, 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.
22. Petersen I, Johnson A, Islam A, Duckworth G, Livermore D, Hayward A. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. Bmj. 2007;335(7627):982.
23. Rabie T, Curtis V. Handwashing and risk of respiratory infections: a quantitative systematic review. Tropical medicine & international health : TM & IH. 2006;11(3):258-67.
24. Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. Bmj. 2009;339:b3675.
25. Del-Rio-Navarro B, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL. Cochrane Review: Immunostimulants for preventing respiratory tract infection in children. Evid-Based Child Health. 2012;7(2):629-717.
26. Schaad UB. OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review. World journal of pediatrics : WJP. 2010;6(1):5-12.
27. Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Di Pietrantonj C. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. Lancet. 2005;365(9461):773-80.
28. Taylor S, Marchisio P, Vergison A, Harriague J, Hausdorff WP, Haggard M. Impact of pneumococcal conjugate vaccination on otitis media: a systematic review. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(12):1765-73.
29. Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation. Health technology assessment. 2008;12(36):iii, ix-x, 1-86.
30. Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. Health technology assessment. 2011;15(5):iii-iv, 1-124.
31. Onakpoya IJ, Hayward G, Heneghan CJ. Antibiotics for preventing lower respiratory tract infections in high-risk children aged 12 years and under. The Cochrane database of systematic reviews. 2015(9):CD011530.
32. NICE. Types of guideline 2014 [Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/types-of-guideline.
33. NICE. Respiratory tract infections (self-limiting): prescribing antibiotics. 2008.
34. NICE. Amantadine, oseltamivir and zanamivir for the treatment of influenza. Technology appraisal guidance [TA168]2009.

35. Health Do. UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018. In: Health Do, editor. 2013.
36. Garau J, Nicolau DP, Wullt B, Bassetti M. Antibiotic stewardship challenges in the management of community-acquired infections for prevention of escalating antibiotic resistance. Journal of global antimicrobial resistance. 2014;2(4):245-53.
37. Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. British Medical Journal. 2007;335(7617):429.
38. Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. Bmj. 2007;335(7627):982.
39. Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. The Journal of antimicrobial chemotherapy. 2011;66(10):2215-23.
40. Rodrigues AT, Roque F, Falcão A, Figueiras A, Herdeiro MT. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. International journal of antimicrobial agents. 2013;41(3):203-12.
41. Lucas PJ, Cabral C, Hay AD, GHorwood J. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. Scand J Prim Health Care. 2015;33(1):11-20.
42. Barden LS, Dowell SF, Schwartz B, Lackey C. Current attitudes regarding use of antimicrobial agents: results from physicians' and parents' focus group discussions. Clinical pediatrics. 1998;37(11):665-71.
43. Watts R, Vyas H. An overview of respiratory problems in children with Down's syndrome. Archives of disease in childhood. 2013:812-7.
44. Byard RW. Forensic issues in Down syndrome fatalities. J Forensic Leg Med. 2007;14(8):475-81.
45. Bertrand P, Navarro H, Caussade S, Holmgren N, Sánchez I. Airway anomalies in children with Down syndrome: endoscopic findings. Pediatric pulmonology. 2003;36(2):137-41.
46. Gonzalez OR, Gomez IG, Recalde AL, Landing BH. Postnatal development of the cystic lung lesion of Down syndrome: suggestion that the cause is reduced formation of peripheral air spaces. Pediatric Pathology. 1991;11(4):623-33.
47. McDowell KM, Craven DI. Pulmonary complications of Down syndrome during childhood. The Journal of pediatrics. 2011;158(2):319-25.
48. Hamilton J, Yaneza MM, Clement WA, Kubba H. The prevalence of airway problems in children with Down's syndrome. International journal of pediatric otorhinolaryngology. 2016;81:1-4.
49. Tutor JD, Gosa MM. Dysphagia and aspiration in children. Pediatr Pulmonol. 2012;47(4):321-37.
50. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. Clinical & Experimental Immunology. 2011;164(1):9-16.
51. Bloemers BL, Broers CJ, Bont L, Weijerman ME, Gemke RJ, van Furth A. Increased risk of respiratory tract infections in children with Down syndrome: the consequence of an altered immune system. Microbes ad Infection. 2010;12(11):799-808.
52. Kusters MAA, Verstegen RHJ, Gemen EFA, De Vries E. Intrinsic defect of the immune system in children with Down syndrome: a review. Clinical & Experimental Immunology. 2009;156(2):189-93.

53. Bloemers BL, van Bleek GM, Kimpen JL, Bont L. Distinct abnormalities in the innate immune system of children with Down syndrome. The Journal of pediatrics. 2010;156(5):804-9.
54. de Hingh YC, van der Vossen PW, Gemen EF, Mulder AB, Hop WC, Brus F, et al. Intrinsic abnormalities of lymphocyte counts in children with down syndrome. The Journal of pediatrics. 2005;147(6):744-7.
55. Franciotta D, Verri A, Zardini E, Andreoni L, De Amici M, Moratti R, et al. Interferon-gamma- and interleukin-4-producing T cells in Down's syndrome. Neurosci Lett. 2006;395(1):67-70.
56. Verstegen RHJ, Kusters MAA, Gemen EF, De Vries E. Down Syndrome B-Lymphocyte Subpopulations, Instrinsic Defect or Decreased T-Lymphocyte Help. Paediatric Research. 2010;67(5):563-9.
57. Cetiner S, Demirhan O, Inal TC, Tastemir D, Sertdemir Y. Analysis of peripheral blood T-cell subsets, natural killer cells and serum levels of cytokines in children with Down syndrome. Int J Immunogenet. 2010;37(4):233-7.
58. McMillan B, Hanson R, Glubjatnikov G, Sinha S. The effect of institutionalisation on elevated IgD and IgG levels in patients with Down's syndrome. Journal of Mental Deficiency Research. 1975;19(3-4):209-23.
59. Cocchi P, Silenzi M, Ravina A. Neutrophil Viability in Down's Syndrome. JAMA. 1978;240(8):737.
60. Barroeta O, Nungaray L, López-Osuna M, Armendares S, Salamanca F, Kretschmer R. Defective Monocyte Chemotaxis in Children with Down's Syndrome. Pediatric Research. 1983;17:292-5.
61. Akinci O, Mihci E, Tacoy S, Kardelen F, Keser I, Aslan M. Neutrophil oxidative metabolism in Down syndrome patients with congenital heart defects. Environ Mol Mutagen. 2010;51(1):57-63.
62. Cuadrado E, Barrena M. Immune dysfunction in Down's syndrome: primary immune deficiency or early senescence of the immune system? Clinical Immunology and Immunopathology. 1996;78(3):209-14.
63. Broers CJ, Gemke RJ, Weijerman ME, Kuik DJ, van Hoogstraten IM, van Furth A. Frequency of lower respiratory tract infections in relation to adaptive immunity in children with Down syndrome compared to their healthy siblings. Acta Paediatrica. 2012;101(8):862-7.
64. Healy F, Hanna BD, Zinman R. Pulmonary complications of congenital heart disease. Paediatric respiratory reviews. 2012;13(1):10-5.
65. Konstantinopoulou S, Tapia IE, Kim JY, Xanthopoulos MS, Radcliffe J, Cohen MS, et al. Relationship between obstructive sleep apnea cardiac complications and sleepiness in children with Down syndrome. Sleep Med. 2016;17:18-24.
66. Irving CA, Chaudhari MP. Cardiovascular abnormalities in Down's syndrome: spectrum, management and survival over 22 years. Arch Dis Child. 2012;97(4):326-30.
67. Weijerman ME, van Furth AM, van der Mooren MD, van Weissenbruch MM, Rammeloo L, Broers CJ, et al. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. European journal of pediatrics. 2010;169(10):1195-9.
68. Craig B. Atrioventricular septal defect: from fetus to adult. Heart. 2006;92(12):1879-85.
69. Sobey CG, Judkins CP, Sundararajan V, Phan TG, Drummond GR, Srikanth VK. Risk of Major Cardiovascular Events in People with Down Syndrome. PLoS One. 2015;10(9):e0137093.

70. Bianca S, Bianca M, Ettore G. Oesophageal atresia and Down syndrome. Down's syndrome, research and practice : the journal of the Sarah Duffen Centre / University of Portsmouth. 2002;8(1):29-30.
71. Fitzgerald P, Leonard H, Pikora T, Bourke J, Hammond G. Hospital Admissions in Children with Down Syndrome: Experience of a Population-Based Cohort Followed from Birth. PLoS One. 2013;8(8):e70401.
72. So SA, Urbano RC, Hodapp RM. Hospitalizations of infants and young children with Down syndrome: evidence from inpatient person-records from a statewide administrative database. Journal of Intellectual Disability Research. 2007;51(12):1030-8.
73. van Woensel JB, van Aalderen WM, Kimpen JL. Viral lower respiratory tract infection in infants and young children. Bmj. 2003;327(7405):36-40.
74. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. The Journal of pediatrics. 2003;143(5 Suppl):S118-26.
75. Galleguillos C, Galleguillos B, Larios G, Menchaca G, Bont L, Castro-Rodriguez JA. Down's syndrome is a risk factor for severe lower respiratory tract infection due to respiratory syncytial virus. Acta Paediatr. 2016;105(11):e531-e5.
76. Sanchez-Luna M, Medrano C, Lirio J, Group R-S. Down syndrome as risk factor for respiratory syncytial virus hospitalization: A prospective multicenter epidemiological study. Influenza Other Respir Viruses. 2017;11(2):157-64.
77. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA. Antibiotics for acute otitis media: a meta-analysis with individual patient data. The Lancet. 2006;368(9545):1429-35.
78. Charleton PM, Dennis J, Marder E. Medical management of children with Down syndrome. Paediatrics and Child Health. 2010;20(7):331-7.
79. Nisihara R, De Bem RS, Negreiros PH, Utiyama SR, Oliveira NP, Amarante H. Low hepatitis B vaccine response in children with Down syndrome from Brazil. Child Care Health Dev. 2014;40(4):607-9.
80. Kusters MA, Bok VL, Bolz WE, Huijskens EG, Peeters MF, de Vries E. Influenza A/H1N1 vaccination response is inadequate in down syndrome children when the latest cut-off values are used. The Pediatric infectious disease journal. 2012;31(12):1284-5.
81. Weijerman ME, Brand PL, van Furth MA, Broers CJ, Gemke RJ. Recurrent wheeze in children with Down syndrome: is it asthma? Acta Paediatrica. 2011;100(11):e194-e7.
82. Manikam L, Reed K, Venekamp RP, Hayward A, Littlejohns P, Schilder A, et al. Limited Evidence on the Management of Respiratory Tract Infections in Down's Syndrome: A Systematic Review. The Pediatric infectious disease journal. 2016;35(10):1075-9.
83. Bittles AH, Bower C, Hussain R, Glasson EJ. The four ages of Down syndrome. Eur J Public Health. 2007;17(2):221-5.
84. T21RS. Trisomy 21 Research Society [Available from: www.t21rs.org.
85. DSA. Down's Syndrome Association [Available from: www.downs-syndrome.org.uk.
86. DSi. Welcome to the Down Syndrome International (DSi) website! [Available from: www.ds-int.org.
87. DHG. Down's Heart Group... supporting a better life [Available from: www.dhg.org.uk.
88. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. 2011.

89. Sterne JAC, Higgins JPT, ACROBAT-NRSI Robotdgf. A Cochrane Risk Of Bias Assessment Tool: for Non- Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0 . 2014.
90. Yi H, Lanctot KL, Bont L, Bloemers BL, Weijerman M, Broers C, et al. Respiratory syncytial virus prophylaxis in Down syndrome: a prospective cohort study. Pediatrics. 2014;133(6):1031-7.
91. La Mantia I, Grillo C, Mattina T, Zaccone P, Xiang M, Di Mauro M, et al. Prophylaxis with the novel immunomodulator pidotimod reduces the frequency and severity of upper respiratory tract infections in children with Down's syndrome. Journal of chemotherapy. 1999;11(2):126-30.
92. Lockitch G, Puterman M, Godolphin W, Sheps S, Tingle AJ, Quigley G. Infection and immunity in Down syndrome: a trial of long-term low oral doses of zinc. The Journal of pediatrics. 1989;114(5):781-7.
93. Krilov LR, Barone SR, Mandel FS, Cusack TM, Gaber DJ, Rubino JR. Impact of an infection control program in a specialized preschool. American journal of infection control. 1996;24(3):167-73.
94. Licastro F, Chiricolo M, Mocchegiani E, Fabris N, Zannoti M, Beltrandi E, et al. Oral zinc supplementation in Down's syndrome subjects decreased infections and normalized some humoral and cellular immune parameters. Journal of intellectual disability research : JIDR. 1994;38 (Pt 2):149-62.
95. Kashiwagi T, Okada Y, Nomoto K. Palivizumab Prophylaxis Against Respiratory Syncytial Virus Infection in Children with Immunocompromised Conditions or Down Syndrome: A Multicenter, Post-Marketing Surveillance in Japan. Paediatr Drugs. 2017.
96. Pediatrics AAo. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Riskof Hospitalization for Respiratory Syncytial Virus Infection. Pediatrics. 2014;134(2):415-20
.
97. Zuccotti GV, Mameli C. Pidotimod: the past and the present. Italian journal of pediatrics. 2013;39:75.
98. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.
99. NHS. Hospital Episode Statistics [Available from: http://content.digital.nhs.uk/hes.
100. Herrett E, Smeeth L, Walker L, Weston C, Group MA. The Myocardial Ischaemia National Audit Project (MINAP). Heart. 2010;96(16):1264-7.
101. McLennan D, Barnes H, Noble M, Davies J, Garratt E, Dibben C. The English Indices of Deprivation 2010 2011 [Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6320/1870718.pdf.
102. Denaxas SC, George J, Herrett E, Shah AD, Kalra D, Hingorani AD, et al. Data Resource Profile: Cardiovascular disease research using linked bespoke studies and electronic health records (CALIBER). International journal of epidemiology. 2012;41(6):1625-38.
103. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, et al. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. J Infect Dis. 2012;206(11):1652-9.
104. Shah AD, Denaxas S, Nicholas O, Hingorani AD, Hemingway H. Neutrophil Counts and Initial Presentation of 12 Cardiovascular Diseases: A CALIBER Cohort Study. J Am Coll Cardiol. 2017;69(9):1160-9.

105. Walker S, Asaria M, Manca A, Palmer S, Gale CP, Shah AD, et al. Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Heart J Qual Care Clin Outcomes. 2016;2(2):125-40.
106. Kostopoulou O, Porat T, Corrigan D, Mahmoud S, Delaney BC. Diagnostic accuracy of GPs when using an early-intervention decision support system: a high-fidelity simulation. The British journal of general practice : the journal of the Royal College of General Practitioners. 2017;67(656):e201-e8.
107. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet. 2014;384(9945):755-65.
108. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British journal of clinical pharmacology. 2010;69(1):4-14.
109. Millett ERC, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of Community-Acquired Lower Respiratory Tract Infections and Pneumonia among Older Adults in the United Kingdom: A Population-Based Study. PLoS One. 2013;8(9):e75131.
110. Rooney C, Griffiths C, Cook L. The implementation of ICD-10 for cause of death coding – some preliminary results from the bridge coding study. Health Stat Q. 2002;13:31-41.
111. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. Bmj. 2013;346:f2350.
112. GPRD. More Dimensions to Data [Available from: https://www.cprd.com/isac/otherinfo.asp.
113. ISAC. CPRD Independent Scientific Advisory Committee [
114. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383(9932):1899-911.
115. Pujades-Rodriguez M, George J, Shah AD, Rapsomaniki E, Denaxas S, West R, et al. Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1937360 people in England: lifetime risks and implications for risk prediction. Int J Epidemiol. 2015;44(1):129-41.
116. Pujades-Rodriguez M, Timmis A, Stogiannis D, Rapsomaniki E, Denaxas S, Shah A, et al. Socioeconomic deprivation and the incidence of 12 cardiovascular diseases in 1.9 million women and men: implications for risk prediction and prevention. PLoS One. 2014;9(8):e104671.
117. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. The lancet Diabetes & endocrinology. 2015;3(2):105-13.
118. George J, Rapsomaniki E, Pujades-Rodriguez M, Shah AD, Denaxas S, Herrett E, et al. How Does Cardiovascular Disease First Present in Women and Men? Incidence of 12 Cardiovascular Diseases in a Contemporary Cohort of 1,937,360 People. Circulation. 2015;132(14):1320-8.
119. Berni E, Scott LA, Jenkins-Jones S, De Voogd H, Rocha MS, Butler CC, et al. Non-Response to Antibiotic Treatment in Adolescents for Four Common Infections in UK Primary Care 1991-2012: A Retrospective, Longitudinal Study. Antibiotics. 2016;5(3).

120. Mars B, Heron J, Kessler D, Davies NM, Martin RM, Thomas KH, et al. Influences on antidepressant prescribing trends in the UK: 1995-2011. Social psychiatry and psychiatric epidemiology. 2017;52(2):193-200.
121. Renzi C, Lyratzopoulos G, Card T, Chu TP, Macleod U, Rachet B. Do colorectal cancer patients diagnosed as an emergency differ from non-emergency patients in their consultation patterns and symptoms? A longitudinal data-linkage study in England. Br J Cancer. 2016;115(7):866-75.
122. Brookhart MA, Sturmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. Medical care. 2010;48(6 Suppl):S114-20.
123. Sturmer T, Glynn RJ, Rothman KJ, Avorn J, Schneeweiss S. Adjustments for unmeasured confounders in pharmacoepidemiologic database studies using external information. Medical care. 2007;45(10 Supl 2):S158-65.
124. Baena A, Garces-Palacio IC, Grisales H. The effect of misclassification error on risk estimation in case-control studies. Rev Bras Epidemiol. 2015;18(2):341-56.
125. Dosemeci M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? American Journal of Epidemiology. 1990;132(4):746-8.
126. Delgado-Rodriguez M, Llorca J. Bias. J Epidemiol Community Health. 2004;58(8):635-41.
127. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. Pharmacoepidemiology and drug safety. 2010;19(6):618-26.
128. Rusanov A, Weiskopf NG, Wang S, Weng C. Hidden in plain sight: bias towards sick patients when sampling patients with sufficient electronic health record data for research. BMC medical informatics and decision making. 2014;14:51.
129. Schafer JL. Analysis of Incomplete Multivariate Data. No. 72 in Monographs on Statistics and Applied Probability: Chapman & Hall; 1997.
130. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. Journal of public health. 2014;36(4):684-92.
131. Millett ERC, Quint JK, De Stavola BL, Smeeth L, Thomas SL. Improved incidence estimates from linked vs. stand-alone electronic health records. Journal of Clinical Epidemiology. 2016;75:66-9.
132. van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations in R. J Stat Softw 2011 12;45(3):1–67. 2011;45(3):1-65.
133. Klungel OH, Martens EP, Psaty BM, Grobbee DE, Sullivan SD, Stricker BH, et al. Methods to assess intended effects of drug treatment in observational studies are reviewed. Journal of clinical epidemiology. 2004;57(12):1223-31.
134. Uddin MJ, Groenwold RH, Ali MS, de Boer A, Roes KC, Chowdhury MA, et al. Methods to control for unmeasured confounding in pharmacoepidemiology: an overview. International journal of clinical pharmacy. 2016;38(3):714-23.
135. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research. 2011;46(3):399-424.
136. Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. Statistical methods in medical research. 2015.
137. Hripcsak G, Albers DJ. Next-generation phenotyping of electronic health records. Journal of the American Medical Informatics Association : JAMIA. 2013;20(1):117-21.

138. Morley KI, Wallace J, Denaxas SC, Hunter RJ, Patel RS, Perel P, et al. Defining disease phenotypes using national linked electronic health records: a case study of atrial fibrillation. PLoS One. 2014;9(11):e110900.
139. UCL. CALIBER [Available from: https://www.caliberresearch.org/.
140. UCL. CALIBERcodelist [Available from: http://caliberanalysis.r-forge.r-project.org/.
141. Jensen KM, Bulova PD. Managing the care of adults with Down's syndrome. Bmj. 2014;349:g5596.
142. BNF. The essential references book [Available from: https://www.bnf.org/products/books/.
143. Hak E, Rovers MM, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk co-morbidity: the Second Dutch National Survey of General Practice. Fam Pract. 2006;23(3):291-4.
144. Ashworth M, Charlton J, Ballard K, Latinovic R, Gulliford M. Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995-2000. The British journal of general practice : the journal of the Royal College of General Practitioners. 2005;55(517):603-8.
145. Petersen I, Hayward AC, Subgroup SS. Antibacterial prescribing in primary care. The Journal of antimicrobial chemotherapy. 2007;60 Suppl 1:i43-7.
146. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP. Available at http://www.stata.com/stata13/. 2013.
147. (2008) RDCT. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria2008.
148. UCL. What is the Data Safe Haven (IDHS)? [Available from: https://www.ucl.ac.uk/isd/itforslms/services/handling-sens-data/tech-soln.
149. Gill PJ, Goldacre MJ, Mant D, Heneghan C, Thomson A, Seagroatt V, et al. Increase in emergency admissions to hospital for children aged under 15 in England, 1999-2010: national database analysis. Arch Dis Child. 2013;98(5):328-34.
150. PHE. Respiratory syncytial virus (RSV): guidance, data and analysis 2015 [Available from: https://www.gov.uk/government/collections/respiratory-syncytial-virus-rsv-guidance-data-and-analysis.
151. Thompson M, Vodicka TA, Blair PS, Buckley DI, Heneghan C, Hay AD, et al. Duration of symptoms of respiratory tract infections in children: systematic review. British Medical Journal. 2013;347:f7027.
152. Campbell S, Campbell M, Grimshaw J, Walker A. A systematic review of discharge coding accuracy. Journal of Public Health Medicine. 2001;23(3):205-11.
153. Halliday J, Collins V, Riley M, Youssef D, Muggli E. Has prenatal screening influenced the prevalence of comorbidities associated with Down syndrome and subsequent survival rates? Pediatrics. 2009;123(1):256-61.
154. Elmagrpy Z, Rayani A, Shah A, Habas E, Aburawi EH. Down syndrome and congenital heart disease: why the regional difference as observed in the Libyan experience? Cardiovasc J Afr. 2011;22(6):306-9.
155. Bergstrom S, Carr H, Petersson G, Stephansson O, Bonamy AK, Dahlstrom A, et al. Trends in Congenital Heart Defects in Infants With Down Syndrome. Pediatrics. 2016;138(1).
156. de Rubens Figueroa J, del Pozzo Magaña B, Pablos Hach JL, Calderón Jiménez C, Castrejón Urbina R. Heart Malformations in Children with Down Syndrome. Revista Española de Cardiologia 2003;56(9):894-9.
157. Muñoz-López F. Pediatrics, Down's syndrome and allergic disease. International Medical Review on Down Syndrome. 2011;15(1):8-13.

158. Van Goor JC, Massa GG. Increased incidence and prevalence of diabetes mellitus in Down's syndrome. Archives of disease in childhood. 1997;77:183.
159. Arya R, Kabra M, Gulati S. Epilepsy in children with Down syndrome. Epileptic Disorders. 2011;13(1):1-7.
160. Prasher V. Down Syndrome and Thyroid Disorders: A Review. Down Syndrome Research and Practice. 1999;6(1):25-42.
161. Dadvand P, Rankin J, Shirley MD, Rushton S, Pless-Mulloli T. Descriptive epidemiology of congenital heart disease in Northern England. Paediatr Perinat Epidemiol. 2009;23(1):58-65.
162. BHF. Children and Young People Statistics 2013. 2013 May 2013.
163. Asthma UK. Asthma facts and statistics 2017 [Available from: https://www.asthma.org.uk/about/media/facts-and-statistics/.
164. Diabetes UK. Diabetes UK: Facts and Stats (October 2016). 2016.
165. Joint Epilepsy Council. Epilepsy prevalence, incidence and other statistics. 2011.
166. Hunter I, Green SA, MacDonald TM, Morris AD. Prevalence and aetiology of hypothyroidism in the young. Archives of disease in childhood. 2000;83:207-10.
167. Neuzil KM, Zhu Y, Griffin MR, Edwards KM, Thompson JM, Tollefson SJ, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. The Journal of infectious diseases. 2002;185(2):147-52.
168. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010;375(9725):1545-55.
169. Cabral C, Lucas PJ, Ingram J, Hay AD, Horwood J. "It's safer to ..." parent consulting and clinician antibiotic prescribing decisions for children with respiratory tract infections: An analysis across four qualitative studies. Soc Sci Med. 2015;136-137:156-64.
170. Andrews T, Thompson M, Buckley DI, Heneghan C, Deyo R, Redmond N, et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. PLoS One. 2012;7(1):e30334.
171. Falagas ME, Mourtzoukou EG, Vardakas KZ. Sex differences in the incidence and severity of respiratory tract infections. Respiratory medicine. 2007;101(9):1845-63.
172. Busse WW, Lemanske RF, Jr., Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet. 2010;376(9743):826-34.
173. Hay AD, Redmond NM, Turnbull S, Christensen H, Thornton H, Little P, et al. Development and internal validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. The Lancet Respiratory medicine. 2016.
174. Gulliford M, Latinovic R, Charlton J, Little P, van Staa T, Ashworth M. Selective decrease in consultations and antibiotic prescribing for acute respiratory tract infections in UK primary care up to 2006. Journal of public health. 2009;31(4):512-20.
175. Ashworth M, Latinovic R, Charlton J, Cox K, Rowlands G, Gulliford M. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. Journal of public health. 2004;26(3):268-74.
176. Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev. 2010;23(1):74-98.
177. Saglani S. Viral infections and the development of asthma in children. Ther Adv Infect Dis. 2013;1(4):139-50.

178. Nissen F, Morales DR, Mullerova H, Smeeth L, Douglas IJ, Quint JK. Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). BMJ open. 2017;7(8):e017474.
179. Little P, Stuart B, Andreou P, McDermott L, Joseph J, Mullee M, et al. Primary care randomised controlled trial of a tailored interactive website for the self-management of respiratory infections (Internet Doctor). BMJ open. 2016;6(4):e009769.
180. Minnes P, Steiner K. Parent views on enhancing the quality of health care for their children with fragile X syndrome, autism or Down syndrome. Child Care Health Dev. 2009;35(2):250-6.
181. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci. 2015;282(1821):20143085.
182. Schuez-Havupalo L, Toivonen L, Karppinen S, Kaljonen A, Peltola V. Daycare attendance and respiratory tract infections: a prospective birth cohort study. BMJ open. 2017;7(9):e014635.
183. NHSDigital. Learning disabilities health check scheme, England, 2016-17. 2017.
184. Clark JE, Hammal D, Hampton F, Spencer D, Parker L. Epidemiology of community-acquired pneumonia in children seen in hospital. Epidemiol Infect. 2007;135(2):262-9.
185. Hawker J, Olowokure B, Sufi F, Weinberg J, Gill N, Wilson R. Social deprivation and hospital admission for respiratory infection: an ecological study. Respiratory Medicine. 2003;97(11):1219-24.
186. Public Health England. PHE guidance on use of antivirals for the treatment and prophylaxis of influenza. 2014.
187. Centers for Disease Control and Prevention. Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). 2011.
188. Perez-Padilla R, Fernandez R, Garcia-Sancho C, Franco-Marina F, Aburto O, Lopez-Gatell H, et al. Pandemic (H1N1) 2009 virus and Down syndrome patients. Emerg Infect Dis. 2010;16(8):1312-4.
189. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. The New England journal of medicine. 1988;318(26):1728-33.
190. Froud R, Eldridge S, Lall R, Underwood M. Estimating the number needed to treat from continuous outcomes in randomised controlled trials: methodological challenges and worked example using data from the UK Back Pain Exercise and Manipulation (BEAM) trial. BMC medical research methodology. 2009;9:35.
191. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-79.
192. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, et al. Methods for constructing and assessing propensity scores. Health services research. 2014;49(5):1701-20.
193. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010;13(2):273-7.
194. Sturmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med. 2014;275(6):570-80.
195. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotics for respiratory infections. The Cochrane database of systematic reviews. 2013(4):CD004417.

196. Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. The Cochrane database of systematic reviews. 2016;2:CD007880.
197. Fahey T, Stocks N, Thomas T. Systematic review of the treatment of upper respiratory tract infection. Arch Dis Child. 1998;79(3):225-30.
198. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: A Randomized Clinical Trial. JAMA. 2015;314(19):2034-44.
199. Roggen I, van Berlaer G, Gordts F, Pierard D, Hubloue I. Centor criteria in children in a paediatric emergency department: for what it is worth. BMJ Open. 2013;3(4).
200. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The Diagnosis of Strep Throat in Adults in the Emergency Room. Medical Decision Making. 1981;1(3):239-46.
201. Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. Acta Psychiatr Scand. 2008;117(6):412-9.
202. Bender R. Using and Interpreting Adjusted NNT Measures in Biomedical Research. The Open Dentistry Journal. 2010(4):72-6.
203. Currie CJ, Berni E, Jenkins-Jones S, Poole CD, Ouwens M, Driessen S, et al. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. BMJ. 2014;349:g5493.
204. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. Bmj. 2010;340:c2096.
205. Ashdown HF, Raisanen U, Wang K, Ziebland S, Harnden A, investigators* A. Prescribing antibiotics to 'at-risk' children with influenza-like illness in primary care: qualitative study. BMJ open. 2016;6(6):e011497.
206. Horwood J, Cabral C, Hay AD, Ingram J. Primary care clinician antibiotic prescribing decisions in consultations for children with RTIs: a qualitative interview study. The British journal of general practice : the journal of the Royal College of General Practitioners. 2016;66(644):e207-13.
207. Health RcoPaC. British Paediatric Surveillance Unit 2016 [Available from: http://www.rcpch.ac.uk/bpsu.
208. Forssell G, Hakånsson A. Risk factors for respiratory tract infections in children aged 2-5 years. Scandinavian Journal of Primary Health Care. 2009;19(2):122-5.
209. Koch A. Risk Factors for Acute Respiratory Tract Infections in Young Greenlandic Children. American Journal of Epidemiology. 2003;158(4):374-84.
210. Schomberg LEE, Garner JL, Porter JW, Bahadur K, Ross L, Kosky CA, et al. P261 Does the provision of a rescue pack keep patients with chronic obstructive pulmonary disease (COPD) at home? Thorax. 2011;66(Supplement 4):A174.
211. Chaintarli K, Ingle SM, Bhattacharya A, Ashiru-Oredope D, Oliver I, Gobin M. Impact of a United Kingdom-wide campaign to tackle antimicrobial resistance on self-reported knowledge and behaviour change. BMC Public Health. 2016;16:393.
212. Public Health England. Taking ANTIBIOTICS when you don't need them puts you and your family at risk. 2017.
213. Choi EK, Yoo IY. Resilience in families of children with Down syndrome in Korea. Int J Nurs Pract. 2015;21(5):532-41.
214. Department of Health PHE, Department for Environment, Food & Rural Affairs and Veterinary Medicines Directorate. Antimicrobial Resistance (AMR) 2016 [Available

from: https://www.gov.uk/government/collections/antimicrobial-resistance-amr-information-and-resources.
215. Excellence NIfHaC. NICE publish draft guidelines aimed at changing behaviour to reduce antimicrobial resistance. 2015 [Available from: https://www.nice.org.uk/news/press-and-media/nice-publish-draft-guidelines-aimed-at-changing-behaviour-to-reduce-antimicrobial-resistance.
216. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet. 2007;369(9560):482-90.
217. Ali A, Scior K, Ratti V, Strydom A, King M, Hassiotis A. Discrimination and other barriers to accessing health care: perspectives of patients with mild and moderate intellectual disability and their carers. PLoS One. 2013;8(8):e70855.
218. Tomita K, Sano H, Chiba Y, Sato R, Sano A, Nishiyama O, et al. A scoring algorithm for predicting the presence of adult asthma: a prospective derivation study. Prim Care Respir J. 2013;22(1):51-8.
219. Hay AD, Birnie K, Busby J, Delaney B, Downing H, Dudley J, et al. The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness. Health technology assessment. 2016;20(51):1-294.
220. Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). The Cochrane database of systematic reviews. 2013(11):CD009764.