UCL SCHOOL OF PHARMACY
Department of Practice and Policy
BMA House, Tavistock Square
WC1H 9JP

# Impact of Seven-Valent Pneumococcal Conjugate Vaccination (PCV7) on Childhood Pneumococcal Diseases in the UK

**Aisha El-Turki**

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**University College London School of Pharmacy**

**PLAGIARISM STATEMENT**

This thesis describes research conducted in the School of Pharmacy, University Collage of London between March 2009 and February 2013 under the supervision of Professor Ian Wong, Professor David Taylor and Dr Paul Long. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

September 13th 2013

Signature Date

**ABSTRACT**

*Streptococcus pneumoniae* is the leading cause of infectious childhood conditions such as Otitis Media (OM) and Pneumonia. Amoxicillin is the recommended first-line treatment for these indications. But because of growing resistance to penicillin based and other antibiotics prevention via effective immunisation is a more desirable approach. PCV7 was introduced in the UK in 2006. Studies conducted in the USA and Europe have shown that the use of this vaccine successfully reduces the incidence of OM and pneumonia. Yet its impact on community antibiotic use in the UK has not to date been adequately described.

This thesis presents the findings of two retrospective cohort studies that analysed the diagnosed incidence of OM and pneumonia and the associated antibiotic prescribing, using the IMS DA and THIN GP databases. The extensive data manipulation conducted shows that the overall number of (all cause) pneumonia episodes in children recorded by GPs declined by 14% between 2006 and 2010. Associated antibiotic prescribing fell by 10%. In addition, the research presented here identified a fall of more than a third in primary care recorded OM diagnoses and antibiotic prescribing for the treatment of OM in children between 2006 and 2010.

These data represent new evidence that the introduction of the original conjugated PCV7 contributed to a decline in antibiotic prescribing by GPs. However, additional prescribing behaviour change drivers were involved and consumption by patients may have fallen faster than the available data sets suggest.

The PCV7 has now been replaced by the PCV13. Against this background a range of additional policy questions are discussed. They include issues relating to bacterial serotype replacement trends and virulence shifts, and the implications of effective infant and child protection for the health of older adults at high risk of contracting pneumococcal infections.

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Finally appreciation is extended to my father, mother, brothers and sisters, for their love, support and encouragement throughout my life. I dedicate this thesis to all of them.

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| ADRs | Adverse Drug Reactions |
| AOM | Acute Otitis Media |
| ARDS | Acute Respiratory Distress Syndrome |
| ATC | Anatomical Therapeutic and Chemical |
| BNF | British National Formulary |
| BOOP | Bronchiolitis Oblitersons Organizing Pneumonia |
| CAP | Community Acquired Pneumonia |
| CAT | Campaign on Antibiotic Treatment |
| CBC | Complete Blood Count |
| CDC | Center for Disease Control and Prevention |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CI | Confidence Interval |
| CONSORT | Consolidation Standards for Reporting of Trials |
| COP | Cryptogenic Organizing |
| COVER | Cover of Vaccination Evaluated Rapidly |
| CRP | C-Reactive Protein |
| CSOM | Chronic Suppurative Otitis Media |
| CT | Computerised Tomography |
| DOH | Department of Health |
| FDA | Food and Drug Administration |
| GMC | Geometric Mean Concentration |
| GP | General Practitioner |
| GPRD | General Practice Research Database |
| HAP | Hospital Acquired Pneumonia |

| | |
|---|---|
| HES | Hospital Episode Statistics |
| Hib | Haemophilus influenzae type b |
| HPA | Health Protection Agency |
| ICD-10 | International Classification of Diseases |
| ICH | International Conference of Harmonization |
| IMSDA | Intercontinental Medical Statistics Disease Analyser |
| IPD | Invasive Pneumococcal Disease |
| IRR | Incidence Rate Ratio |
| ISEAC | Independent Scientific and Ethical Advisory Committee |
| ITS | Interrupted Time Series |
| ITT | Intention-To-Treat |
| MIC | Minimum Inhibitory Concentration |
| NAP | National Advice to the Public |
| NHS | National Health System |
| NICE | National Institute for Health and Clinical Excellence |
| NIPD | Non-Invasive Pneumococcal Disease |
| NP | Necrotizing Pneumonia |
| NP | Nasopharyngeal |
| NVT | None Vaccine Type |
| OM | Otitis Media |
| OME | Otitis Media with Effusion |
| PCR | Polymerase Chain Reaction |
| PCT | Primary Care Trusts |
| PCV13 | Pneumococcal Conjugate Vaccine with 13 serotypes |
| PCV7 | Pneumococcal Conjugate Vaccine with 7 serotypes |
| PHE | Public Health of England |

| | |
|---|---|
| PPV23 | Polysaccharide Pneumococcal Vaccine with 23 serotypes |
| QOF | Quality and Outcomes Framework |
| QUAROUM | Quality of Reporting of Meta-Analysis |
| RCT | Randomised Control Trial |
| RR | Ratio Rate |
| RSIL | Systemic Infection laboratory |
| RSV | Respiratory Syncytial Virus |
| SARS | Sever Acute Respiratory Syndrome |
| SD | Standard Deviation |
| SE | Standard Error |
| SE-MREC | South East Multicentre Research Ethics Committee |
| SIgA | Secretory Immunoglobulin Antibodies |
| SMAC | Standing Medical Advisory |
| SP | Streptococcus Pneumonia |
| SRC | Scientific Review Committee |
| THIN | The Health Improvement Network |
| TM | Tympanic Membrane |
| TT | Tympanostomy Tube |
| UCL | University College London |
| UK | United Kingdom |
| UNICEFE | United Nation Children's Fund |
| US | United State |
| VAP | Ventilator Associated Pneumonia |
| VT | Vaccine Type |
| WHO | World Health Organization |

## OVERVIEW OF THESIS CHAPTERS

### CHAPTER ONE: INTRODUCTION

This presents a broad overview of information and issues relevant to this thesis and the content of each subsequent chapter.

### CHAPTER TWO: RESEARCH TOOLS AND METHODOLOGY

This chapter provides details of the research tools and methodology used throughout this thesis.

### CHAPTER THREE: SYSTEMATIC & LITERATURE REVIEW

This chapter reviews the current literature in order to assess what is already known to date about the efficacy and adverse events linked with PCV7 use in children. It primarily assesses the efficacy of PCV7 in preventing pneumococcal infection diseases, including factors like serotype specific antibody concentrations and geometric mean concentrations (GMCs). It secondarily investigates the local and systemic adverse drug events associated with the administration of the PCV7 to children.

### CHAPTER FOUR: VALIDATION STUDY FOR THE IMMUNISATION RECORDS IN IMS DATA FOR CHILDREN AGED UP TO 2 YEARS

This compares the percentage of children receiving PCV7 in the IMS DA with national data (COVER) and seeks to validate PC7 records in a sample of randomly selected children aged 0-2 years in IMS DA through a GP questionnaire based survey. It is of note in this context that in the UK immunisations are usually given in GP surgeries. However, various other healthcare professionals such as practice nurses, health visitors and school nurses can also administer vaccines to children.

Not all of these professionals have direct access to the patients' electronic record. This can lead to under-recording of immunisation rates in GP's computerised records. To the best of our knowledge there has been no study carried out to validate the immunisation records in GP practice for the IMS. The research findings reported in this chapter therefore add new knowledge.

## CHAPTER FIVE: IMPACT OF PCV7 ON THE INCIDENCE OF OM AND ANTIBIOTIC PRESCRIBING FOR OM IN CHILDREN AGED BETWEEN 0-18 YEARS OLD IN UK GENERAL PRACTICE

Data on the annual incidence of OM and antibiotic prescribing patterns in children before and after the introduction of PCV7 between 2002 and 2010 into the UK primary care are presented, stratified by age and gender. Interrupted time series analyses is used to evaluate the impact of PCV7 on OM before and after its introduction, which allows for factors such as seasonal variations to be taken into account.

It is noted that OM is the most frequent GP diagnosis in sick children. Studies from the United States (US) and continental Europe have shown that the incidence of OM and antibiotic prescribing has reduced since the introduction of PCV7 in children. Other work has reported a similar decline in UK OM diagnosis and antibiotic prescribing for OM treatment that may be related to the introduction of national guidance in 1997 to restrict the use of antibiotic for OM treatment. However, this research throws new light onto trends in OM management in General Practice since the introduction of PCV7 into UK in 2006.

**CHAPTER SIX: IMPACT OF PCV7 ON THE INCIDENCE OF PNEUMONIA AND ANTIBIOTIC PRESCRIBING FOR PNEUMONIA IN CHILDREN AGED BETWEEN 0-15 YEARS IN UK GENERAL PRACTICE**

The analysis offered in this chapter describes annual pneumonia incidence rates related to antibiotic prescribing patterns in children recorded between 2002 and 2010 in UK primary care, stratified by age and gender. It is noted that in the US all cause pneumonia admissions in children under 2 years of age fell by 39% within 2 years of the introduction of a mass immunisation using PCV7. Likewise in England hospital admission data showed reductions in serotyped pneumonia cases of around 20% in children aged 0-15 years within 2 years of PCV7's introduction. However, the impact of PCV7 on the diagnosis and level of antibiotic treatment for all cause pneumonia in primary care in the UK has until now been unclear.

**CHAPTER SEVEN: OVERALL DISCUSSION**

Thus chapter summarises and discusses critically the overall findings and public health policy and practice implications of the findings of this thesis against the background of the wider body of relevant research available. Future research topics are also identified.

# CHAPTER ONE: INTRODUCTION

## 1. BACKGROUND

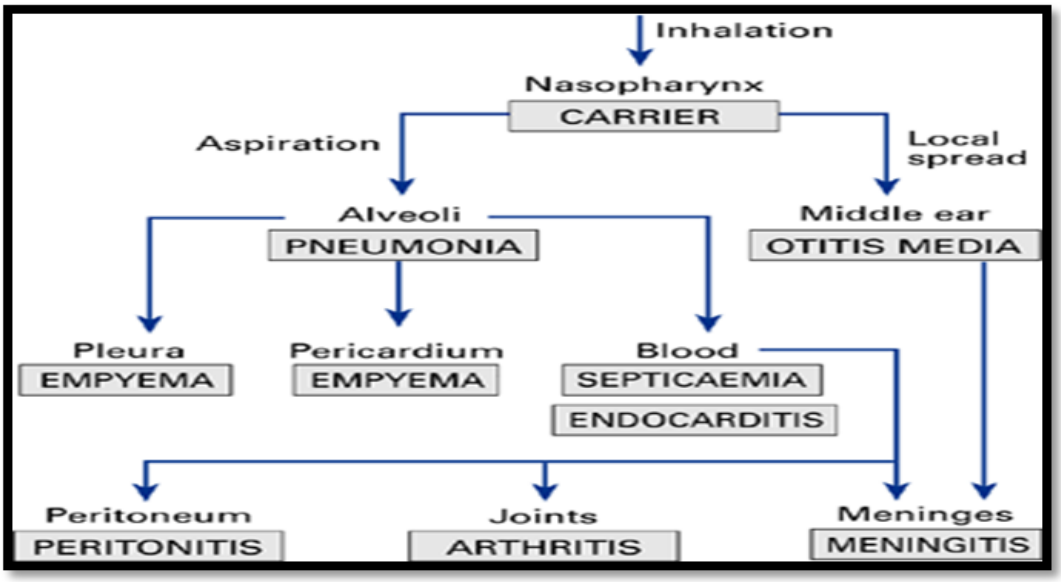
This study examines the impact of seven-valent pneumococcal conjugate vaccine (PCV7) on childhood pneumococcal diseases in the UK. Its main focus is on this vaccine's role in preventing Otitis Media (a non-invasive pneumococcal disease) and pneumonia (an invasive pneumococcal disease) and its consequent impacts on associated antibiotic prescribing. As an introduction to the area, pneumococcal disease is outlined in this Chapter. This is followed by a closer look at classifications of Otitis Media and pneumonia, the associated burden of disease, relevant risk factors, pathology and complications, diagnosis and clinical management. There is then an overview of the PCV7 itself, and the rising number of cases of antibiotic resistance that led to its introduction is noted. Data on the vaccine's safety and efficacy is reviewed, and the schedule of administration in this country described. This study focuses on the PCV7 and its impact following its introduction in 2006. But readers should be aware that in 2010, in part due to increasing cases of serotype replacement disease, a vaccine with a broader coverage of 13 serotypes (PCV13) replaced the initial vaccine.

### 1.1 PNEUMOCOCCAL DISEASES

In 1881 a U.S Army physician called George Sternberg first isolated the pneumococcus bacterium. From 1920, the organism was termed *Diplococcus pneumoniae*, due to the appearance of the organism in the form of two joined cells of Gram positive anaerobic bacteria. In 1974, however the organism was renamed *Streptococcus pneumoniae (S. pneumoniae)* as it grows in chains in liquid media (Gillespie and Hawkey, 2006).

*S. pneumoniae* causes pneumococcal infections including pneumonia, septicaemia, meningitis, otitis and sinusitis. Pneumococcal infection spreads from one person to another by droplet inhalation from the respiratory tract (Ledingham and Warrell, 2000) (Table 1.1).

**Table 1.1: The Pathway of Pneumococcal Infection**
(Taken from Ledingham and Warrell, 2000)



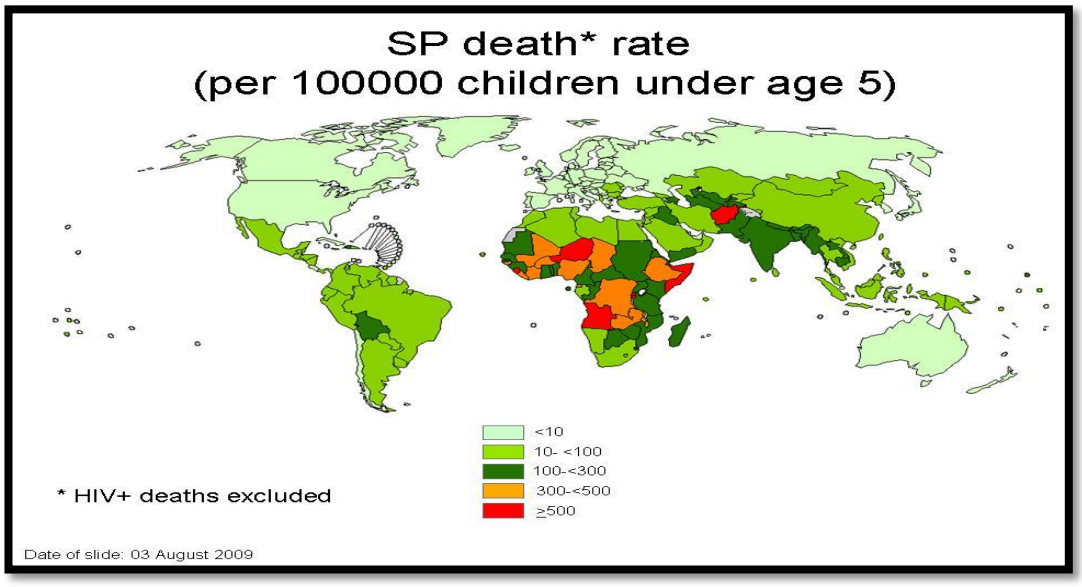

Individuals with immature or weakened immune systems are at higher risk of developing a pneumococcal infection. This typically includes infants and children under two years of age, many adults over 65 years of age and other younger individuals with an underlying health condition such as HIV or types 1 and 2 diabetes (Fireman *et al.,* 2003).

*S. pneumoniae* is ubiquitous. Some 55% of healthy children have at any one time *S. pneumonia* colonies in their nasopharynx (Pettigrew *et al.,* 2006; Pettigrew *et al.,* 2008). It can spread from the nose and throat to the upper and lower respiratory tract to cause Otitis Media (OM) and/or pneumonia.

The bacterium also has the ability to spread from localised infection sites in the middle ear and lungs to cause life threatening invasive meningitis infections. It has been reported that there are over a thousand cases of pneumococcal meningitis in the United States (US) and one million cases worldwide annually, with a 30-80% mortality rate (Marra & Brigham, 2001).

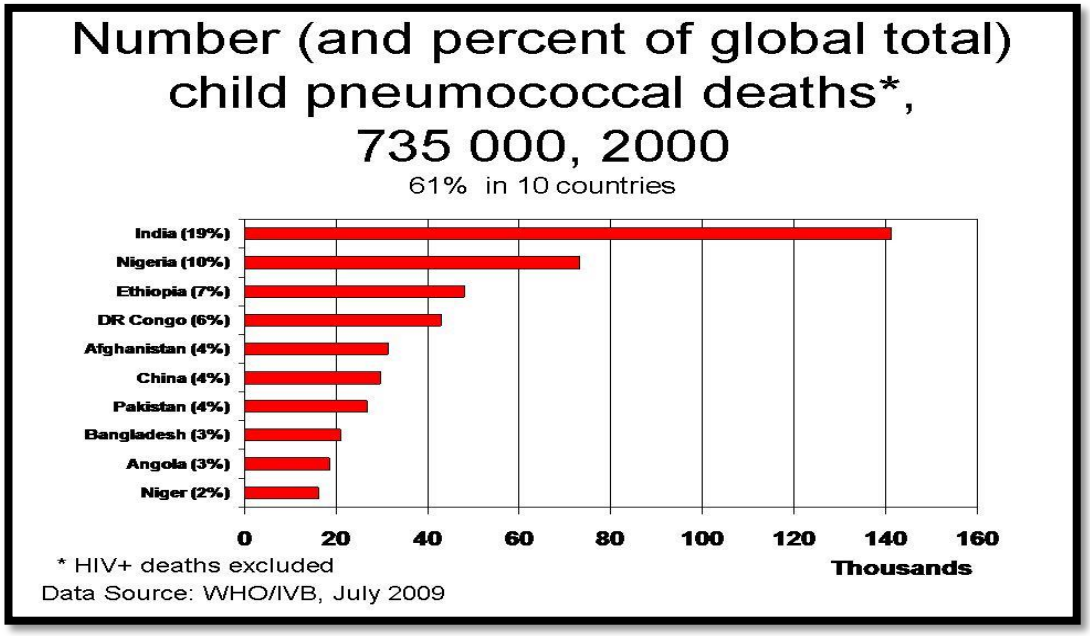
The global disease burden caused by pneumococcal infections is difficult to estimate, but considerable. However, several reports published by the World Health Organization (WHO) suggest that pneumococcal disease rates are highest in children under 5 years of age. With immune system maturation the prevalence of these diseases declines in adequately fed older children and healthy young adults. The WHO estimates that up to one million deaths per annum worldwide are caused by pneumococcal disease amongst children aged under 5 years. It is the leading cause of mortality and morbidity in young children, with some 140,000 reported deaths annually in India alone (Table 1.2).

**Table 1.2: Estimated pneumococcal deaths and cases**
(Taken from WHO, 2013)



Moreover, six countries (India, Nigeria, Ethiopia, the Democratic Republic of Congo, Afghanistan and China) account for more than half of all pneumococcal deaths worldwide (Table 1.3) (Chaloner-Larson, Anderson & Egan, 1997; WHO, 1999; WHO, 2007, WHO, 2013).

**Table 1.3: Number of child pneumococcal deaths**
(Taken from WHO, 2013)




Pneumococcal diseases are either invasive or non-invasive. These two discrete types of infection are described below.

### 1.1.1 INVASIVE PNEUMOCOCCAL DISEASES

Invasive pneumococcal disease (IPD) includes pneumonia (lung infection), meningitis (inflammation of the meninges, the protective membranes covering the brain and spinal cord) and septicaemia (infection of the blood) (Table 1.4) (Department of Health (DOH), 2006).

There are more than 1 million deaths due to pneumococcal pneumonia and meningitis combined in young children every year worldwide (WHO, 1999). The Health Protection Agency (HPA – now part of Public Health England) has estimated that 5,000-6,000 cases of IPD occur every year in England and Wales, of which approximately 530 are amongst children aged under 2 years (HPA, 2010).

**Table 1.4: Symptoms and complications related to pneumococcal infection** (DOH, 2006)

| Disease caused by pneumococcal infection | Symptoms | Serious complications |
|---|---|---|
| Pneumonia | Cough, breathing difficulties, chest pains, fever, headache, confusion | Can lead to septicaemia (bacteria in the blood stream) where the infection can spread to the lining of the heart (pericarditis) or brain (meningitis) |
| Septicaemia (blood poisoning) | Fever, confusion, low blood pressure (shock) | Can cause death |
| Meningitis (inflammation around the brain) | Confusion, fever, headache | Can cause death. Five out of ten cases of meningitis result in permanent damage including deafness, intellectual impairment, speech and language problems, paralysis, cerebral palsy, epilepsy and blindness. |
| Bronchitis | Coughing, mucus secretion | |
| Peritonitis (inflammation of the abdomen) | Abdominal pain, fever | Can cause death |

### 1.1.2 NON-INVASIVE PNEUMOCOCCAL DISEASES

Non-invasive pneumococcal disease is less serious but much more common than IPD. It occurs outside the major organs or the blood stream and includes Otitis Media (a middle ear infection most often found in children), sinusitis (infection of the sinuses) and bronchitis (infection of the airways without the systemic infection and degree of inflammation in the alveoli characteristic of pneumonia).

More than 60,000 diagnosed cases of pneumococcal Otitis Media occur in England and Wales every year (Lawrenson *et al.*, 1998; National Institute for Health and Clinical Excellence (NICE), 2007, HPA, 2010). In the US (with five times the UK population) there are believed to be seven million cases of Otitis Media caused by *S. pneumoniae* every year (Marra & Brigham, 2001*).*

## 1.2 OTITIS MEDIA

**Overview**

As already noted, OM is a condition that involves inflammation of the middle ear, behind the tympanic membrane. This is usually caused by bacterial infection such as *S. pneumoniae, Moraxella catarrhalis* and non-typeable *Haemophilus influenza,* or viral upper respiratory tract infections caused by organisms such as Respiratory Syncytial virus, Rhinovirus, Adenovirus, Parainfluenza and Coronavirus. On occasions OM is associated with both bacterial and viral pathogens. The infection(s) involved typically first causes a sore throat, cold, or other respiratory problems and then spreads to the middle ear (Doherty, 2008; American Academy of Pediatric Medicine Subcommittee on the Management of Acute Otitis Media, 2004; Bradley *et al.,* 2008).

There are three different types of OM (National Institute on Deafness and other Communication Disorder, 2002; Klein and Pelton, 2012b; Bluestone and Klein, 1983) They are Acute Otitis Media (AOM) (inflammation of the middle ear); Otitis Media with Effusion (OME) (fluid & mucus remain after AOM inflammation); and Chronic Suppurative Otitis Media (CSOM) (perforation of the tympanic membrane). In terms of morbidity, OM is the most frequent occurring diagnosis in children in general practice (Congeni, 2003). Its incidence varies with the incidence of risk factors such as Eustachian tube dysfunction, bacterial and viral load, immune response and host and environmental factors (see below).

Most children who develop OM initially exhibit behaviors and symptoms such as pulling or rubbing of the ear, fever, irritability, poor feeding, restlessness at night and cough (Bluestone and Klein, 1983; Klein and Pelton, 2012a; Klein and Pelton, 2012b).

It is estimated that three out of every five children will have suffered from AOM by their third birthday, with the peak incidence rate occurring between six and eleven months. Between 50% and 85% of all children experience at least one episode (Rovers *et al.,* 2004).

*S. pneumoniae* is the most common bacterial pathogen causing OM. Accurate OM diagnosis is ideally needed to ensure appropriate treatment although approximately, 80% of AOM cases spontaneously resolve within three days without antibiotic therapy. Analgesics such as paracetamol or ibuprofen may be required to reduce distress (O'Neil, 1999).

Immediate prescription of antibiotics is normally recommended when children affected are under two years of age, in children with a frequent history of OM, and for those with symptoms that do not resolve or have become worse 72hr after diagnosis (Little *et al*., 2001).

Antibiotics have been prescribed for the treatment of OM since the 1940s. It has for some decades been the most common indication for a child to receive an antibiotic, accounting for 14% of all antibiotics prescribed to children aged 3 months to 15 years between 1991 and 2007 in the UK (Thompson *et al*., 2008). Amoxicillin is the recommended first-line antibiotic treatment (Bluestone and Klein, 2001; Gonzales, 2001). Although as already observed most cases of OM will resolve spontaneously, complications can occur. These may include perforation of the eardrum, hearing loss, mastoiditis, meningitis, brain abscesses and blood clots (Klein, 2001).

### 1.2.1 CLASSIFICATION OF OTITIS MEDIA

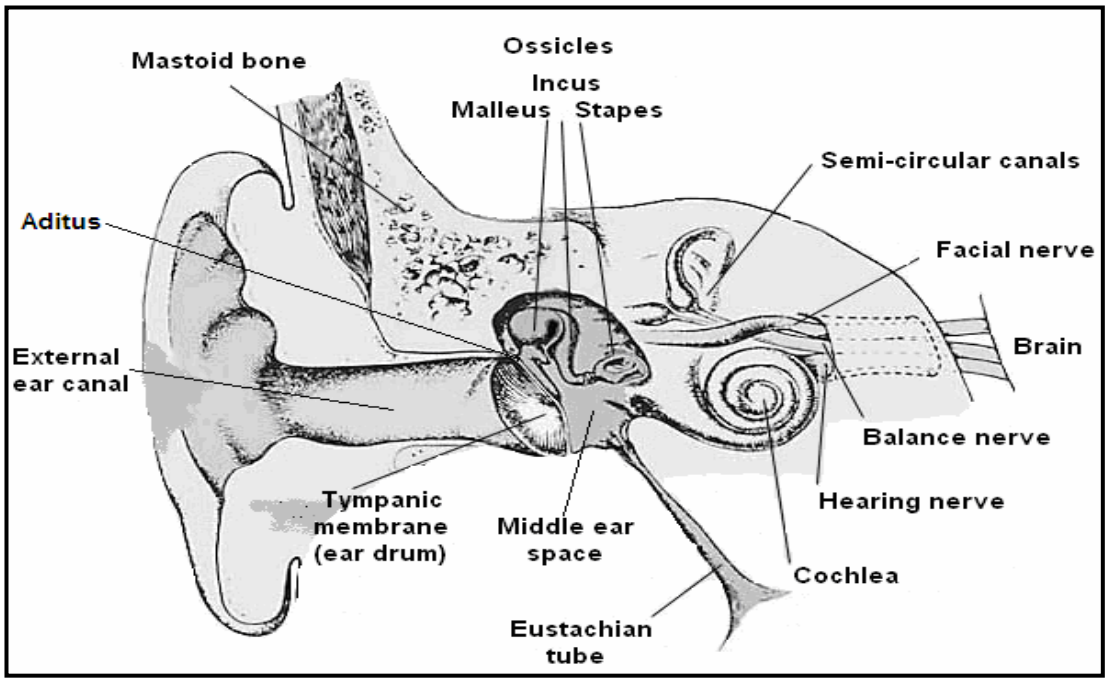
Figure 1.1 shows the physiological setting in which Otitis Media can develop as an inflammatory middle ear condition, often after an upper respiratory tract infection (URTI) that initially causes symptoms such as sore throat and subsequently spreads to the middle ear (Bradley *et al.,* 2008).

As noted above, there are three different types of OM:

**Acute Otitis Media (AOM):** Inflammation occurs in the middle ear causing ottorhea (discharge from the ear), bulging tympanic membrane, fever and/or irritability associated with fluid and mucus build-up.

Recurrent AOM is diagnosed if the child had four or more episodes of AOM within a six-month period (National Institute for Health and Clinical Excellence, 2000).

**Figure 1.1: Schematic diagram of the ear**
(Taken from Doherty, 2008)




**Otitis Media with effusion (OME):** The fluid and mucus remain after AOM inflammation has subsided. It also referred to as secretory Otitis Media or glue ear (National Institute on Deafness and other Communication Disorder, 2002; Klein and Pelton, 2012b).

**Chronic suppurative Otitis Media (CSOM):** Perforation of the tympanic membrane and ottorhea resulting in fluid and mucus to be discharged through the membrane (Bluestone and Klein, 1983).

### 1.2.2 BURDEN OF DISEASE

Otitis Media is one of the most frequent diagnoses in sick children. It historically accounts for over one in every ten of all GP child and young adult consultations in the UK primary care setting (Congeni, 2003). It has been reported that there are more than 63,000 diagnosed cases of pneumococcal OM in England and Wales every year (HPA, 2012). Young children are predisposed to AOM due to their incompletely developed Eustachian tubes and immature immune systems (Klein and Pelton, 2012b). It is estimated that more than two-thirds of children experience one or more episodes of AOM by their third birthday: about half experience three or more episodes. It has also been reported that approximately 50-85% of all children experience at least one episode of AOM (Taylor *et al.,* 2012; Rovers *et al.,* 2004).

### 1.2.3 RISK FACTORS

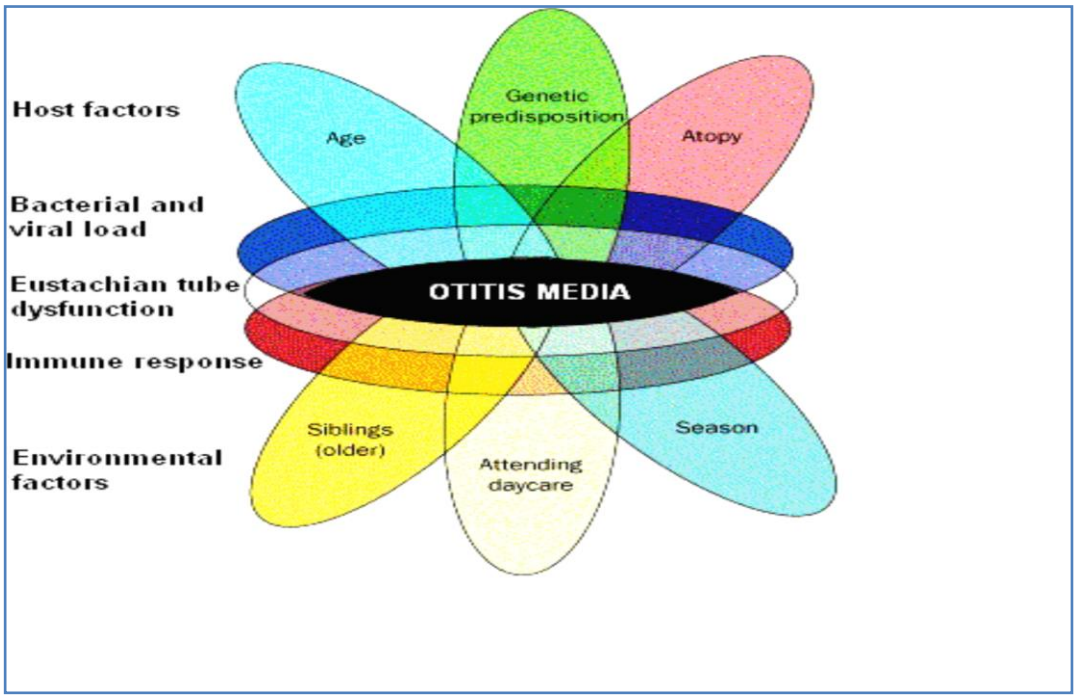
As mentioned earlier, the onset of OM occurs in association with bacterial and viral load alongside factors such as Eustachian tube dysfunction, immune response levels and other host and environmental factors (Figure 1.2). In order to facilitate the prevention and management of Otitis Media all such risk factors need to be addressed in an appropriate manner.

#### 1.2.3.1 HOST FACTORS

**Young age:** An Australian prospective study demonstrated that there is an association between the frequency of AOM episodes and the age of the children affected. The younger the age of the child the higher the frequency of episodes (Massa *et al.,* 2009).

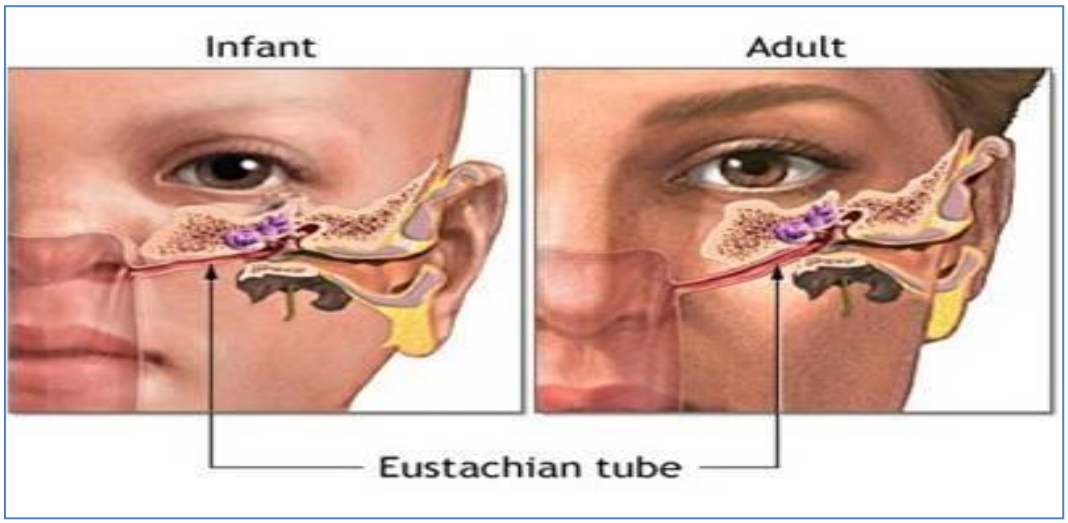
There are two reasons for this. Firstly, an infant's immune system is still developing, making it harder for children to fight infections and justifying the use of antibiotics more readily than when older children and young adults are being treated. Secondly, children have undeveloped Eustachian tubes.

**Figure 1.2: Risk factors involved in the pathogenesis of Otitis Media**
(From Rovers *et al.,* 2004)




As shown in figure 1.3, in younger ages the Eustachian tube is shorter, narrower/more horizontal and 'floppier' than it is in adult subjects. This impedes air flow and, if the child has an infection, organisms can easily reflux from the nasopharynx into the middle ear (Bluestone, 1996; National Library of Medicine, 2012). During the first two years of life, maturation of both the immune system and the Eustachian tube will gradually take place. Therefore, the highest incidence rate of OM usually occurs in children aged less than two years (Rovers *et al.*, 2004).

**Figure 1.3: Eustachian tube in a young child compared to an adult**
(National Library of Medicine, 2012)




**Genetic predisposition:** As a majority of children will suffer at least one episode of Otitis Media it is not instantly obvious that there is a genetic predisposition to the disease. However, evidence from a variety of studies suggests that there is a genetic component to susceptibility to OM.

It is, for instance, three times more likely for a child to develop recurrent OM if he/she is born into a family where their siblings have had recurrent OM as compared to those born into an unaffected family (Teele, Klein and Rosner,1989; Uhari, Mantysaari and Niemela, 1996).

Although the latter observation might be linked to environmental factors, twin studies also suggest that there is a strong genetic component determining the predisposition of a child to OM infection. Monozygotic twins (identical) have a greater similarity between their OM histories than dizygotic (non-identical) twins (Casselbrant and Mandel, 1999; Rovers *et al.*, 2002).

**Gender:** AOM occurs more frequently in boys than girls *"as is true for most infectious diseases of childhood"* (Klein, 2001).

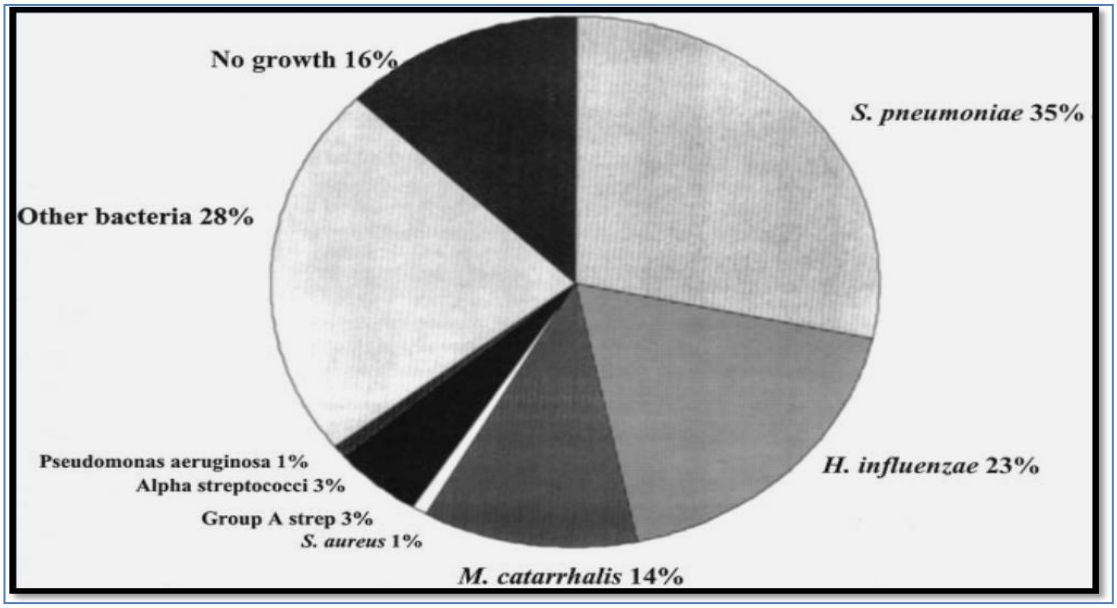
**Race:** Children from certain racial/ethnic groups, including Native Americans, and American and Canadian Inuits appear to have an increased incidence of severe AOM (Klein, 2001). However, this may be an artefact associated with relative deprivation levels, and the frequent failure of North American researchers in particular to distinguish between class and social justice related factors as opposed to inherent race/ethnicity linked traits.

**Atopy/allergies:** Hypersensitivity reactions and allergies may also predispose to OM. A child with a food allergy may have an abnormal reaction which activates the immune system. This may in turn result in inflammatory responses, and increase the mucus and fluid in the middle ear during such an episode (Arroyave, 2001; Rovers *et al.,* 2004). The affected child may consequently become more vulnerable to opportunistic ear infections.

#### 1.2.3.2 BACTERIAL AND VIRAL INFECTION

As shown in figure 1.4, the most common bacterial pathogens that cause OM are *S. pneumoniae* followed by *Haemophilus Influenza* and *Moraxella Catarrhalis*. Viruses (such as *Syncytial* virus) alone or with bacterial pathogens are believed to be an increasing cause of OM (Rovers *et al.*, 2004), although the evidence underpinning this assertion is limited.

**Figure 1.4: Distribution of bacterial isolates in 2807 children with middle ear cultures from children with OM**
(Taken from Pelton, 2000)




### 1.2.3.3 EUSTACHIAN TUBE DYSFUNCTION (ETD)

The Eustachian tube links the middle ear with the back of the nose. It normally stays closed until subjects swallow, yawn or chew. This allows fresh air to enter the middle ear and discharge any mucus that is present.

Such actions in addition play a vital role in maintaining a healthy middle ear by equalising the middle ear pressure with the air pressure outside the head (ie there is a ventilator function). They also protect against ascending secretions or pathogens (protective function) and clear secretions towards the nasopharynx (clearance function) (Bluestone, 1996; Rovers *et al.*, 2004).

In ETD the narrow Eustachian tube is totally or partially blocked. This means that air cannot enter into the middle ear. Thus air pressure equalisation is not possible and the eardrum is pushed inward and becomes taught and does not vibrate when impacted by sound waves (National Library of Medicine, 2008).

Impaired Eustachian tube function is the most important risk factor in the pathogenesis of OM (Bluestone, 1996). Following a respiratory tract infection, the Eustachian tube may become congested, leading to the proliferation of pathogenic organisms.

#### 1.2.3.4 IMMUNE RESPONSES

The secretory immunoglobulin IgA and IgG2 help the body to defend against OM infection. Secretory IgA inhibits bacterial and viral pathogen adherence and reduces nasopharyngeal bacterial colonisation, whilst IgG2 antibodies initiate an immunological response against pneumococci polysaccharide capsules (Kurono *et al.*, 1991; Lim and Mogi, 1994). Therefore low levels of these secretory immunoglobulin may increase a child's risk of OM infection (Stenfors and Raisanen, 1993; Sanders *et al.*, 1995).

#### 1.2.3.5 ENVIRONMENTAL FACTORS

**Siblings:** Having older (and to a lesser degree younger) siblings is one of the most important risk factors for developing OM in infants and children (Rovers *et al.*, 2004). This relates to, in non-immunised populations, the statistical risk of novel exposure to causal organisms.

**Child-care:** Receiving care outside the home is another important early AOM determinant. Rovers *et al* (1999*)* undertook a meta-analysis that found a strong relationship between attending child-care and the prevalence of OM. Further, a study by Ingvarsson *et al* (1985) found that in such circumstances it is more likely for children to develop OM before the age of two years as compared to those aged between 2 to 3 years old.

A second relevant factor is the number of children in the child-care environment. Marx *et al* (1995) and Dewey *et al* (2000) both reported that the relationship between attending child-care from early age and OM is significantly affected by the group size, which logically correlates with infection risk.

**Season:** Seasonal climatic variations strongly influence the occurrence of OM in children. As is generally true with other pneumococcal-mediated infections in all population groups the prevalence rate of OM increases during the north European winter. For instance, Rovers *et al* (2000) reported that the prevalence rate of OM is twice as high in winter as summer.

**Breast feeding:** Several studies have reported that breast-feeding is inversely associated with the frequency of OM infections. That is, it provides protection. This is due to the fact that the antibody content of human milk will interfere with the attachment of bacteria to the nasopharyngial (NP) epithelial cells.

The immunological components that are present in human milk (including secretory immunoglobulin antibodies (sIgA) and lactoferrin) are thought to provide passive protection against NP colonization which provides protection against the subsequent development of OM (Cripps, Otczk and Kyd, 2005; Sabirov *et al.,* 2009).

**Exposure to tobacco smoke:** Tobacco smoke inhalation is associated with vulnerability to *S. pneumoniae* infection. Children who live in a smoke-filled environment are susceptible to ciliary function damage in the paediatric airway which increases the probability of their contracting chronic OM (National Institute for Health and Clinical Excellence, 2000; Ebby, 2005; Brauer *et al.,* 2006; Cheraghi *&* Salvi, 2009; Wang *et al.,* 2012).

**Air pollution:** Air pollution is another environmental factor that increases the frequency of OM (Kim *et al.*, 1996; Brauer *et al.*, 2006; Zielhuis *et al.,* 1990). The mechanisms involved are likely to overlap with, and interact synergistically with, tobacco smoke related harm.

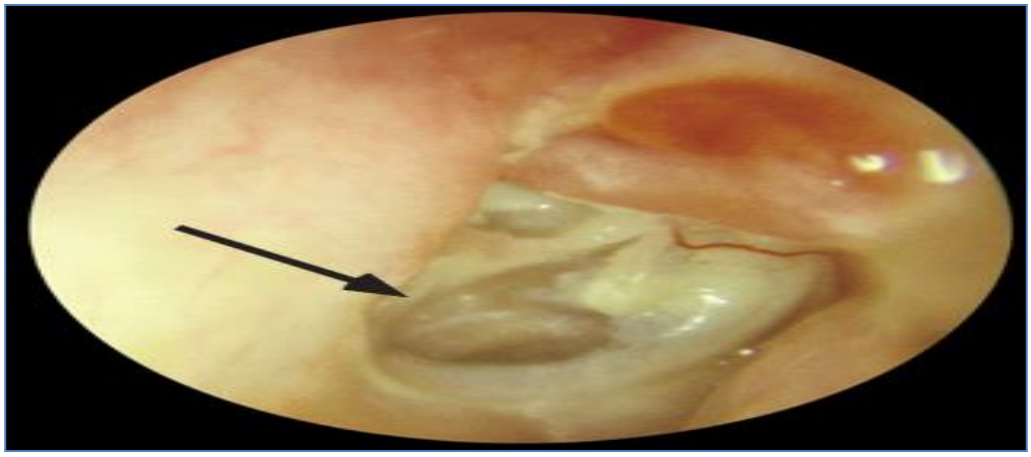
### 1.2.4 PATHOLOGY AND COMPLICATIONS

Severe and recurrent OM is the major cause of contracted childhood deafness, which has 'knock on' affects on language and communication skills (Rovers *et al.*, 2004). It may also affect mental state.

If the eardrum becomes severely weakened a cholesteatoma can occur (Figure, 1.5). This involves the accumulation of a protein called keratin within the middle ear. In extreme cases it may grow to envelop the ossicles that present in the middle space and serve to transmit sounds between air and the cochlea which consequently results in conductive hearing loss (Klein and Pelton, 2012b).

**Figure 1.5: Cholesteatoma (arrow) is a growth of desquamated, stratified, squamous epithelium**

(From Klein and Pelton, 2012b)



OM usually occurs by spreading the pathogens from the middle ear cleft to the surrounding structure of the ear. Two types of complication may occur: intratemporal (which occur within the temple) or intracranial (which occur within the cranium). This may result in not only chronic perforation of the tympanic membrane and/or chronic suppurative Otitis Media, but also distressing and sometimes potentially disabling or fatal disorders like mastoiditis, petrositis, meningitis, brain abscesses, extradural abscesses, subdural empyema and suppurative lateral sinus thrombosis (Klein, 2001).

### 1.2.5 DIAGNOSIS

The diagnosis of AOM is usually based upon a combination of observed symptoms and physical findings. They include ear pain, ear tugging or rubbing, otorrhoea, fever, excessive crying in the younger age group, poor appetite, headache and vomiting.

A related history in contexts like hearing difficulties, together with information on social interaction, behaviour, function in the educational setting and speech and language development can also be important to deriving an initial diagnosis and to differentiating between different types of OM, in addition to which specific examinations are normally needed.

It has been argued that all GPs or alternative health professionals should have an appropriate training as to how they use otoscopes to detect the presence of the middle ear inflammation. The level of accuracy in detecting the presence of middle ear fluid using this technique should be no less than 80% to 90% (Scottish Intercollegiate Guidelines Network, 2012).

### 1.2.6 CLINICAL MANAGEMENT

Most cases of Otitis Media are self-limiting. That is, they spontaneously resolve without the need for any intervention (Glasziou *et al*, 1997). Nevertheless, in some cases active treatment is necessary. The two main interventions available are a) antibiotic therapy and b) myringotomy, with or without the surgical insertion of tympanostomy tubes.

#### 1.2.6.1 TYMPANOSTOMY TUBES AND MYRINGOTOMY

Myringotomy (*myringa* is the Latin word for the eardrum) involves making a small incision in the eardrum to relieve pressure caused by an excessive buildup of fluid in the middle ear. In order to prevent recurrent infections and the possible perforation of the tympanic membrane (TM) a small tympanostomy tube (TT) can be inserted.

There are two different types of TT, constructed of different materials. They are namely short–term tubes, which can stay in the TM for 8 to 18 months (more recommended for children due to the sensitivity of the ear drum) and long-term tubes, which can stay in the TM for more longer periods (Isaacson, 2012).

In the US TT insertion is a frequent reason for children having to receive a general anesthetic. About 7% of children in the United States have tympanostomy tubes inserted by the age of three (Derkay, 1993; Vaile *et al., 2006;* Kogan *et al.*, 2000). A study by Rosenfeld and Bluestone (2003) found that even though the impact of surgery is variable, children with recurrent AOM who receive TT have avoided – at least in the US settings – two diagnosed episodes of AOM a year as compared to those not undergoing TT insertion.

#### 1.2.6.2 ANTIBIOTIC ADMINISTRATION

Historically in the UK, OM has been the primary reason for antibiotic prescribing in children. Amoxicillin is the recommended first-line drug, due to its powerful effect on (ie low Minimum Inhibitory Concentration or MIC for) both *S. pneumoniae* and *H. influenzae*. However, erythromycin may alternatively be used for those with allergic reactions to penicillins, even though it is less effective against *H. Influenza*. The latter causes a quarter to a fifth of all AOM cases. Azithromycin and clarithromycin can also be used as alternative treatments that are effective against all the main pathogens of AOM (Craig and Andes, 1996; BNF for children, 2012).

The antibiotic treatment goal for OM is to sterilise the middle ear fluid. In order to achieve this effective concentration must logically be reached for an appropriate period of time. Judging this can be problematic, but for uncomplicated ear infections five days is normally considered sufficient to clear the infection. Longer durations are needed in some cases (BNF for Children, 2012). However, two days medication with high-dose antibiotics for OM has been suggested as an alternative approach designed to reduce the development of antibiotic-resistance (Oxford Childhood Infection Study Group, 2009).

Resistance of *S. pneumoniae* to penicillin and other beta-lactam based antibiotics has been increasing globally (see, for instance, Ruhe et al, 2004, and Vanderkooi et al, 2005). Such problems have been identified as high priority concerns by authorities such as the immediate past and the current Chief Medical Officers for England. The main mechanism involved is the introduction of mutations in genes encoding for penicillin-binding proteins (Albrich *et al.*, 2004). Many factors affect the development of antibiotic resistance but prior antibiotic use and a record of frequent infection are amongst the most common.

There is a strong relationship between antibiotic consumption and the prevalence of the antibiotic-resistance bacteria. The higher antibiotic prescribing countries have higher levels of antibiotic-resistance. It has been claimed, for instance, that 10-40% of pneumococcal isolates in the US exhibited penicillin-resistance compared to less than 1% from the Netherlands (Albrich *et al.*, 2004; De Neeling *et al.*, 1996; Committee on Infectious Diseases, 1997).

Moreover, a Finnish study has shown that a reduction of 50% in antibiotic prescriptions resulted in a corresponding reduction of resistant bacteria (Seppala *et al.*, 1997) and there is also UK community evidence linking prescribing volumes to laboratory identified resistance levels. (Note, for example, Howard *et al.,* 2001.)

Systematic review based evidence, UK-based government reports and clinical practice guidelines may all have influenced GP antibiotic prescribing for OM. Clinical guidelines state antibiotic prescription for AOM to be of limited benefit in most AOM cases, and recommend analgesics for children with this diagnosis. There is evidence that when these are used for limited periods most of the OM symptoms will resolve without the need for antibiotic therapy (Cates, 2003). For example, a multi-centre randomised control trial including 219 children aged one to six years with uncomplicated OM found that ibuprofen or paracetamol significantly reduce earache in two days (Bertin *et al.*, 1996).

A recent meta-analysis of ten randomised controlled trials was conducted to investigate which age group with OM episodes should be treated with antibiotics. It found that these medicines were most beneficial for children younger than two years with bilateral acute OM and those with AOM and ottorhea. The authors recommend the use of adequate analgesia and an observational approach in children with ‘mild’ disease (Sanders *et al.*, 2010).

Even in the 1950s there were doubts about using antibiotics for the treatment of OM. A study by the English GP John Fry (1958), for instance, reported that 78% of OM episodes resolved without requiring antibiotic treatment.

Additionally, a subsequent Cochrane Collaboration systematic review concluded that there is a limited role for antibiotics in the treatment of OM, as most of the cases resolve without any complication (Glasziou *et al.*, 1997). Since 2003 in the UK delayed antibiotic prescribing has been advocated, in particular for children aged two years and above (SIGN, 2003; PRODIGY, 2004; Rovers *et al.*, 2006; NICE, 2008).

This means that GPs provide the prescription, but advise the parents to delay their use in case the symptoms resolve spontaneously. (This practice has implications regarded the utility of data sets such as those provided by IMS – see below.). Yet most commentators agree about the benefit of using antibiotics for children under two years of age, despite the attendant antibiotic resistance risks. Increasing the latter must in time increase the prevalence of drug-resistant organisms, and consequently drive up morbidity and mortality levels along with health-care costs.

The case for the use of effective *S. pneumoniae* vaccines in large part rests on such observations, along with the fact that even without resistance related problems pneumococcal infection can via its role in causing conditions such as meningitis on occasions lead to brain damage or death in young people who have not been protected by immunisation.

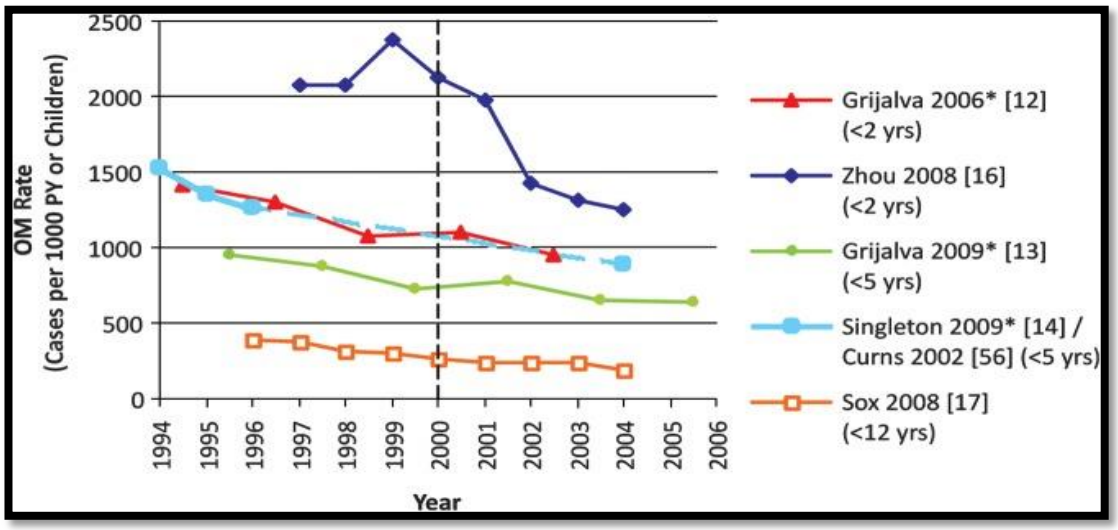
#### 1.2.6.3 VACCINES

To contain the development and spread of antibiotic-resistant organisms, the future management of OM should concentrate more on preventive strategies rather than treatment.

After studies to prove the safety and efficacy of the vaccine, pneumococcal conjugate vaccine (PCV7, 2006) was introduced to the UK childhood primary immunisation schedule. This vaccine links *S. pneumoniae* derived material with a stronger diphtheria bacillus derived antigen to elicit a protective response in subjects too young to respond adequately to the previously available polysaccharide based vaccines.

Despite evidence such as that shown in Figure 1.6 from American and other investigators showing PCV7 to be effective in reducing the number of OM related physician consultations and the associated treatment levels in the US environment (Grijalva *et al.*, 2006; Zhou *et al.*, 2008; Taylor *et al., 2012*; Singleton *et al., 2009;* Sox *et al., 2008)* the full impacts of this intervention have not previously been systematically studied in the UK community setting. Later sections of this thesis seek to fill this gap in the current literature.

**Figure 1.6: Trends in Otitis Media rates among observational database studies presenting data for years before and after 7-valent pneumococcal conjugate vaccine introduction in 2000**
(From Taylor *et al., 2012)*

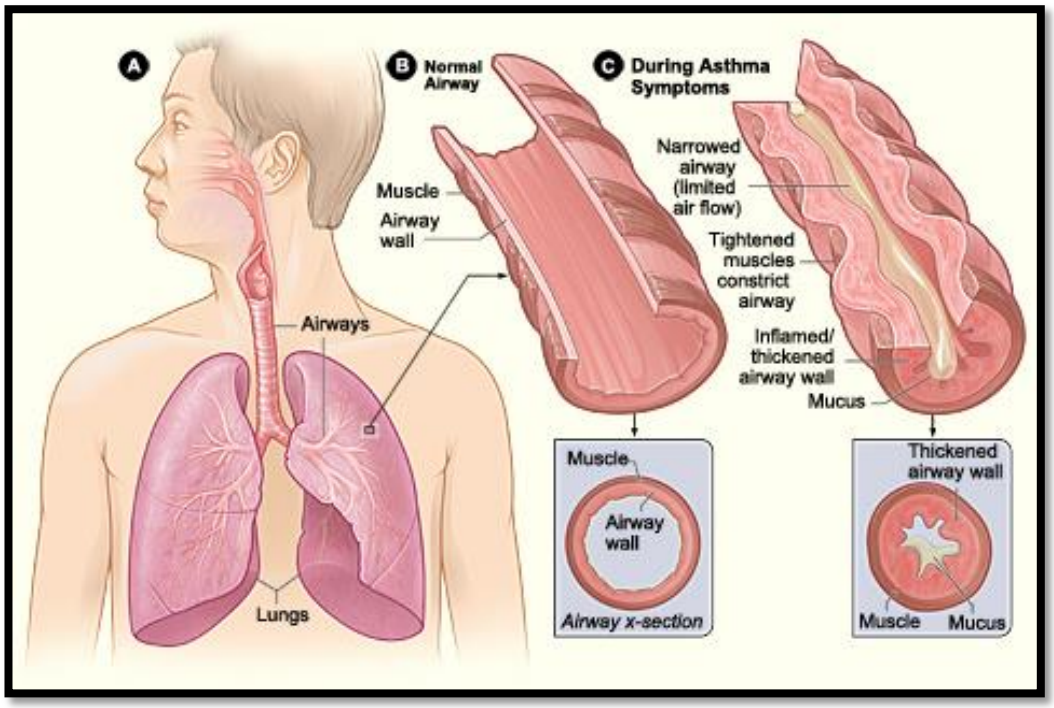


## 1.3 PNEUMONIA

### Overview

Pneumonia is a potentially fatal infection of the air sacs (alveoli) and smaller airways of the lungs (Fig.1.7), which become inflamed and fill with fluid. This reduces their capacity for gaseous exchange.

**Figure 1.7: The location of the lungs and airways in the body**
(National Heart Lung and Blood Institute, 2012)




It is one of the most common infectious diseases in young children, with – in this country – the majority of infections occurring in the autumn and winter (NICE, 2007).

In the UK, according to data from the Hospital Episode Statistics (HES), up to 1% of children aged 0-5 years will contract pneumonia (NICE, 2007). A study by Holmes and Woodhead (1999) suggests that in the UK about one third of individuals with a pneumonia diagnosis are admitted to hospital.

In addition, the HPA recently estimated that in England and Wales each year there are 40,000 GP consultations for pneumococcal disease related community acquired pneumonia (CAP) (HPA, 2010).

Globally, pneumonia accounts for approaching a fifth of all deaths of children under five years old, with an incidence of 0.29 episodes per child-year in low-income countries and 0.05 episodes per child-year in high-income countries (WHO, 2013). World-wide, approximately 156 million new episodes occur each year. (Forty three million in India, 21 million in China, 10 million in Pakistan and 6 million in Bangladesh, Indonesia and Nigeria.) Nineteen percent of all deaths in children aged less than five years were due to pneumonia, of which more than 70% occurred in sub-Saharan Africa and South-East Asia (Kabra, Lodha and Pandey, 2010).

On clinical grounds alone, it can be difficult to diagnose pneumonia. Microbiological examination of sputum (or deeper specimens from the lower respiratory tract obtained by bronchoscopy, or by lung biopsy), x-ray and blood cultures are sometimes recommended to confirm the diagnosis and the causative agent, which in the great majority of cases is viral rather than bacterial.

It may perhaps be argued that in the hospital environment treatment should be started after the organism causing the infection is identified. However, in the community it is rarely possible for this to be achieved, and there is always a possibility of patients' conditions worsening. An alternative way forward can be to start on broad spectrum therapy and as necessary become more specific if and when additional information is gained.

Decisions on therapy are based upon clinical history, and factors such a history of exposure to infection, age, underlying disease and previous therapies, a past history of pneumonia or related conditions, geographic location, severity of illness, clinical symptoms and sputum examination. Once an accurate diagnosis is available therapy should be directed at the organism responsible (Purushothama and Chien, 1996; British Thoracic Society, 2011). The British Thoracic Society Community Acquired Pneumonia (CAP) Guidelines recommend that bacterial pneumonia could be considered in children aged up to 3 years in the presence of a combination of fever >38.5 $^{0}$C, chest recession and a respiration rate of >50/min (British Thoracic Society Standards of Care Committee, 2011).

In most cases, pneumonia can be treated with oral antibiotics such as penicillin. Children may be hospitalised for treatment if they have pneumonia caused by pertussis or other bacterial pneumonia forms that cause high fevers and respiratory distress. Pneumonia can also lead to complications, which are more frequently associated with bacterial rather than viral pneumonia. Purushothama and Chien *(*1996) noted they may include:

- ***Pleural effusion***: excess fluid filling the space that surrounds the lung that impairs breathing by limiting the expansion of the lungs during inhalation.
- ***Empyema:*** collection of pus within a naturally existing anatomical cavity.
- ***Lung abscesses:*** the collection of pus in newly formed cavities.
- ***Pneumatocoeles:*** cavities in the lungs filled with air that may result from pulmonary trauma.
- ***Pneumothorax:*** air/gas present in the pleural cavity.

- ***Pyopneumothorax:*** pus and air or gas in the pleural cavity - e.g. following rupture of a staphylococcal lung abscess in the pleural cavity.
- ***Deep vein thrombosis***
- ***Septicaemia, pericarditis, endocarditis, osteomyelitis, septic arthritis, cerebral abscess, meningitis***
- ***Post-infective bronchiectasis:*** Inflammation of bronchial and allied tissue related to an abnormal build up of mucus in the lung.
- ***Acute renal failure***

### 1.3.1 CLASSIFICATION OF PNEUMONIAS

Pneumonia can be classified in a variety of different ways, most commonly in relation to where it was acquired (community or hospital). It may also be categorised by the area of lung that has been infected or by the type of organism that caused the infection (Dune, 2005). Pneumonia can also be classified on the basis of combined clinical and allied factors such as patient age, risk factors for some pathogens, the presence of other known lung or systemic disease, and whether the person has recently been hospitalised.

#### 1.3.1.1 COMMUNITY ACQUIRED PNEUMONIA (CAP)

Community acquired pneumonia is the most common type of pneumonia. In childhood it is a common cause of hospital admission. However, its severity can range from very mild disease to systemic illness ultimately causing death.

Hence diagnosis and assessment is critical. Clinically, it can be defined as the presence of signs and symptoms of pneumonia in a previously healthy child who has been infected outside hospital. In developed countries pneumonia can be verified radiologically. In the developing world radiological verification may not be possible. In such circumstances CAP is also commonly referred to as acute lower respiratory tract infection (British Thoracic Society of Standards of Care Committee, 2011).

#### 1.3.1.2 HOSPITAL ACQUIRED PNEUMONIA (HAP)

Hospital-acquired pneumonia may be referred to as nosocomial or healthcare-associated pneumonia (HCAP). It becomes apparent during or within 72 hours after the patient been hospitalised for another illness. The infection can be transmitted between patients in several ways, including via mechanical ventilation, when it may be known as ventilator-associated pneumonia (VAP). HAP is characteristically different from CAP in terms of its causes, treatment, and complications. This is because the types of pathogen that the patient may be exposed to in hospital are often different from those normally encountered in the home/community setting.

It tends to have worse outcomes than community-acquired pneumonia, as hospital-acquired pathogens may more frequently include antibiotic resistant bacteria (American Thoracic Society Documents, 2004). Patients with underlying illnesses are also more vulnerable to virulent and less virulent pneumococcal strains alike.

### 1.3.1.3 CATEGORISATION BY CAUSE

Historically, based on the type of pathogen and the symptomology of the patients involved, pneumonia has been referred to as either typical or atypical. However, The American Thoracic Society does not recommend this classification (Ebby, 2005). Based on the cause of infection, pneumonia is today classified as:

- **Bronchiolitis obliterans organising pneumonia (BOOP).** This was first described in the early 1980s. It is also known as cryptogenic organising pneumonitis (COP). It is caused by inflammation of the small airways of the lungs and it characterised by the presence of granulation tissue inside the distal air spaces (Al-Ghanem *et al.,* 2008).
- **Eosinophilic pneumonia.** This occurs when eosinophils invade the lungs. It quite often occurs in response to infection with a parasite or after exposure to certain environmental insults.
- **Chemical pneumonia.** This condition can also be known as chemical pneumonitis. It is caused by chemical toxins, which may enter the body by inhalation or skin contact. If the toxic substance is an oil, this is known as lipoid pneumonia.
- **Aspiration pneumonia.** Aspiration pneumonia or pneumonitis is caused by aspirating oral or gastric contents, either while eating or after reflux or vomiting, which causes bronchopneumonia. It is the leading cause of death in hospital and patients based in nursing homes.
- **Dust pneumonia.** Dust pneumonia is normally caused by exposure to dust storms. The dust progresses into the alveoli of the lungs, stopping the cilia from moving and so preventing the lungs from clearing themselves.

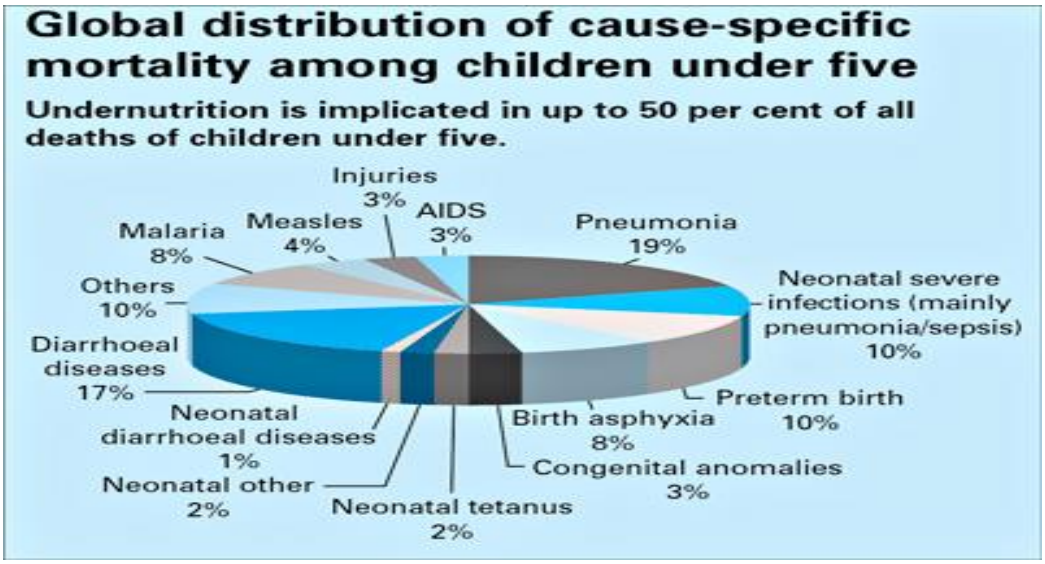
- **Necrotising pneumonia.** Necrotising pneumonia includes pneumonias that cause significant necrosis (apoptosis or other death) of lung cells. Sometimes lung abscesses may occur. Anaerobic bacteria such as *staphylococcus aureus, klebsiella pneumoniae and streptococcus pyogenes* are the predominant causal microbes (Sheppard *et al.,* 2007).
- **Opportunistic pneumonia.** This mostly occurs in immunocompromised individuals, such as those with AIDS and receiving chemotherapy for cancer. The main pathogens mainly responsible include cytomegalovirus and pneumocystis and mycobacterium, as well as a range of other pathogens (Sheppard *et al.,* 2007).
- **Double pneumonia.** This is a traditional term used for acute bilateral lung infection, acute respiratory distress syndrome (ARDS). It is more likely today to be known as bilateral pneumonia (Girard & Bernard, 2007).
- **Severe acute respiratory syndrome (SARS).** This is a highly transmittable and form of pneumonia with a high case mortality ratio which first occurred in 2002 in China. SARS is caused by the SARS corona virus, a previously unknown pathogen. The last recorded occurrence was in 2003 (Sheppard *et al.,* 2007).

### 1.3.2 BURDEN OF DISEASE

Pneumonia is the leading cause of death in children under five years old (Figure 1.8). Even today it causes more mortality than AIDS and malaria combined, accounting for up to 2 million child deaths each year. This represents approximately one in five child deaths worldwide and an incidence of 0.05 episodes per child-year (Rudan *et al.,* 2004; Kabra Ladha and Pandey, 2010).

In the UK, according to data from the Hospital Episode Statistics (HES) records, around 1% of all children aged 0-5 years old experience pneumonia (NICE, 2007). A study by Holmes *et al* (1999) suggests that in the UK about one third of people with a pneumonia diagnosis are admitted to hospital. In addition, the Health Protection Agency (HPA) estimates that in England and Wales each year there are 40,000 GP consultations for pneumococcal related CAP (HPA, 2010).

**Figure 1.8: The State of the World's Children 2008, Child Survival UNICEF**
(Adapted from United Nations Children's Fund, 2007)




### 1.3.3 RISK FACTORS

In order to facilitate the prevention and management of pneumonia, it is necessary to understand the risk factors described below.

### 1.3.3.1 HOST FACTORS

**Young age:** As with OM, pneumonia is most commonly found in young children (Dunn *et al.,* 2005; Cilla *et al.,* 2008. A study by Koshy *et al* (2010) found that the highest admission rates for bacterial pneumonia were in the youngest age groups (0-4 years old). Also, Michelow *et al* (2004) found that, pneumonia pathogens were found in 92% of children aged under 6 months, while a randomised, double blind, placebo-controlled vaccine probe trial in Phillipines indicate that a third of young children with a pneumonia diagnosis had pneumococcal pneumonia (Lucero *et al.,* 2009). Moreover, a study by Myles *et al* (2009) using a longitudinal, general practice database covering the period between 1991 and 2003 found that pneumonia most common in children aged under 4 years.

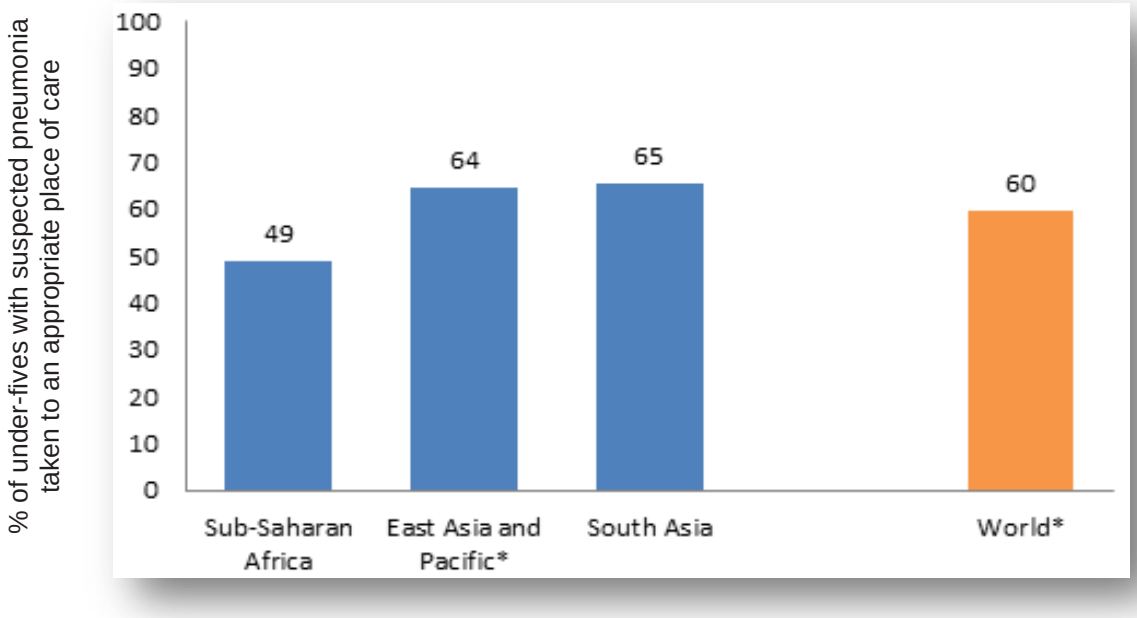
**Male gender:** As is true for most infectious diseases of childhood, pneumonia occurs more frequently in boys than girls (Klein, 2001). In 2007 a study by Clark *et al* found that in the UK incidence rates of pneumonia are higher in males than females at all ages (Harris *et al*., 2011).

**Geographical location:** In the US, over 1 million children and adults are admitted to hospital for pneumonia each year (Center for Disease Control and Prevention/CDC, 2009). Outside the developed world a report by the United Nations Children's Fund (UNICEF) stated that, between 2006-2011, the highest levels of care-seeking for pneumonia for children aged under 5 years were found in South Asia and East Asia & the Pacific excluding China

with 65% and 64% respectively, followed by 49% in sub-Saharan Africa (United Nations Children's Fund, 2012 – see Figure 1.9.)

**Atopy/ allergy:** As with other infectious diseases, atopic reactions and allergies may also predispose subjects to pneumonia (See Arroyave, 2001).

**Figure 1.9: Proportion of children under five with suspected pneumonia taken to an appropriate health-care provider, 2007–2012.**
(Taken from United Nations Children's Fund, 2012)




* Excludes China.

### 1.3.3.2 BACTERIAL AND VIRAL LOAD

Pneumonia is commonly caused by infection with fungal, viral or bacterial pathogens or a combination of such agents (WHO, 2012). Although there are a number of viruses associated with CAP the predominant one is, as in the case of OM, Respiratory Syncytial virus (RSV). This has been detected in similar proportions of children with pneumonia in the community and in hospital (Harris *et al.,* 2011).

In the UK, during a six month winter 'flu season, pneumonia was found in 16% of children infected with *Influenza A* (Laundy *et al.,* 2003).
However, several other viruses are regularly associated with pneumonia. They include Adenovirus, Rhinovirus, Varicella Zoster virus, Cytomegalovirus, Herpes Simplex and various Enteroviruses.

Overall, viruses appear to account for more than 30% of CAP cases in childhood. They are more frequently identified in children <1 year old (77%) compared with over 2 years (59%) (Cilla *et al.,* 2008). However, *S. pneumoniae* is the leading bacterial cause of pneumonia. Prospective studies reported that *S. pneumoniae* accounts for 30-50% of such cases, followed by *Hemophilus influenza*. In the latter context type b (Hib) has in the past typically caused 10-30 % of pneumonia cases. But it has now almost disappeared in immunised populations.

*Mycoplasma* and *Chlamydia* infections are equally common in school aged children. Even though *S. Aureus and Klebsiella pneumoniae* infections are less frequently recorded in children they impose a significant morbidity burden and can cause severe pneumonia (Nelson, 2000; Rudan, 2008).

It is difficult to quantify precisely the proportion of CAP caused by bacteria as they can be difficult to detect. Although, for example, *S. pneumoniae* is known to be the most common bacterial cause of CAP it is comparatively rarely found in blood cultures. The available data indicate that it is in practice found in only 4-10% of CAP cases (Clark *et al.,* 2007; Cilla *et al.,* 2008) although a review of lung tap studies found that *S. pneumoniae* had been identified in 39% of such cases (Vuori-Holopainen and Peltola 2001).

Yet 90% of children (n=34) in Finland who had a lung aspirate, either by culture or by using polymerase chain reaction (PCR) techniques, were found to have *S. pneumoniae* (Vuori-Holopainen *et al.,* 2002).

In fact, *S. pneumoniae* causes about a third of radiologically confirmed cases of pneumonia in children under 2 years. *Haemophilus influenzae* type b (Hib) is known to be the second most common cause of bacterial pneumonia (WHO, 2012). It is in older children that other pathogens such as Chlamydia and Mycoplasma are more commonly found (Kurz *et al.,* 2009).

#### 1.3.3.3 GASTRIC ACID INHIBITORS

The use of gastric acid inhibitors is known to be associated with increased pneumonia risk in adults. A single study has suggested this may also be true in children (Canani *et al.,* 2006).

#### 1.3.3.4 IMMUNE RESPONSES AND PRE-EXISTING DISEASE

Most healthy children can fight off respiratory infections with their natural defenses. However, those whose immune systems are compromised are at higher risk of developing pneumonia. A child's immune system may be weakened due to, for instance, malnutrition or an immuno deficiency. For related reasons the risk of children contracting pneumonia is also increased in those with pre-existing illness such as symptomatic HIV infections and measles (WHO, 2012).

### 1.3.3.5 ENVIRONMENTAL FACTORS

The following environmental factors also increase a child's susceptibility to pneumonia:

**Exposure to tobacco smoke:** As mentioned earlier, smoking is associated with *S. pneumonia* infections. Parental smoking significantly contributes to child morbidity and mortality associated with this bacterium. Smoke-filled environments contribute to the incidence of both upper and lower respiratory tract infections (National Institute for Health and Clinical Excellence, 2000; Ebby, 2005).

**Other air pollution:** Indoor air pollution that results from cooking and heating with biomass fuels (such as wood or dung) can also increase the incidence of pneumonia in children (WHO, 2012).

**Season:** The season another important environmental factor affecting the prevalence of CAP, especially for young children. In the northern hemisphere *w*inter sees a predominance of laboratory reported invasive pneumococcal disease and hospital admissions due to confirmed pneumococcal infections.

A study by Melegaro *et al* (2006) showed that the incidence of CAP in December and January is 3-5 times higher than in August.

In addition another study published in 2009 by Senstad *et al.* reported a low incidence of hospital CAP in summer and a peak in January.

### 1.3.4 PATHOLOGY AND COMPLICATIONS

Children with CAP may present with complications such as empyema and/or a lung abscess. The complications that are most commonly associated with CAP include the following:

**Pleural effusions and empyema.** Pleural effusions and empyema common occur in patients with pneumonia. They are mainly caused by *S. pneumoniae*. Pleural effusion is defined as a collection of fluid in the space between the linings (pleura) of the lung.

Empyema involves the presence of pus in the pleural space. Excessive amounts of fluid and pus can impair breathing by limiting the expansion of the lungs during ventilation. These complications are more commonly found in patients admitted to hospital. One percent of CAP cases develop pleural effusion compared to 40% of cases admitted to hospital (Harris *et al*., 2011). It has, however, been reported that in England the rate of admission with a diagnosis of empyema increased over the last decade, most commonly in children aged less than 5 years (Buckingham *et al*., 2003).

**Necrotising pneumonias.** Necrotising pneumonias (NP) are defined as multiple small cavitations without enhancing margins, mainly caused by the adenovirus. Certain serotypes of pneumococcal disease are more likely to lead to necrotising pneumonia than others (Sheppard *et al.,* 2007; Bender *et al.*, 2008). Following a complicated pneumonia diagnosis, NP has been increasingly recognised due to the use of CT scans of the chest (Kliegman, 2006).

**Septicaemia and other metastatic infections.** Pneumonia can also accompany other or more extensive systemic infections. Children with septicaemia and pneumonia are more likely to need high dependency or intensive care management. However, metastatic infections other than septicaemia are very rarely associated with pneumonia (Harris *et al*., 2011).

**Haemolytic Uraemic Syndrome.** Haemolytic uraemic syndrome (HUS – which involves red blood cell destruction and can result in permanent kidney damage) is rarely caused by *S. pneumoniae.* Yet a recent case series study reported that out of 43 cases of pneumococcal HUS, 35 presented with pneumonia (Waters, 2007).

**Long term sequelae.** In 2004 a study by Eastham *et al.* found that children who have had an episode of CAP are more likely to suffer from prolonged cough (19%), chest wall shape abnormalities (9%) and asthma (23%).

### 1.3.5 SYMPTOMS AND DIAGNOSIS

CAP in childhood is a common cause of hospital admission, although its severity can range from very mild disease to systemic illness and death. Early diagnosis and assessment is therefore critically important.

Most children are initially seen by their GP. If indicative symptoms such as cyanosis, difficulty in breathing and/or signs of dehydration are present an immediate referral to hospital should be made. But in infants and young children the signs and

symptoms of pneumonia can be unspecific. Broad indicators like fatigue, fever, chills, headache, coughing, pain in the stomach or chest, vomiting, diarrhea and a loss of appetite are common with pneumonia.

Further, even in the case of young children who have been hospitalised after being correctly diagnosed with pneumonia, subjects may still experience symptoms for weeks after being treated and discharged. Their symptoms may only gradually subside in the days and weeks after returning home (NICE, 2007).

In general, a combination of fever and cough is suggestive of pneumonia. Other respiratory findings (e.g., tachypnea – unusually rapid breathing – and a sense of having to make an increased effort to breath) leading subsequently to coughing may also be significant. Coughing may not be a clinical feature initially since the alveoli have few receptors involved in cough responses. It begins when the products of infection irritate ‘cough receptors’ in the airways. The longer fever, cough, and other respiratory findings are present, the greater the possibility of pneumonia.

A definitive diagnosis of pneumonia is usually made not only on symptoms but also on radiographic and microbiological diagnosis (NICE, 2007). Most cases of pneumonia are initially diagnosed clinically. GPs and paediatricians typically make the diagnosis after a physical examination, based on the child's signs and symptoms. But when necessary (and normally in the hospital environment) a chest X-ray and blood cultures are recommended, along with other tests such as a complete blood count (CBC) and C-reactive protein (CRP). If the responsible clinician thinks that the child has pneumonia oxygen saturation levels are also likely to be taken, especially if the child is experiencing breathing difficulties.

Testing for Respiratory Syncytial virus infections (RSV), flu, and other viral causes of pneumonia can also be helpful, as and when the relevant facilities are available. Sputum cultures can also be taken. However, this technique is not as helpful in infants and young children as it is in other groups because it is often hard to obtain an adequate sputum sample (NICE, 2007; Inannelli, 2011).

### 1.3.6 CLINICAL MANAGEMENT

As with other infectious diseases, treatment depends on the underlying cause of the infection. However, in most cases, pneumonia can be treated with oral antibiotics, which can be prescribed by a GP. The vast majority of cases of childhood pneumonia can be and are managed effectively within the home. Hospitalisation is mainly recommended in infants aged two months and younger and in cases where there is trouble breathing, dehydration, high fever, and the need for oxygen (WHO, 2012).

#### 1.3.6.1 ANTIBIOTICS

The management of a child with CAP involves a number of decisions regarding treatment with antibiotics. If it is decided that antibiotics should be used subsequent questions may appropriately include ‘which type of antibiotic and by which route?’, ‘when should the route of antibiotic administration be changed from intravenous to oral?’ and ‘for how long should the antibiotic therapy be continued?’.

The major problem in deciding whether to treat a child with CAP with antibiotics or not is the difficulty in distinguishing between bacterial pneumonia (which would benefit from antibiotic treatment) from non-bacterial pneumonia (which would not) (Harris *et al.,* 2011).

As already noted, amoxicillin is normally recommended as the first choice for oral antibiotic therapy in children of less than five years of age as it is effective against most organisms that cause CAP, as well as being well tolerated and cheap (British Thoracic Society Standards of Care Committee, 2011). Alternative recommended oral treatments can include co-amoxiclav, cefacolor, erythromycin, clarithromycin and azithromycin.

A meta-analysis of 27 randomised trials of antibiotic treatment for childhood CAP confirmed that amoxicillin is a robust alternative to co-trimoxazole for the treatment of ambulatory patients (Kabra *et al*., 2010). However, world-wide only around 30% of children with pneumonia receive the antibiotics they need (WHO, 2012).

Children should ideally be hospitalised if they have pneumonia caused by pertussis or other bacterial pneumonias that cause high fevers and respiratory distress. Untreated or missed diagnosis of pneumonia can progress to severe and potentially life-threatening complications (Purushothama *et al.,* 1996).

Resistance to antibiotics among bacterial pathogens is increasing and is of global concern. It is in part driven by the overuse of antibiotics, although even when they are used correctly resistance to such medicines will in time tend to emerge.

It has the potential to impact on therapeutic choices and there is worldwide concern about increasing antibiotic resistance among pneumococcal strains and its eventual impact on treatment for pneumonia and invasive pneumococcal disease (Goossens *et al.,* 2005).

From 1998 to 2000, the estimated global rate of penicillin resistance in *S. pneumoniae* was about 18%. Rates of resistance to co-trimoxazole among strains of *S.pneumoniae* and *H. influenzae* are generally high. In the UK however, penicillin resistance is less prevalent.

Pneumococcal penicillin non-susceptibility in pneumococci causing bacteraemia increased in the 1990s to 6.7% in 2000, and has since declined to around 4% in 2007. Geographical variations range from 1.5% in the East Midlands to 8.0% in London area. This is in contrast to much of mainland Europe. Resistance rates are between 25-50% France and Spain (HPA 2010, Harries, 2011).

National campaigns to reduce antibiotic prescribing have led to a reduction in prescribing in some countries (Goossens *et al.,* 2006). Nevertheless, the appearance of high-level penicillin and multidrug-resistant *S.pneumoniae* strains has led to an increase in incidence of antibiotic treatment failure (Jacobs, 1999; Barry, 1999).

In particular, children who have recently received antibiotics are at increased risk of acquiring a resistant strain of *S. pneumonia*. This can lead to additional morbidity, mortality and raised health care costs (Jacobs, 1999).

A logical approach to reducing the incidence of pneumonia in children and avoiding other forms of *S.pneumoniae* related harm is therefore through prevention by vaccination (Hyde *et al.,* 2001; Kaplan and Mason, 2002).

### 1.3.6.2 VACCINES

In 2000, PCV7 was licensed in the US for use among infants and young children to prevent pneumococcal infectious diseases such as pneumonia. The UK's routine immunisation programme has also offered protection against these infections with the introduction of PCV7 in 2006 for children at ages 2, 4 & 13 months old.

In the United States there was after the introduction of PCV7 a reported 39% decrease in hospital admission rates for pneumonia in children under 2 years (Grijalva *et al.,* 2007). The HPA/Public Health England has in this country also reported a reduction in the rate of IPD cases caused by the seven serotypes in PCV7 in children aged under and over 5 year olds since the introduction of the PCV7 (HPA, 2009).

A recent study in the UK using HES data found that following the inclusion of PCV7 in the national childhood immunisation programme, pneumonia hospital admission rate in England declined by 20% in children aged 0-15 years within 2 years (Koshy *et al.*, 2010). With the introduction of the conjugate pneumococcal vaccine, indirect evidence of vaccine efficacy for the prevention of pneumonia can be used to assess the contribution of *S.pneumoniae* to CAP management.

In children under 2 years trials have consistently shown a decrease in radiologically confirmed pneumonia from 23% in the Phillipines (Lucero *et al.,* 2009) to 37% in the Gambia (Cutts *et al.,* 2005) and 25.5% in California (Hansen *et al.,* 2006). The observed effect has been most striking in the first year following vaccine introduction with a 32%+ incidence reduction, as compared with a lower 23% reduction at the end of 2 years (Black *et al.,* 2002).

Although there is robust evidence that the introduction of PCV7 has decreased the occurrence of IPD and NIPD due to vaccine serotype bacteria, its impact on the overall incidence of OM and pneumonia and related antibiotic prescribing in the UK is less clear. An observational cohort study utilising two UK general practice-based databases was therefore designed in order to generate a better understanding of such questions. However, before this research is described it is relevant to discuss further factors underlying the introduction of the vaccine and aspects of its efficacy and safety in pediatric use.

## 1.4 SEVEN-VALENT PNEUMOCOCCAL CONJUGATE VACCINATION (PREVNAR 7®, PCV7)

### 1.4.1 ANTIBIOTIC RESISTANCE AND THE INTRODUCTION OF THE PCV7

There are two types of antibiotic resistance, inherent and acquired resistance. These are caused by either random gene mutations or horizontal gene transfers between bacteria. The mechanisms of antibiotic-resistance include modification, inactivation or destruction of the antibiotic; reduced effective antibiotic intake; increased antibiotic excretion via pump mechanisms; alteration of the drug's target and activation of an alternative metabolic pathway that avoid reliance on processes linked to the antibiotic's site of action.

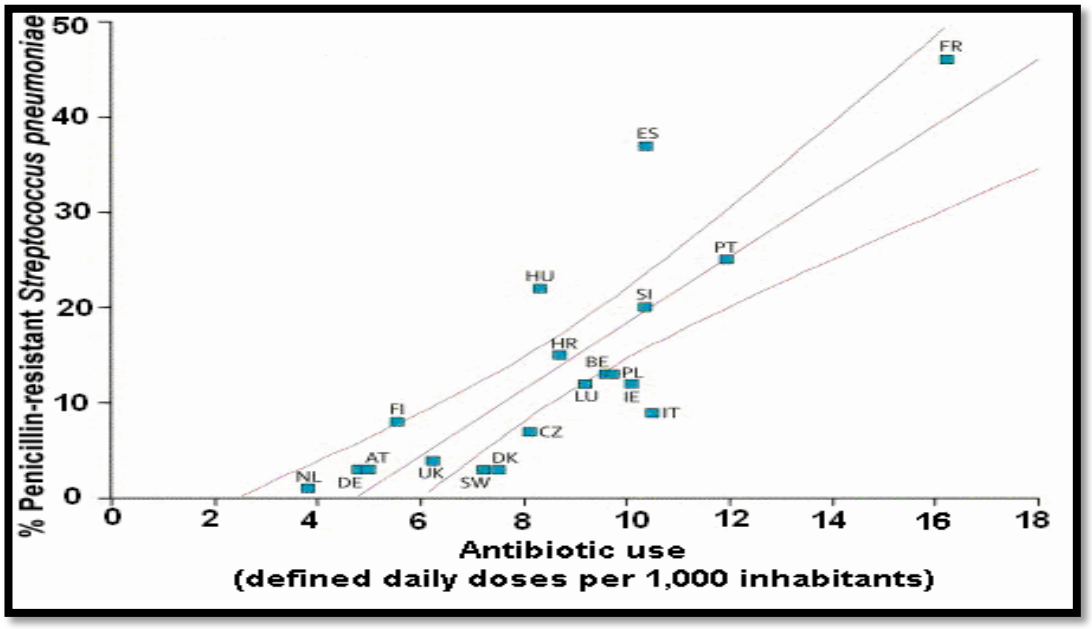
Once resistant bacteria persist spontaneously they can infect individuals in the wider community, e.g. schools and workplaces (Standing Medical Advisory Committee, 1998). Many studies demonstrate the link between the use of antibiotics and the development of antibiotic-resistance (Gold and Moellering, 1996) in both inpatient (McGowan, 1983) and outpatient settings (Reichler *et al.*, 1992).

Acquired antibiotic-resistance is not present in bacteria that pre-date the antibiotic period (Hughes and Datta, 1983) and resistant bacterial strains have continually emerged following antibiotic usage (Standing Medical Advisory Committee, 1998). The high consumption of antibiotics is recognised as the main cause of emerging resistance to antibiotic treatment.

Goossens *et al.* (2005) compared rates of penicillin prescribing and penicillin-resistance in 26 countries across Europe. Penicillin consumption was found to vary significantly.

The highest rate was in France, where the highest levels of resistance were recorded, whilst the lowest rates of both prescription and resistance were seen in The Netherlands (Figure 1.10).

**Figure 1.10: Correlation between penicillin use and rates of penicillin-resistant *Streptococcus pneumoniae* across European countries in the year 2000**
(From Goossens *et al.*, 2005)




**Key:**
AT=Austria; BE=Belgium; HR=Croatia; CZ=Czech Republic; DK=Denmark; FI=Finland; FR=France; DE=Germany; HU=Hungary; IE=Ireland; IT=Italy; LU=Luxembourg; NL=Netherlands; PL=Poland; PT=Portugal; SI=Slovenia; ES=Spain; UK=England only

Other studies have documented a link between antibiotic use and resistance at the individual patient-level. Steinke *et al* (2001) demonstrated that the risk of an individual being colonised by resistant bacteria increases following recent use of antibiotics. The authors conducted a case-control study of 13,765 people, whereby antibiotic exposure in subjects with trimethoprim-resistant isolates was compared with antibiotic exposure in subjects with trimethoprim-susceptible isolates.

It was found that exposure to trimethoprim, or any other antibiotic, within the previous 180 days increased the risk of colonisation with trimethoprim-resistance bacteria.

Nasrin *et al* (2002) conducted a prospective cohort study of 461 children aged less than two years old. It was found that children who had received a β-lactam antibiotic had twice the risk of being colonised with penicillin-resistant pneumococci within the two months following treatment compared to those who did not receive a β-lactam antibiotic. This risk increased by 4% for each additional day of β-lactam use within the six months prior to testing. Furthermore, a recent prospective cohort study of 119 children presenting to primary care with acute respiratory tract infection reported that the risk of isolating a β-lactamase producing pneumococci from a child's throat doubled at two weeks following treatment with amoxicillin (Chung *et al.,* 2007).

A study by Brook and Gober (2005) also confirmed the positive correlation between antibiotic use and the development of antibiotic-resistance. The authors investigated the antibiotic susceptibility of bacteria isolated from the nasopharynxes of children with acute Otitis Media and compared it with children with recurrent Otitis Media that had developed between four to six weeks after a previous ear infection that had been treated with amoxicillin.

Resistance was found in 12% (37/320) of the isolates obtained from the acute Otitis Media group compared to 39% (99/256) from the recurrent Otitis Media group ($P<0.05$).

As it has been confirmed that antibiotic use is linked to the development of antibiotic-resistant bacteria, it follows theoretically that reducing antibiotic use should slow the development of new resistance to antibiotics.

Reduced antibiotic use would also decrease adverse reactions related to antibiotic exposure and lower costs associated with antibiotic prescribing, albeit that any savings generated would be offset by the costs and possible consequences of the measures employed to curb antibiotic usage.

National campaigns to reduce antibiotic prescribing in some countries have, as previously reported, led to reduction in prescribing levels (Goossens *et al.,* 2006). In the UK specifically Butler *et al* (2007) demonstrated that amongst laboratory samples from general practice populations, lower levels of antibiotic-resistance were significantly associated with reduced antibiotic prescribing in the practice.

The appearance of high-level penicillin and multidrug-resistant *S. pneumoniae* strains has led to an increase in incidence of antibiotic treatment failures (Jacobs, 1999; Barry, 1999). In particular, children who have recently received antibiotics are at increased risk of acquiring a resistant strain of *S. pneumoniae*, which can lead to an increased risk of morbidity, mortality and health costs (Jacobs, 1999).
Such observations underpin the case for purchasing and supplying PCV7 and its successors (Hyde *et al.,* 2001; Kaplan and Mason, 2002).

### 1.4.2 WHAT IS PCV7?

In US, the first pneumococcal polysaccharide vaccine was licensed for use with 14-valent serotype array in 1977.

This was followed by a 23-valent serotype product in 1983, offering protection against almost 90% of recorded pneumococcal infections. However, these vaccines were ineffective in young children under 2 years of age because they induce a T-cell independent antibody response that it too limited to be effective in children with immature immune responses and hence does not result in become imprinted in their immunologic memories.

In February 2000, a new polysaccharide-protein conjugate vaccine was introduced in US, following its being licensed by the Food and Drug Administration (FDA) for use amongst infants and young children. It was specifically designed to have an enhanced immunogenicity in younger children (Kellner *et al.,* 2005; Sleeman *et al., 2001*). The mechanisms by which conjugation achieves this end cannot be explored in detail here. But they in essence involved linking a weak antigen to a stronger antigenic carrier in a manner which confers the immunological properties of the latter upon the former.

Following its introduction in the US PCV7 was marketed in Europe and elsewhere, and many other countries introduced this vaccine into their immunisation programmes (Table 1.5).

Immunisation schedules differ between countries, but the initial dose is usually given before the child is six months of age (Gomes *et al.,* 2009). In 2007, the WHO recommended that all countries incorporate PCV7 in their national infant immunisation programs (WHO, 2007).

PCV7 is a heptavalent vaccine that contains seven serotypes of pneumococcus cell membrane sugars conjugated with Diphtheria $CRM_{197}$ proteins.

It is a sterile solution of saccharides of the capsular antigens of *S. pneumoniae.* There are 91 serotypes of pneumococcal bacteria. PCV7 offers protection against seven of the most common polysaccharide (chemically activated to make saccharides) serotypes that are resistant to antibiotics (4, 6B, 9V, 14, 18C, 19F, and 23F), each of which is grown separately in a soy peptone broth.

**Table 1.5: Prevenar introduction in European countries**
(Taken from Gomes *et al.,* 2009)

| COUNTRY | EXTENT of VACCINATION PROGRAMME | IMPLEMENTATION DATE | COMMENTS/NOTES |
|---|---|---|---|
| Austria | Universal | 2004 (September) | |
| Belgium | Universal | 2005 (January) | |
| Bulgaria | NO VACCINATION PROGRAMME | | |
| Cyprus | Universal | 2008 (August) | |
| Czech Republic | Risk Based | 2007 (January) | |
| Denmark | Universal | 2007 (October) | |
| Estonia | NO VACCINATION PROGRAMME | | |
| Finland | Risk Based | 2009 (January) | |
| France | Universal | 2006 (June) | |
| Germany | Universal | 2006 (July) | |
| Greece | Universal | 2006 (March) | Fully reimbursed since March 2008 |
| Hungary | Universal | 2008 (October) | |
| Ireland | Universal | 2008 (September) | |
| Italy | Universal/Risk Based | 2005 (May) | Differences on regional basis |
| Latvia | NO VACCINATION PROGRAMME | | |
| Lithuania | NO VACCINATION PROGRAMME | | |
| Luxembourg | Universal | 2004 (October) | |
| Malta | Risk Based | 2007 (January) | |
| The Netherlands | Universal | 2006 (June) | |
| Norway | Universal | 2006 (July) | |
| Poland | NOVACCINATION PROGRAMME | | |
| Portugal | NOVACCINATION PROGRAMME | | Administered on voluntary basis and suggested by the Portuguese society of paediatric for children under then 2 years |
| Romania | NOVACCINATION PROGRAMME | | |
| Slovakia | Universal | 2008 (April) | |
| | Risk Based | 2006 (January) | |
| Slovenia | Risk Based | 2005 (September) | Fully reimbursed since September 2005 |
| Spain | Risk Based | 2001 (June) | |
| Sweden | Universal | 2009 (January) | |
| UK | Universal | 2006 (September) | |

Each 0.5ml dose of the vaccine has been formulated to contain 2 µg of each saccharide for serotype 4, 9V, 14, 18C, 19F, and 23F. It also contains 4 µg of serotype 6B giving a 16 µg total saccharide per dose, plus approximately 20 µg of $CRM_{197}$ carrier protein and 0.125 mg of aluminum in the form aluminum phosphate adjuvant. The original manufacturer and other sources claimed that the serotypes in PCV7 are responsible for approximately 80% of the most severe pneumococcal infections among children under five years of age (Wyeth-Lederal Vaccine, 2000; Wuorimaa & Kayhty, 2002; Advisory Committee on Immunization Practices, 2000).

In the UK, PCV7 was licensed in 2001. From 2002 it was recommended for children at high risk of pneumococcal disease and in September 2006 it was recommended for all infants as part of the routine childhood immunisation programme. The perceived benefit of the vaccine introduction is to decrease the incidence of the infectious disease caused by pneumococcal bacteria. This consequently protects children who are unable to receive the vaccine through herd immunity (DOH, 2006). It has since been found to similarly reduce the risk of *S. pneumonia* in older and other immune-compromised adults, adding unexpectedly to the cost effectiveness of childhood immunisation.

### 1.4.3 PCV7 EFFICACY AND SAFETY

In the US in 2001, one year after the introduction of the PCV7, there was a 69% drop in the rate of invasive pneumococcal diseases in children less than 5 years of age (Black *et al.,* 2002; Whitney *et al.,* 2003).

By 2004, it was reported that hospital admissions for community acquired pneumonia had also declined by 39% (95% Confidence Interval CI 22–52) and that rates of hospitalisation for pneumococcal meningitis had decreased by 66% (95% CI 56.3-73.5) in children younger than 2 years of age (Grijalva *et al.,* 2007; Tsai *et al.,* 2008).

Studies from the US and continental Europe have also shown that the incidence of OM and linked antibiotic prescribing rates have fallen since the introduction of PCV7 for children (Fireman *et al.,* 2003; Poehling *et al.,* 2007; Poehling *et al.,* 2006). Moreover, the frequency of tympanostomy tube insertion in young children in the US has declined since the introduction of PCV7 (Isaacson, 2012).

The safety profile for PCV7 is accepted as being comparable to that of other infant vaccines such as those used to protect against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b (Hib). Many studies have shown that PCV7 is highly immunogenic, well-tolerated and safe when co-administration for infants at age 2, 3 and 4 months, with a booster dose at 12-15 months (Schmitt *et al.,* 2003; Oosterhuis *et al.,* 2007; Knuf, 2006). The HPA is monitoring the impact of the current vaccination programme weekly, by following IPD admissions in England, Wales and Northern Ireland in relevant age groups to evaluate the effectiveness of the current schedule. It is also seeking to identify risk factors for vaccine failure and monitor evidence of serotype replacement trends.

Between July 2005 and June 2006, the HPA reported 797 cases of IPD in children aged less than 5 years old compared to 470 cases by the end of epidemiological year 2007/2008 (a decrease of 41%).

However, there was no significant reduction in cases in children aged 5 years or older (Kaye *et al.,* 2009; WHO, 2007, Whitney *et al.,* 2006).

### 1.4.4 ADVERSE EFFECTS

PCV7 is contraindicated in children with known hypersensitivity to the diphtheria toxoid or latex. It should not be given to children with thrombocytopenia or coagulation disorders that would contraindicate intramuscular injection (Wyeth-Lederle Vaccines, 2000). In clinical trials, fever >38.0°C, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, and rash or hives were reported more frequently in the PCV7 vaccinated group within two to three days compared with the unvaccinated group. It is has been reported that within 48 to 72 hours of vaccination patients/vaccinated subjects may also experience oedema, pain or tenderness, redness, inflammation or skin discoloration, mass, or local hypersensitivity at or around the injection site (Rennels *et al*., 1998; Black *et al.,* 2000; Wyeth-Lederle Vaccines, 2000).

### 1.4.5 WHO SHOULD RECEIVE THE PCV7 VACCINE?

Before its effective replacement it was recommended that this vaccine should be given to all infants from two months of age. This is because infants are at highest risk for pneumococcal disease. In the US, the recommended immunisation series from the FDA consisted of three doses at two month intervals (2,4,6 months) followed by a fourth dose at 12-15 months of age.

Catch-up vaccination was recommended for children between 2 and 5 years old who missed the PCV7 introduction (American Academy of Pediatrics, 2000; Wyeth-Lederle Vaccines, 2000).

In the UK, PCV7 was given at two and four months of age. To provide longer-term protection, a booster dose was given at about 15 months of age. A catch-up programme was also recommended for children younger than 2 years old at the time of the new schedule's launch, because these children are at an increased risk of pneumococcal disease compared to older children. However, it was decided that older children should only be offered the vaccine if they fell into a high-risk group, such as those with a heart condition, chronic lung/liver disease, diabetes mellitus or a weakened immune system.

Importantly, it has been observed that following the introduction of PCV7 the non-vaccine *S. pneumoniae* serotypes may replace vaccine serotypes (Hendrickson *et al.,* 2008; Kaye *et al.,* 2009). This gave rise to increasing concerns that PCV7 does not contain all of the common and invasive strains. Hence a broader pneumococcal vaccine containing thirteen serotypes (PCV13, Prevenar 13) replaced PCV7 in the UK in April 2010 (Department of Health, 2010). The HPA suggested that 50% of the remaining burden of invasive pneumococcal disease in this country was preventable by switching from PCV7 to PCV13 (Kaye *et al.,* 2009). The UK was one of the first countries to include PCV13 into its national vaccination programme.

## 1.5 SUMMARY

Pneumococcal bacteria are responsible for invasive pneumococcal diseases such as pneumonia, meningitis, respiratory tract infection and septicaemia, together with less dangerous but more prevalent non-invasive diseases such as Otitis Media. *S. pneumoniae* is the leading cause of bacterial pneumonia in children, and it has been observed in approximately a quarter of children hospitalized for pneumonia.

Antibiotics are frequently prescribed as soon as pneumonia is suspected. Untreated or missed diagnoses of pneumonia can progress to severe illness with potentially life-threatening complications.

OM is a common infection in younger children. Although AOM occurs at all ages, this condition, which is defined by the presence of fluid in the middle ear accompanied by acute signs or symptoms of middle ear inflammation, is most prevalent in infancy. The majority of OM cases do not require antibiotic treatment. However, for children with continuous symptoms for more than 3 days or with frequent history of OM or younger than two years of age, amoxicillin is the recommended first-line treatment in uncomplicated cases.

Very rarely, OM progresses to severe life-threatening outcomes. In part to offset the threat of pneumococcal resistance to penicillin and other antibiotics, the UK's routine immunisation programme has offered protection against these infections with the introduction of the PCV7 in 2006 for the protection of infants. For unvaccinated children aged under 2 years a catch-up programme was also introduced.

Studies from the US and continental Europe have shown that PCV7 has had a downward impact on the incidence of pneumococcal diseases such as OM and pneumonia. In the UK a study was designed in order to answer questions relating to the overall prevalence and treatment of childhood *S. pneumoniae* infections in the GP setting.

## CHAPTER TWO: STUDY DESIGN, RESEARCH TOOLS AND METHODOLOGY

This chapter presents details of the design, research tools and methodology used throughout this thesis.

### 2.1 STUDY DESIGN

In order to decide which study design to use for this research, it was necessary to weigh up the advantages and disadvantages of the possible options (Table 2.1).

**Table 2.1: Advantages and disadvantages of possible designs**

| Types of Study | Advantages | Disadvantages |
|---|---|---|
| **Randomised Controlled Trial (RCT)** | • Can draw conclusions on causality and effectiveness of treatments<br>• Bias and confounding can be avoided<br>• Multiple outcomes can be investigated | • Expensive<br>• Time consuming<br>• Requires complex design and analysis |
| **Cohort study** | • Can discover the time sequence of events<br>• Can investigate multiple outcomes | • Often expensive<br>• Bias could happen due to loss of follow-up<br>• Limited to one exposure |
| **Case- Control Study** | • Can be quick and cheap<br>• Can investigate multiple exposure | • Difficult to determine the time sequence of event<br>• Limited to one outcome |

To investigate the impact of the PCV7 on pneumococcal diseases such as OM and pneumonia a retrospective cohort study design was selected. In order to eliminate observer/recall bias and to ascertain the time sequence of events, it is advantageous to use a pre-existing database of patient medical records in primary care, rather than recruiting naïve subjects. This approach is efficient in terms of time and resources used. The databases available are discussed below.

## 2.2 RESEARCH TOOLS

Computer based systems have become a vital feature of UK primary care. Most general practitioners (GPs) in the United Kingdom use computers to manage their practices in terms of storing information on the patient's past illnesses and drug therapy, and to write prescriptions for drugs. Ninety six percent of them now access their patients' medical records electronically (Pemberton *et al.*, 2003). This electronic patient information can be combined into one database and utilised for medical research purposes (Lawrenson *et al.*, 1998).

Most of the UK population's contacts with the National Health Service (NHS) are through general medical practice, where 98% of care episodes are delivered. The advantage of using routine in-practice GP-based databases for research purposes is that it is low cost, the databases cover a large population and the data usually spans a significant time period (Powell *et al.*, 2003). Therefore, using a routine database of patient medical records is much more efficient in terms of time and resources than unnecessarily recruiting patients. This also reduces observer bias and recall bias, and reduces inaccuracy and incompleteness because data is captured at the time.

In the UK, there are six longitudinal databases of patient medical records. Before elucidating the database that will be used in this study, it is worth highlighting or giving a brief overview of each database.

QRESEARCH is a database that analyses the accuracy and completeness of data from other sources: Prescription Events Monitoring (PEM), Prescription Pricing Authority (PPA), General Practice Research Database (GPRD), the IMS Disease Analyzer (IMS DA), and The Health Improvement Network (THIN). QRESEARCH is one of the world's largest computerised databases of anonymised patient health records. It contains data from about 10 million patients, from 602 UK general practices. However, it is a relatively new database having been created in 2002. Additionally, data regarding 100,000 patients is the maximum that any researcher is able to release from the dataset (QRESEARCH, 2009; QRESEARCH, 2012).

PEM and PPA are different types of datasets that do not qualify as observational health care databases and are not useful for paediatric medication research studies, due to limitations of important data such as vaccination records and age recording for each patient respectively. GPRD and THIN together count as the largest computerised general practice' databases of anonymous patient data, however, it is hazardous to use GPRD to study medication in children (Wong and Murray, 2005). IMS DA is a complex and secure database in the UK on aspects of studying medicines in children. Therefore, in order to conduct this retrospective cohort study, both the IMS DA and THIN databases will be used as both can be used for paediatric drug utilisation, pharmacovigilance and pharmacoepidemiological research; and they provide primary indications for antibiotic use and immunisation records.

THIN and IMS DA have been extensively used and their advantages and limitations are widely understood (Wong and Murray, 2005). The characteristics of each of these two databases will now be addressed.

### 2.2.1 IMS DISEASE ANALYSER (IMS DA) DATABASE

IMS (formerly known as Intercontinental Medical Statistics) is a UK private international healthcare information company, specialising in the collection of anonymised, longitudinal, general practice patient medical records and interpretation of anonymised patient medical information for research purposes. Established in 1992, IMS holds data on over 2 million patients and has information on more than 95 million prescriptions from about 125 computerised general practices with more than 500 general practitioners (GPs). It represents approximately 2% of the total UK census population. Of the 2 million patients, almost 40% have at least ten years of follow-up data available (De Lusignan *et al.,* 2002; Wong and Murray, 2005). IMS data provides information on patient demographic and clinical details including both the reason for GP consultation and the indication for the actual prescription.

#### 2.2.1.1 RECORDABLE INFORMATION

Contributing GPs are provided with guidelines that define an electronic record of all patients' consultations. This includes (De Lusignan *et al.,* 2002; Wong and Murray, 2005):

• Demographics, including date of birth and gender of patient.

- Indication coded by GPs via Read Codes and then mapped to ICD-10 codes by a team of experts in medical classification and adjusted for internal consistency.
- Treatment, including drug substance, drug class, formulation, strength, dosage and frequency, coded via the ATC classification system.
- Treatment linked to indication.
- Treatment linked to cost.
- Test results linked to diagnosis.
- Referrals and procedures, e.g. X-rays, surgery.

GPs enter the data into the database via a computer package (Torex-Meditel System 5). This allows linkage of prescription and clinical indication data (De Lusignan *et al.,* 2002). However, the level of completeness of these data varies from one GP to another according to the level of detail the GP records (Linsell *et al.,* 2006).

In the IMS DA UK database, there are four different data tables. These include: patients, problems, notes and therapy data. The 'Patients' table data includes age, sex, date of registration, etc. The 'Problems' table contains all patients' diagnoses using (ICD-10 and Read) codes and text. In the 'Notes' table, data comprises all details from patients' consultations, such as diagnoses, prescriptions, referrals and test results. And in the 'Therapy' table data consists of medications and doses prescribed and issued to patients. All data relating to each individual patient are linked via a unique patient identification number. However, the data are fully anonymised and no identifiable details, such as postcode or NHS number, are recorded.

The general practices contributing data to IMS DA UK operate via fully electronic patient medical records. Prescriptions, referrals and tests can only be generated by entering the patient's details and the relevant treatment/procedure code into the database. Moreover, drugs prescribed by hospital doctors or other specialists will not appear in IMS DA data unless the treatment is to be continued. Thus the data is likely to be relatively complete.

#### 2.2.1.2 DATA QUALITY, COMPLETENESS AND REPRESENTIVNESS

Checks are employed in order to monitor the quality of information submitted by all contributing GPs. Data quality markers are used to ensure that the data contained within the IMS DA UK database is of specified quality standard. Hence, in order to be included and retained within IMS DA UK, GPs must meet a minimum data quality score. The score is based upon ten different assessment criteria, as outlined in Box 2.1 (De Lusignan *et al.,* 2002; Clayton, Thompson and Meade, 2008). These scores are then reported back to the contributing general practices on a quarterly basis in order to highlight the areas of data recording that require improvement.

This feedback system has been shown to significantly improve the quality of data contained within the IMS DA UK database. A newsletter addressing coding issues within IMS DA UK, compiled by an expert panel of GPs, is also distributed to contributing GPs every six months. GPs receive approximately £400 per year as an incentive to meet the minimum data quality scores for all ten assessment criteria (De Lusignan *et al.*, 2002). A validation study demonstrated that the IMS DA database has reliable, consistent and complete data (Lawrenson *et al.,* 1998).

**Box 2.1: The ten data quality markers used within the IMS DA UK database** (Taken from De Lusignan et al., 2002)

1) Percentage of registered patients for whom there has been a change in record over the previous twelve months
2) Percentage of patients with year of birth and gender recorded
3) Percentage of problems or diagnoses with Read Code of level 3 or lower
4) Percentage of notes linked to problem or diagnosis
5) Percentage of notes in which Read Code is level 3 or lower
6) Number of prescriptions issued per week per 1,000 registered patients
7) Complete dose and regimen details related to dose-effect or adverse drug reaction
8) Proportion of acute prescriptions issued linked to a problem or diagnosis
9) Proportion of repeat prescriptions linked to a problem or diagnosis
10) Ratio of acute prescriptions issued to chronic prescriptions

The patient population contained within the data is demographically similar to that of the total UK population at any given point in time in terms of age and gender. Although there is under-representation of smaller practices, the practices included in the IMS DA are broadly representative of general practices across the whole of the UK (Wong and Murray, 2005).

#### 2.2.1.3 IMS DA STRENGTHS AND LIMITATIONS

The following is a summary of the strengths and limitations of the IMS DA database:

**Strengths:**

- Large computerised database
- Data are reliable, consistent and complete.

- Representative of the total UK population by age and gender distribution.
- Largely representative of general practices in the total UK census population.
- Prescriptions are directly linked to the clinical indication, for both acute and chronic conditions.
- Additional information can be sought via GP questionnaires, such as vaccination record
- Availability of denominator data enables researchers to calculate prevalence and incidence rates (excellent research tool for pharmaco-epidemiological research).
- Free from observer and recall bias.
- Minimal training required prior to using it as a research tool (Lawrenson *et al.,* 1998; Wong and Murray, 2005).

**Limitations:**

- Possible coding errors/misclassification.
- Presence of missing data.
- No information on socio-economic status or ethnicity.
- No information on whether prescriptions are dispensed or taken.
- Data collection is not for research purposes and hence, not geared towards answering specific research questions (Lawrenson *et al.,* 1998; Strom, 2006).

### 2.2.1.4 ETHICAL APPROVAL

All studies that use IMS DA UK data must be approved by the Independent Scientific and Ethical Advisory Committee (ISEAC).

### 2.2.2 THE HEALTH IMPROVEMENT NETWORK (THIN) DATABASE

The Health Improvement Network (THIN) database is an anonymised primary care patient record from information entered by GPs, used to support drug safety and epidemiological studies. It was set up in November 2002, and is a collaboration between two companies with an established name in primary care computing: EPIC, a non-profit making organisation that facilitates access to electronic research data, and Cegedim, a European healthcare software and research company who develop and supply the Vision general practice computer system to over 1800 GP practices in the UK.

The data are collected weekly by THIN and sent monthly to EPIC who, supply the data to researchers for studies approved by the nationally accredited ethics committee, South East Multicentre Research Ethics Committee (SE-MREC) (Cegedim, 2012).

#### 2.2.2.1 RECORDABLE INFORMATION

THIN collects anonymous patient data, this include past history and prescriptions from practices using a system called, the Vision practice management system, where it has already been recorded in the normal routine of the practice. Data collected from the practice system are anonymised at the collection stage; thus, no identifying information will be available to THIN. The data are organised in files by individual practice and progressed to provide researchers with access to demographic, medical, and prescription information at an individual patient level.

In addition, there is information on referral to specialists, diagnostics, and laboratory results, some lifestyle characteristics with other measurements taken in the GP practice. Moreover, In the THIN database, there are six different data tables - see table 2.2 below.

More than 330 practices using Vision software have joined the scheme. Currently, the THIN dataset contains data from over 514 general practices with a total of over 10 million patients of which approximately 2.4 million are actively registered with the practice's medical records and can be followed prospectively. The remaining patients will still have historical data but have either left the practice or died. Most of these contributing practices have recorded several years of data on their system (UCL, 2012; Cegedim, 2012).

#### 2.2.2.2 DATA QUALITY, COMPLETENESS AND REPRESENTIVENESS

As well as establishing a new primary care research data resource, THIN is improving the data recording of contributing practices. In addition to providing free training to the practices, THIN data are subjected to computerised validation to measures the completeness and accuracy of recording. These results are fed back to the practices with more information on how to improve quality and correct omissions. They are also supported by free training seminars to address any issues and encourage more efficient use of their computer systems.

The comprehensive information on data quality of individual practices is shared with researchers so that, if appropriate, they can select subsets of practices with strengths in specific areas of data collection.

**Table 2.2: Main file types of THIN data**
(Taken from University College of London (UCL) The Health Improvement Network (THIN) Research team, 2012).

| | |
|---|---|
| **PATIENT** | Age, sex, registration date when entering the practice, and date when leaving the practice |
| **MEDICAL** | Medical diagnoses, date of diagnosis, and location (e.g., GP's office, hospital, consultant) of the event and an option for adding free text; referrals to hospitals and specialists. |
| **THERAPY** | All prescriptions along with the date issued, formulation, strength, quantity, and dosing instructions, indication for treatment for all new prescriptions (inferred from cross reference to medical events on the same date), and events leading to withdrawal of a drug or treatment. |
| **ADDITIONAL HEALTH DATA (AHD)** | Vaccinations and prescription contraceptives; miscellaneous information such as smoking, height, weight, immunizations, pregnancy, birth, death, and laboratory results. |
| **POSTCODE VARIABLE INDICATORS (PVI)** | Postcode linked area based socio-economic, ethnicity and environmental indices |
| **CONSULTATION** | Date, time and duration of consultation |
| **STAFF** | Gender and roles of staff who entered the data |

A complete computerised record of the patient's healthcare is recorded whilst the patient is registered with their GP. Significant historical events are entered from a summary transferred from the paper notes. However, the THIN dataset is created from

data collected from the GP's medical record system and will imitate only those events that are supposed to be relevant to the patient's care.

During consultation, all medical conditions and symptoms reported to GPs are recorded on the computer. These consultations build up long computerised the patient's medical histories. Medical conditions are recorded using the Read code. This is a hierarchal system, and the codes may be cross-referenced to the International Classification of Diseases (ICD10). Information of the type of specially is routinely recorded on referrals to secondary care.

Secondary information received by the GP is recorded and entered retrospectively; this includes details on hospital admissions, discharge medication and diagnosis, outpatient consultation diagnosis, investigation and treatment outcomes. In terms of GP prescriptions, prescribing is particularly well recorded since the computerised entry made by the doctor is also used as the prescription form with a copy being printed for the patient to present it at the pharmacy.

The Read code classification is used to code specific diagnoses, and a drug dictionary based on data from the MULTILEX coding system classification is used to code drugs. Prescriptions not issued from the computer, such as controlled drugs, immunisations, private prescriptions, and drugs prescribed during home visits should all be entered, but there is a possibility of under-recording with such items (UCL, 2012; CEGEDIM, 2012). In most cases a medicine prescribed for the first time can be temporarily related to the medical event record (symptom or diagnosis) even though there is not a permanent link between a therapy record entry and an entry in the medical records.

Also as in IMS DA database drugs prescribed by hospital doctors or other specialists will not appear in the THIN data unless the treatment is to be continued. However, due to the constraints of specialist/hospital prescribing budgets many prescriptions issued outside of the GP practice will usually only be enough to cover the first 7 days. After this time the patient will be required to visit their GP for a further prescription, and again for any subsequent ones. These therefore will be entered into THIN data.

Since the database holds comprehensive prescribing and disease information it allows healthcare researchers to be able to study the natural history of disease, monitor drug safety and carry out any risk management studies. Prescribing analysis can examine therapy/treatment indication and use. The data collected is audited regularly and the participating general practices are subjected to a number of quality checks. The quality of the information in the database has been validated in many of independent studies and has been found to be high (Maguire *et al*., 2008; Mayles, 2009).

#### 2.2.2.3 THIN DATABASE STRENGTHS AND LIMITATIONS

The following text offers a summary of the strengths and limitations of the THIN database (UCL, 2012; Cegedim, 2012):

**Strengths:**

- It is population-based data, representative of the majority of the population within the UK.
- It allows maximum scope for researchers in terms of study design (i.e. cohort, case-control, and case-series).

- It is representative of general practices in the UK census population.
- The data includes some longitudinal data, allowing long-term follow-up of patient histories, making longitudinal studies possible.
- Reduces time and costs as data does not need to be collected.
- Control subjects can be from the same population source.
- Relatively rare exposures or outcomes of any medication can be examined.
- It is not subject to recall bias or researcher bias, as there is no reliance on patient recall or researchers to collect the data.

**Limitations:**

- Coding errors/ misclassification.
- Missing data.
- Prescriptions are not directly linked to the clinical indication.
- No information on ethnicity, occupation, employment, and/or socio-economic status.
- Not appropriate for studies examining over the counter drugs.
- Not appropriate for studies looking at laboratory test results.
- Not appropriate for studies requiring follow-up of over 5.5 years.

#### 2.2.2.4 ETHICAL APPROVAL

All studies that use THIN data must be approved by the Scientific Review Committee (SRC).

## 2.3 JUSTIFICATION OF THE DATASETS USED IN THIS STUDY

The advantages and limitations of the THIN and IMS DA UK databases were considered when determining their utilisation within this study. Table 2.3 demonstrates the differences.

**Table 2.3: Comparison of the THIN and IMS DA UK databases**

| Characteristics | Database | |
|---|---|---|
| | THIN | IMS DA UK |
| **Year established for the database** | 2002 | 1992 |
| **Percentage of UK population represented** | ~ 5% | ~2% |
| **Total number of patients** | ~10 million | ~3 million |
| **Number of patients currently registered** | ~2.4 million | ~1 million |
| **Prescribing and indication data directly linked** | No | Yes |
| **The availability of primary and secondary care data** | Yes | Yes |
| **Access to patients' entire medical history while registered in the database** | Yes | No |

A major limitation of both THIN and IMS DA UK, which is common to any routinely collected medical database, is coding misclassification. This relates to how GPs record diagnoses. Another limitation is that collected data is not geared towards a specific research question, unlike in a prospective study.

Thus, although, the aforementioned databases may not be comparable for all subjects, using a database of patient medical records such as the THIN and IMS DA UK remained the most efficient means of obtaining data for the purpose of this research.

Both THIN and IMS DA contains information on demographics, prescriptions, diagnoses and referrals. Although, indications are not directly linked to prescriptions in THIN they are linked in IMS DA. However, THIN has information on hospital admission and results of laboratory tests. Both the THIN and IMS DA UK are excellent research tools for examining the incidence of pneumococcal diseases. Best practice for this type of analysis suggests that any trends in disease incidence should be confirmed in two independent databases, therefore both were used.

## 2.4 DEFINITIONS AND STATISTICAL METHODS

The following section provides a description of the epidemiological definitions and statistical methods used throughout this study.

### 2.4.1 AGE CLASSIFICATION

The classification of children into age-groups provides a means of investigating age-related differences in disease incidence and antibiotic prescribing trends. Age-groups for this study were defined as 0-1 years, 2 to 5 years, 6 to 10 years and 11 to 15 years.

The International Conference of Harmonisation (ICH) guidelines, recommend classifying age-groups as preterm newborn infants, term newborn infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years) and

adolescents (12 to 16/18 years), based upon physiological and developmental considerations (International Conference of Harmonisation, 2000). However, in this study a narrower age-grouping is applied. This enables a more detailed reflection of the age-related differences in disease incidence and antibiotic prescribing than would have been possible if the ICH age-group classification was applied.

### 2.4.2 INCIDENCE

Incidence is a measure of the number of new events occurring during a given time period in a specified population. The incidence rate refers to the rate at which these new events occur and takes the dynamics of the population into account, whereby the numerator is the number of new events in a defined time period and the denominator is the population at risk of the event during the relevant period, expressed as child-years (Last, 2001).

$$\textbf{Incidence rate} = \frac{\textbf{Number of new events in a defined time period}}{\textbf{Number of people at risk of event during this time period}}$$

Descriptive analysis will be conducted for patient demographics and prescription data throughout the study. To describe the study cohort, the age and gender distribution and total person-years of patients will be calculated.

Antibiotics are generally used to treat bacterial infections such as acute Otitis Media and pneumonia (recorded in the IMS DA and THIN database respectively) so a child may be infected and receive antibiotics more than once within the same year. Thus, each

episode of illness and prescription will be counted as a new infection and a new prescription and it will contribute to the numerator more than once in any given year.

### 2.4.2.1 INCIDENCE RATE CALCULATION FOR OM DIAGNOSIS AND ANTIBIOTIC TREATMENT FOR OM

Diagnoses of OM will be based on Read Code classifications. To obtain insight into the medical conditions of the children and how they are being treated, all indications for antibiotic prescriptions will be investigated in the IMS DA. Antibiotic prescribing patterns for OM will be compared with the total antibiotic trend during the study period. Annual, age and gender-specific incidence rates for OM and antibiotic prescribing will be calculated per 1000 person/child years.

$$\textbf{Incidence rate for OM} = \frac{\textbf{Number of OM episodes in a particular year}}{\textbf{Number of person-years in paediatric population in a particular year}}$$

Also, within the IMS DA, antibiotics listed under the ATC therapeutic levels main group J01 (antibacterial for systemic use) will be utilised in the data analysis.

$$\textbf{Incidence rate of AB prescribing} = \frac{\textbf{Number of antibiotic prescriptions for OM in a particular year}}{\textbf{Number of person-years in paediatric population in a particular year}}$$

### 2.4.2.2. INCIDENCE RATE CALCULATION FOR PNEUMONIA DIAGNOSIS AND ANTIBIOTIC TREATMENT FOR PNEUMONIA

Pneumonia diagnosis will be classified on Read Code (Appendix 7). To obtain an insight into the medical conditions of the children and how they are being treated, all indications for antibiotic prescriptions will be investigated in the THIN database. Antibiotic prescribing patterns for pneumonia will be compared with the total antibiotic trend during the study period. Annual, age, and gender-specific incidence rates for pneumonia and antibiotic prescribing will be calculated per 1000 person-year population of the THIN data.

$$\textbf{Incidence rate for pneumonia} = \frac{\textbf{Number of pneumonia episodes in a particular year}}{\textbf{Number of person-years in paediatric population in a particular year}}$$

In the THIN database, antibiotics are listed under the BNF code (antibacterial for systemic use), which is based on data from the MULTILEX classification and will be utilised in the data analysis.

$$\textbf{Incidence rate of AB prescribing} = \frac{\textbf{Number of antibiotic prescriptions for pneumonia in a particular year}}{\textbf{Number of person-years in paediatric population in a particular year}}$$

Incidence rate will be calculated using Poisson distribution with a 95% confidence interval (CI). A chi-squared test or $\chi^2$ test will be used to compare the prescribing trends before and after the introduction of PCV7. Data manipulation and analysis will be conducted using STATA/SE 11.0 for Windows (Statistical Software: Release 9.1. College Station, TX, USA).

### 2.4.3 CONFIDENCE INTERVALS

Confidence intervals are a range of values for the interested constructed variable. It provides a range (confidence interval) of sampling error amount that is present in a study, and this range has a specified probability (confidence level) of including the true value of the variable.

Moreover, if the confidence interval is narrow, this indicates good precision that any effect outside of this range will be ruled out of the study. However, if the confidence interval is wide, this indicates poor precision.

This usually occurs if the study's size is relatively small. If the confidence interval does not include the no-effect/null value (1.0) then the result is deemed statistically significant and vice-versa (Webb *el al.,* 2005, Davies & Crombie, 2009). The confidence interval used in this study is the 95% confidence interval (95% CI). This provides a range that the reader can be 95% confident that it contains the true value of the interested variable, which was based on the Poisson distribution (possibility distribution of a number of events occurs in a specific period of time), as the analyses were concerned with child-year incidence rates of infection diseases (Webb *et al.,* 2005, Davies & Crombie, 2009, Last, 2001).

### 2.4.4 *P*-VALUES

*P*-values provide a measure of the probability of whether an observed association might be due to any chance occurrence during the study period. In most epidemiological studies, and throughout this study, a result with a probability value of less than 5% ($P<0.05$) is considered unlikely to have occurred by chance and is, thus, deemed statistically significant (Last, 2001). Moreover, in relation to confidence intervals, if the 95% CI does not include the no-effect/null value (1.0), then the corresponding *P*-value will be <0.05 and the result termed as statistically significant and vice versa (Webb, Bain and Pirozzo, 2005).

## 2.5 METHODOLOGY

Overall this study can be viewed as involving four study strands (Table 2.4). Initially, a systematic review and meta-analysis were performed. Following this review the study aims and objectives were defined.

**Table 2.4: The Study Strands - Respective Methodologies and Data Sources**

| Study Strand | Methods | Data Source |
|---|---|---|
| 1. Literature Review | Systematic Review<br>Meta-Analysis | Randomised Controlled Trials |
| 2. Study of GP based vaccination records | Validation study | IMS DA, COVER and questionnaire |
| 3. OM study | Retrospective cohort study | IMS DA |
| 4. Pneumonia study | Retrospective cohort study | THIN |

However, for the purposes of clarity each of the study strands will now be addressed in turn, and their respective aims, objectives and methods discussed.

### 2.5.1 Study strand ONE – Systematic Review and Meta-analysis

#### 2.5.1.1 Definitions

A systematic review is a way to combine the results from different, published or unpublished studies. These are mainly the results of clinical trials that deal with the same conditions or same type of therapy. Systematic review has through time become an integral part of evidence-based medicine and an important method because of its:

- **Efficiency**: systematic review of pre-existing studies is more time saving and economically efficient than performing a whole new studies of a certain intervention for instance. It summarises all available results and stops unnecessary studies being performed.
- **Consistency:** the results of a systematic review can be generalised to a bigger and wider population than any one single study.
- **Precision:** in combination with meta-analysis this can give greater ability to detect effects that are of interest.
- **Reduction:** systematic reviews have the ability to reduce large amounts of information into a manageable size.

The demand of evidence-based medicine has grown and became so big that a group of clinicians, consumers and methodologists have created what is called The Cochrane Library.

This is a platform for systematic reviews performed by the Cochrane collaboration. Additionally the Cochrane Library includes different evidence based health care databases (Egger *et al.,* 2001; Hemingway& Brereton, 2009).

In order to assess the reliability of any systematic review and individual trials two guidelines have been designed. These are the Consolidated Standards for Reporting of Trials (CONSORT) and the Quality Of Reporting Of Meta-analyses (QUORUM) (Needleman, 2000). They help to standardise the reporting of clinical trials and meta-analyses.

**2.5.1.1.1 Consolidated Standards for the Reporting of Trials (CONSORT) and the Quality of Reporting of Meta-analyses (QUAROUM).**

**Consolidated Standards for Reporting of Trials (CONSORT)**

The CONSORT guideline has been developed by a group of journal editors, clinical researchers and biostatisticians. From 1996, 70 biomedical journals using randomised controlled trials (RCTs) adopted this guideline.

It consists of different items that should be included in a RCT publication listed in a checklist. These items include a clearly described hypothesis, protocol, randomisation, blinding, follow up and analysis. Moreover, it can provide a clear guidance on how to construct better trials, which in turn should improve the quality of future research. It is a way to get authors to be transparent when it comes to reporting a RCT. This is important for the reader to be able to understand interpretations, study design, and assessment of validity. For this sole purpose, a checklist and flow diagram have been designed to help researchers when setting up a RCT (Needleman, 2000; Turpin, 2005).

**Quality of Reporting of Meta-analyses (QUAROUM)**

The QUAROUM is another guideline, which has been developed to improve the quality of reporting of research methods. To aid evaluation of any systematic review, the QUAROUM guideline has also set out a checklist and flow diagram (Needleman, 2000; Turpin, 2005). The checklist includes asking if any information is missing which can be linked to biased estimates of treatment. This is important information for the reader to judge the reliability and the relevance of included studies.

The flow diagram gives directions in how to describe the flow of patients through the entire trial. This includes how they are allocated, how they are randomised and by whom. If the trial is blinded, it should be stated who is blinded to it. It asks for descriptive information regarding four different stages of a RCT: enrollment (how many participants there are in each group), intervention allocation (explain the nature of intervention), follow up and analysis (Petrie & Sabin, 2009).

**2.5.1.1.2 Meta-analysis**

Meta-analysis is a statistical method whereby analysis combines data from different studies with the same outcome in order to improve the reliability of the results. The first step in doing a statistical meta-analysis is performing a systematic review as explained earlier. To conduct a meta-analysis requires a comprehensive search strategy using several electronic databases (Crombie, Davies, 2009).

#### 2.5.1.1.3 Intent to treat (ITT)

The idea behind the intent to treat strategy is to include all subjects in a group, regardless of whether they were withdrawn from the trial, missed a dose, did not complete the whole treatment, or did not comply entirely with the inclusion criteria (Hollis & Campbell, 1999). This is an important component when looking at effectiveness, and if not performed, the effectiveness of a treatment may be overestimated. Therefore, it takes into account all enrolled patients.

### 2.5.1.2 Systematic literature review of the study

A recent review of pneumococcal conjugate vaccines did not adequately address the efficacy of PCV7 in the paediatric population (Huss *et al.,* 2009). Therefore, a systematic review was undertaken to investigate the efficacy of the vaccine, its level of adverse events in children aged 0-10 years, and to review the current literature in order to assess what is already known.

#### 2.5.1.2.1 Aims & objectives:

The aim of this systematic review was to investigate the efficacy and adverse effects of PCV7 in children aged between 0-10 years. The outcomes of interest are described below:

- Primary outcome: the efficacy of PCV7 in preventing pneumococcal diseases. The serotype specific antibody concentrations, geometric mean concentration (GMC) were investigated.

- Secondary outcome: the adverse effects of PCV7. The local and systemic adverse drug events associated with the PCV7 were investigated.

**2.5.1.2.2 Methods**

**2.5.1.2.2.1 Search strategy:**

A systematic review of the literature published between January 1990 to January 2010 was undertaken using the following electronic sources: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Meta-Register of Controlled Trials (www.controlled-trial.com), WHO Clinical Trial Register (http://www.who.int/ctrp/en/) and the Clinical Trials Government database (http://www.clinicaltrials.gov/).

Hand searching was also carried out to examine the reference lists of identified studies. The search strategies for the literature review are described in Table 2.5.

**Table 2.5: Search terms will be used to search relevant articles from electronic databases**

| Condition | | Drug | | Population | | Study Design |
|---|---|---|---|---|---|---|
| Invasive pneumococcal diseases (IPD) OR Otitis Media OR acute Otitis Media OR Otitis Media effusion OR middle ear infection OR middle ear inflammation OR respiratory tract infection OR bronchiectasis OR pneumonia OR meningitis OR neisseria meningitidis OR meningococcal OR pneumococcal meningitis OR bacteraemia | AND | 7-valent pneumococcal conjugate vaccine OR heptavalent pneumococcal conjugate vaccine OR PCV7 OR Prevnar OR pneumococcal vaccine OR PCV OR pneumococcal immunisation OR pneumococcal immunization OR pneumococcal vaccination | AND | infants OR children OR child OR neonates OR baby OR babies OR paediatric OR pediatric OR toddlers | AND | randomised-controlled study OR randomised controlled trial OR randomized controlled trial OR randomized controlled study OR cohort study OR panel study OR double blind method OR double blind trial OR single blind trial OR triple blind trial OR blind trial OR randomised double blind placebo controlled trial OR randomized double blind placebo controlled trial OR single blind method OR single masked method OR single blind procedure OR controlled clinical trial OR crossover studies OR crossover trials OR crossover designs |

**2.5.1.2.2.2 Study selection criteria:**

*Inclusion Criteria*

- Literature published from randomised controlled trials (RCTs), investigating the efficacy and side effects of 7-valent pneumococcal conjugate vaccine (PCV7) to prevent pneumococcal infections.
- Children aged 0-10 years.
- No language restrictions.

Two reviewers (Aisha El-Turki, Abir Ali) independently performed the electronic searches in January 2010. Any articles that clearly did not meet eligibility criteria in the systematic review were rejected on initial review. A standardised data extraction form was used to record all data from the papers meeting the inclusion criteria for review (Egger *et al*., 2001). The standardised form included study design, trial duration, mean age of participants, gender, number of participants in treatment and placebo group, interventions, and the assessment of intention-to-treat (ITT) analysis. The QUORUM (Quality of Reporting of Meta-analysis) guidelines were used for reporting the results of the systematic review (Moher *et al.,* 1999; Moher *et al.,* 2001; Needleman, 2000).

**2.5.1.2.2.3 Dealing with missing data**

The reviewers directly contacted the study authors three times to obtain missing information in the articles. If the reviewers were unable to obtain the missing information, the missing data were given replacement values.

For example, where standard deviations (SD) were not reported, these were obtained from standard errors (SE), confidence intervals, t values or p values (Higgins and Green, 2009).

#### 2.5.1.2.2.4 Statistical analysis

The meta-analysis used a random effects model with RevMan 5.0.20 (Oxford, UK: The Cochrane Collaboration, 2009). Due to the low number of included studies, funnel plot analyses were unable to be performed in order to assess publication bias.

### 2.5.2 Study strand TWO – Validation Study

#### 2.5.2.1 Background

In the UK, children are vaccinated at GP practices and their immunisation records are recorded in the GP computer systems. In addition to GP practices, other healthcare professionals such as practice nurses, health visitors, and school nurses can also administer vaccines to children (Immunisation against infectious disease, 2006). For those children who are vaccinated by other health care professionals outside GP practices, their immunisation records may not be recorded in the general practice computer system. Therefore, immunisation records may be under-recorded in GP practices.

In January 1987, the Cover of Vaccination Evaluated Rapidly (COVER) scheme was first set up to monitor immunisation coverage data for children in England and Wales (White *et al*., 1995).

In May 2002, data started to be collected from Primary Care Trusts (PCTs) in England and all the immunisation records were collected amongst children aged one, two and five years old from the PCTs. Prescribing trends of PCV7 taken from IMS DA will be compared with national statistical data [Cover of Vaccination Evaluated Rapidly (COVER)], which estimates the vaccine (PCV7) coverage reached approximate 90-95% of children (NHS Immunisation Statistics, 2012). COVER is a national programme to monitor immunisation coverage data in children.

This analysis will enable us to expand and integrate knowledge of OM and pneumonia and their management in children in the wake of the PCV7 programme; also, it can provide a comprehensive understanding of the efficacy of PCV7 use in UK primary care. It is believed that no previous studies have been carried out to validate immunisation records in GP practice taken from the IMS DA. Therefore, a validation study was conducted through GP questionnaires to investigate immunisation recording in children aged 0-2 years in general practice.

#### 2.5.2.2 Aims of the study

- To investigate PCV7 immunisation recording in children aged 0-2 years in general practice.
- To compare the percentage of immunisation recording in general practice (recorded in IMS DA) with COVER programme data.
- To investigate the association between vaccine consumption and the incidence of OM in children aged 0- 2 years old by using individual patient-analyses.

### 2.5.2.3 Methods

#### 2.5.2.3.1 Study design

This study was designed to investigate PCV7 immunisation recording in children aged 0-2 years in general practice. A letter (4 December 2010) was sent to GPs with a questionnaire asking a single question: has this child had the Prevnar 7® vaccine? (Appendix 1a &1b). All children who were born in 2008 were identified and their records were followed for 2 years.

To validate the study, firstly, the percentage of PCV7 vaccinated children born in 2008, in the IMS DA database was calculated and compared with the COVER data.
Secondly, children of the same age (0-2years) without a PCV7 record in the primary care setting, in IMS DA database, were validated through the questionnaire sent to their General Practitioners.

#### 2.5.2.3.2 Study population

Prior to sending the questionnaire to the GPs, the overall number of questionnaires required for this study had to be estimated using Epi Info™ version 3.5.1. This is open source software designed for epidemiological research. It offers resources for use in counting and measurement in descriptive and analytic studies, undertaking stratified analysis with exact confidence limits, matched pair and person-time analysis, sample size and power calculations, and other evaluation statistics (CDC, 2013).

In IMS DA database, there are approximately 18,000 children aged 0-2 years registered per year. Based on the COVER data (HPA, 2009), it was assumed that 10% of children (1,800) will be without a PCV7 immunisation record. A worst-case scenario was that 5% of these patients were immunised but unrecorded. Therefore, the sample size needed to detect this worst-case scenario would be 138 patients, with 95% confidence interval (Table 2.6). If the questionnaire response rate was 80%; then 173 questionnaires would be needed.

**Table 2.6: Sample size calculation (WHO, 2009)**

| **Sample size calculation** | |
|---|---|
| Total Population Size: | 1,800 |
| Expected Frequency: | 2.50% |
| Worst Acceptable: | 5.00% |
| Confidence level required | Sample size |
| 80% | 62 |
| 90% | 100 |
| **95%** | **138** |
| 99% | 226 |
| 99.9% | 342 |
| 99.99% | 445 |

Identification of children without PCV immunisation records in the IMS DA database were identified by searching for prescription and event codes corresponding to vaccination listed in (noteread44or5code) (Appendix 2) and ATC code (J07A7).

This identified all vaccinated and unvaccinated children registered with the IMS DA Database between 1st January 2008 and 31st December 2010, aged between 0-2 years (born in 2008 and followed for the following two years (up to 2010). Ethical approval for this study strand was obtained from ISEAC and a summary of their consent is at Appendix 3.

### 2.5.3 Study strand THREE – OM Cohort Study

#### 2.5.3.1 Aims and objectives

**The aim of this study strand:**

To describe the incidence rates of OM and antibiotic prescribing patterns in children and adolescents before and after the introduction of PCV7 between 2002 and 2010 in the UK primary care setting stratified by age and gender.

**Objectives:**

1) To determine the annual incidence of OM diagnosed in the UK primary care setting.
2) To determine the annual incidence of OM diagnosed in primary care stratified by age and gender.
3) To estimate antibiotic prescribing patterns associated with OM.
4) To estimate antibiotic prescribing patterns associated with OM by age and gender.

### 2.5.3.2 Methods

#### 2.5.3.2.1 Study design

A retrospective cohort study was conducted on data between 2002 and 2010 taken from IMS Disease Analyzer (IMS DA) database. Information held on the database includes patient demographics, indications for treatment and prescription details.

Prescribed drugs are coded based on the Anatomical Therapeutic Chemical (ATC) classification (European Pharmaceutical Market Research Association, 2010) (Appendix 4) and medical diagnoses are coded to Read Code (Appendix 5). Ethical approval for this study strand was obtained from the Independent Scientific and Ethical Advisory Committee (ISEAC) and the summary of their comments are included (Appendix 3).

#### 2.5.3.2.2 Study population

**Inclusion criteria**

Children and adolescents aged 0 to 18 years with OM diagnoses between the 1$^{st}$ of January 2002 and the 31$^{st}$ of December 2010 were identified. For inclusion, all patients needed to be registered with a GP who contributed data to the database for at least 6 months (except children less than 6 month of age). Children temporarily registered with their general practice were excluded to avoid duplication of event data and inaccurate child-year calculations, as these children were most likely registered in another practice.

#### 2.5.3.2.3 Data extraction

Cases of OM were identified by searching the entire collection of electronic records of all children and adolescents in the IMS DA data over the study period for those who had diagnostic codes relating to a diagnosis of OM or middle ear infection with read-code. All codes were validated by Professor Mike Sharland.

Antibiotic prescriptions for OM were identified by searching the IMS DA database for all therapy codes corresponding to antibiotics (i.e. drugs listed under the ATC therapeutic main group J01, antibacterial for systemic use). Drugs for treatment of tuberculosis and leprosy were not included. Patient ages were recorded at the date the antibiotic was prescribed.

#### 2.5.3.2.4 Data analysis

OM is an acute infection that can recur and if not treated properly it may develop into OME and/or CSOM from the same episode. In instances of repeat infection antibiotic resistance may develop, so a child may have to receive treatment more than once for the same episode. Therefore, each episode of more than 30 days due to OM and each antibiotic prescription counted as a new infection and a new prescription. This thirty day screening period was set on the advice of Professor Mike Sharland.

In addition, as OM is more commonly observed in the younger age group, data were split into the following age ranges in order to investigate the incidence of OM by age (<2 year old, 2-5 years old, 6-10 years old, 11-15 years old and 16-18 years old). Age and calendar year-specific incidence rates were calculated for OM diagnosis and antibiotic prescribing for OM, per 1,000 child-years at risk in the IMS-DA. The incidence rate of OM diagnosis/ antibiotic prescriptions for OM was defined as the number of the disease/ treatment event divided by the total number of child-years at risk of OM in a paediatric population (aged 0 to 18 years) in a particular year.

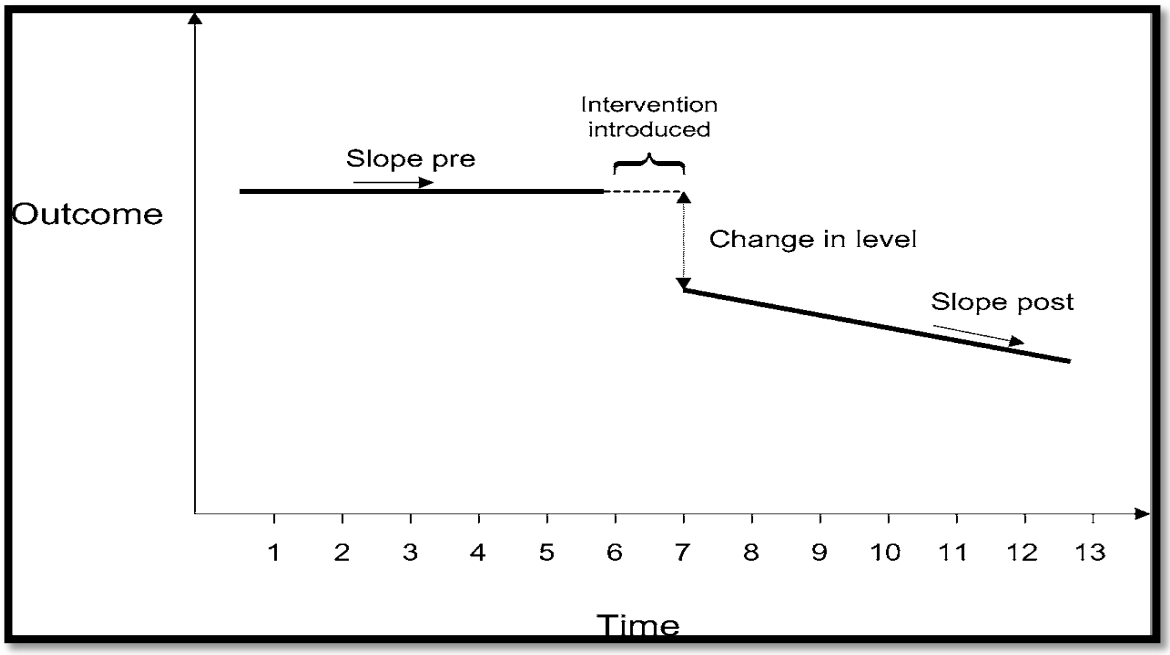
Ninety-five percent confidence intervals were generated using Poisson approximation. Additionally, a chi-square test (Cochran-Armitage test for trend) was used to examine the yearly trend of incidence rate of OM, as well as, the antibiotic prescribing for OM. A *P-value* of less than 0.05 was considered statistically significant.

To evaluate the effectiveness of PCV7 for pneumococcal diseases an Interrupted Time Series (ITS) design was used. It is an experimental method used to determine the impact of a complex intervention. It is a set of data which is used to study change in a variable over time that consists of a time-ordered sequences of measurements.

Data are collected at multiple instances over time, before and after an intervention, to detect whether the intervention has an effect significantly greater than the underlying secular trend. Also time series enable the timing and the nature of change to be examined (Matowe *et al.,* 2003). For more details see Figure 2.1.

In this study, the causal hypothesis was that observations made after the introduction of the vaccine will have a different level and/or slope as compared with previously. (Grijalva *et al*. (2007) used this method of analysis in their studies.)

**Figure 2.1: The effect sizes estimated by time series regression analysis of an interrupted time series design.** (Taken from Ramsay *et. al.,* 2003)




Interrupted Time Series analysis using segmented regression modeling was employed to examine the impact of PCV7 on OM incidence before and after its introduction and to control for seasonal effects, by comparing the quarterly change of OM episode in children aged less than 2 years old before and after the introduction of PCV7. Data from IMS DA was extracted. PCV7 was introduced to UK practice in September 2006, so the study period was defined as pre-PCV7 (2003-2005) and post-PCV7 (2007-2009). The year 2006 was defined as a transitional period.

Slope change is a comparison of the pre-PCV7 and post-PCV7 when the quarterly OM episode level is plotted over time in months. All data management and analysis was carried out using Stata version 11.0 (Statistical Software: Release 11.0 College Station, TX).

### 2.5.4 Study strand FOUR – Pneumonia Cohort Study

#### 2.5.4.1 Aims and objectives

Even though a reduction in pneumonia incidence and antibiotic prescribing for pneumonia has been demonstrated in other countries, it still remains unclear if there have been any changes in pneumonia management in UK General Practice since the introduction of PCV7.

**The aim of this study strand is:**

To describe the incidence rates of pneumonia and antibiotic prescribing in children and adolescents before and after the introduction of PCV7 between 2002 and 2010 in the UK primary care stratified by age and gender.

**Objectives:**

- To determine the annual incidence of pneumonia diagnosed in the primary care setting.
- To determine the annual incidence of pneumonia diagnosed in primary care stratified by age and gender.
- To describe antibiotic prescribing patterns associated with pneumonia.

- To describe antibiotic prescribing patterns associated with pneumonia by age and gender.

### 2.5.4.2 Methods

#### 2.5.4.2 1 Study design

A retrospective cohort study was conducted using The Health Improvement Network (THIN) database. Information held on the database includes patient demographics, indications for treatment and prescription details. Descriptive analysis will be conducted for patient demographics and prescription data.

With THIN database, antibiotics are listed under the BNF code (antibacterial for systemic use), based on data from the MULTILEX classification, which will be utilised in the data analysis (appendix 6). Diagnoses of pneumonia will be classified based on Read Code (refer to appendix 7). Ethical approval for this study was obtained from the Scientific Review Committee (SRC). A summary of their comments is included at Appendix 8.

#### 2.5.4.2.2 Study population

Children and adolescents aged 0 to 15 years with pneumonia diagnoses between the 1st of January 2002 and the 31st of December 2010 were identified. For inclusion, all patients needed to be registered with a GP who contributed data to the database for at least 6 months.

#### 2.5.4.2.3 Data extraction

Pneumonia was identified by searching the entire collection of electronic records of all children in THIN database over the study period for those who had diagnostic codes relating to a diagnosis of pneumonia with a respective read-code. Over the study period all codes were validated by one of our clinical team (Prof. Mike Sharland).

Antibiotic prescriptions for pneumonia were identified by searching THIN database for all therapy codes corresponding to antibiotics (i.e. drugs listed under BNF code for antibacterial for systemic use respectively). Patient ages were recorded at the date the antibiotic was prescribed.

#### 2.5.4.2.4 Data analysis

As long as pneumonia is one of the most common infectious diseases in young children and as antibiotics are prescribed when pneumonia is suspected, resistance by the bacteria may occur, so a child may receive antibiotics more than once for the same episode. Therefore, each episode of more than 30 days due to pneumonia and each antibiotic prescription were counted as a new infection and a new prescription. The thirty days screening period was set on the advice of one of our clinical team based on his clinical expertise (Prof. Mike Sharland).

As pneumonia is more commonly observed in younger age group, data were split into the following age ranges in order to investigate the incidence of pneumonia stratified by age (<2 year old, 2-5 years old, 6-10 years old and 11-15 years old).

In the THIN database, the incidence rate of pneumonia was defined as the number of each pneumonia episodes divided by the person year in the paediatric population (aged 0 to 15 years) in a particular year. The incidence rate of prescribing was defined as the number of antibiotic prescriptions divided by the person-year paediatric population (aged 0 to 15 years) in a particular year.

The incidence rate was calculated using Poisson distribution with a 95% confidence interval (CI). A chi-square test was used to compare the prescribing trend before and after the introduction of PCV7. A *P-value* of less than 0.05 was considered statistically significant. Data manipulation and analysis was conducted using STATA/SE 11.0 for Windows (Statistical Software: Release 9.1. College Station, TX, USA).

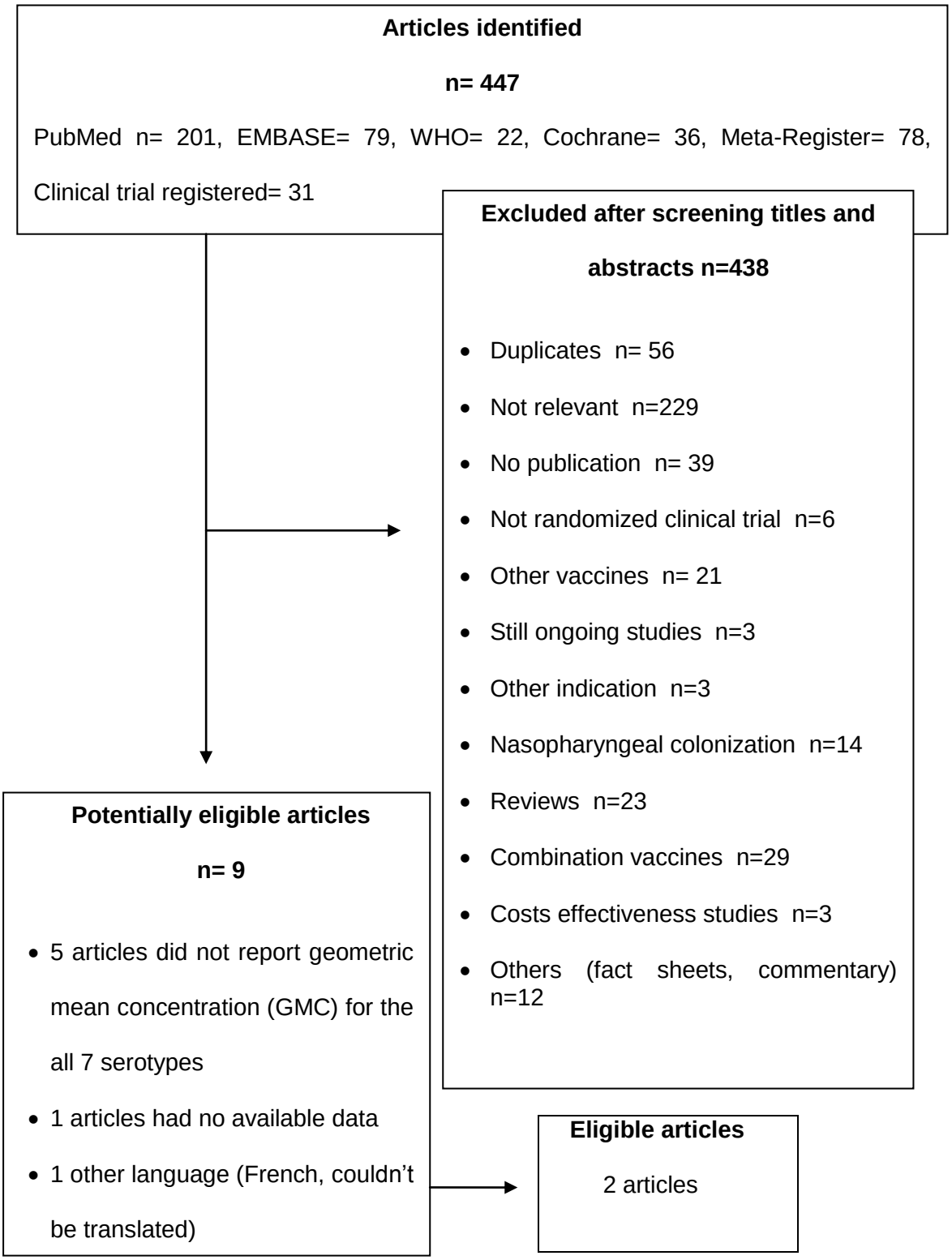
## CHAPTER THREE: SYSTEMATIC REVIEW & META-ANALYSIS

This chapter addresses the results of the systematic review and meta-analysis that were performed for this study in order to investigate the efficacy of the vaccine and the respective adverse events caused by the vaccine in children aged 0-10 years.

### 3.1 RESULTS

Based on the initial search strategies (discussed in Chapter 2), 447 articles were identified. The title, abstract or the full text article were then reviewed for relevance, and 438 articles were excluded for various reasons (refer to Figure 3.1). Of these, 9 articles were deemed relevant for scrutiny of the full text article. However, at this point 7 studies were excluded; with 2 studies remaining which were included as they met the inclusion criteria (refer to Table 3.1). Meta-analysis could be performed on the two studies and all calculations were performed according to ITT.

**Figure 3.1: Identification and selection of eligible trials for inclusion in the systematic review**



The reported characteristics and main findings from the 2 eligible individual studies are described in Table 3.1.

**Table 3.1: Data extracted from the included studies**

| | |
|---|---|
| Author | **Cheng Li, R *et al*** |
| Year | 2008 |
| Location | China |
| Objective | Primary objective was to evaluate the safety of PCV7 versus control group given at 3,4, and 5 months<br><br>Secondary objective to evaluate the immunogenicity of PCV7 given concurrently with DTaP versus control |
| Study Design | Open label, controlled, randomized study |
| Population | 800 previously unimmunized Chinese infants of 3-4 month of age |
| Outcome | Safety assessment: child is monitored for 30 min after injection, local and systematic side effects are looked at.<br><br>Parent to fill out diary for 4 days after vaccination.<br><br>To decide immunogenicity, 3 ml blood retrieved from 55 infants from every group. |
| Results | After immunisation, increase in GMC in groups 1 and 2 but decline in group 3.<br><br>**Local reactions**: Erythema , induration/swelling and tenderness.<br><br>**Systematic**: fever, irritability, decrease appetite, disrupted sleep, drowsiness, vomiting and diarrhea |
| Conclusion | Included in meta-analysis |

| | |
|---|---|
| Author | **Black *et al*.** |
| Year | 2000 |
| Location | USA |
| Objective | Primary objective is to evaluate the efficacy of PCV7 against any invasive disease caused by vaccine serotype.<br><br>Secondary objective is to evaluate the efficacy of PCV7 against clinical OM visits and episodes |
| Study Design | Randomized double-blind trail |
| Population | 37,868 infants |
| Outcome | AOM episode |
| Results | No evidence of any increase of disease caused by non-vaccine serotype.<br><br>Local reactions: redness, swelling and tenderness.<br><br>Systematic reaction: fever |
| Conclusion | Included in meta-analysis |

**The Meta-Analysis**

Within the meta-analysis of the 2 included papers, the local Adverse Drug Reactions (ADRs) used in the analysis were tenderness, redness and swelling. Tenderness was defined as tenderness felt by injection site which did not interfere with leg movement (injection given in hip). Redness was defined as a red area < 2.5 cm around the injection site and swelling was defined as a swelling < 2.5 cm. The systematic ADR was fever of >38 °C. Forest Plots were generated for each ADR.

**What is a "Forest Plot"?**

Results of meta-analyses are usually reported using forest plots. A forest plot is a graphical display of the included studies' results. They were first used in 1970.

It consists of two columns: one displays the study names (left hand column) and the other displays the corresponding mean for the measure of effect (e.g. an odds ratio) and its confidence interval. The point estimate is displayed as a square whose size is proportional to the weight assigned to the study. The confidence interval is displayed as a horizontal line extending on both sides of the mean. In case of using an odds ratio as a measure of effect, the plot will have a natural logarithmic scale to enable presenting the confidence interval symmetrically around the mean. This ensures that values greater than 1 are not over-emphasized. The combined measure of effect obtained from the meta-analysis is represented on the plot as a diamond, the lateral points of which indicate the confidence interval around the mean estimate.

The forest plot also has a vertical line corresponding to “no effect” (i.e. no difference in effect between the study arms). If the horizontal line representing the confidence interval for any individual study crosses this line, this demonstrates that the effect size does not differ from no effect, at the given level of confidence, for the individual study (i.e no difference in effect between the study arms). The same applies to the combined measure of effect representing the meta-analysis result: if the point of the diamond overlaps the line of no effect, the overall meta-analysis result cannot be said to differ from no effect at the given level of confidence (Schünemann *et al.,* 2008; Schriger *et al.,* 2010).

**Local ADRs**

In this study, forest plots have been generated for each ADR after the 3 consecutive vaccine doses (see figures 1-12).

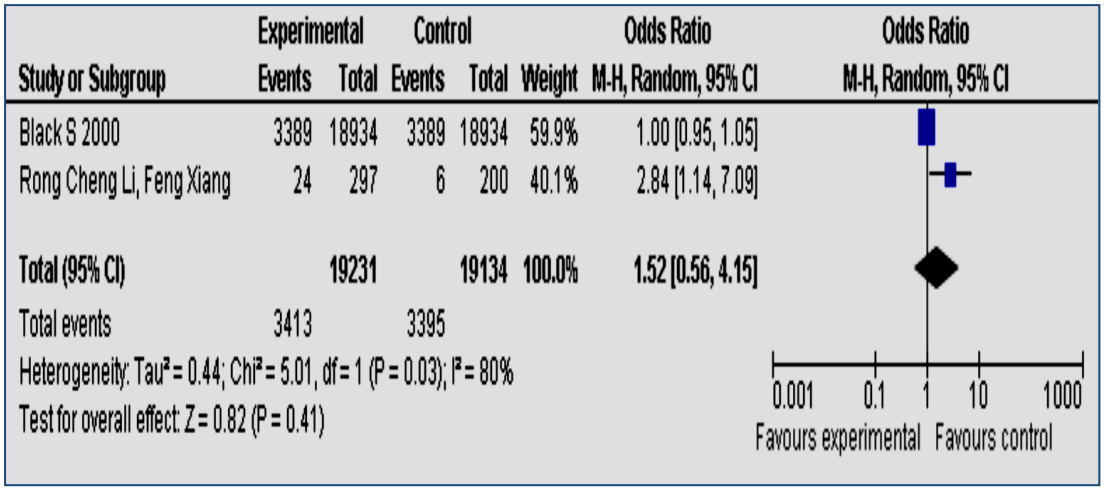
The forest plots present the heterogeneity between the studies and the precision of each study individually as well as in comparison with one another.

The following figures show the forest plots of meta-analysis conducted on the two included studies. Each study is represented by a block, which is proportional to mean precision of the treatment in each study.

The 95 % confidence interval corresponds to the horizontal lines and the width of the centre of the diamond shape represents the average treatment effect across the two studies.

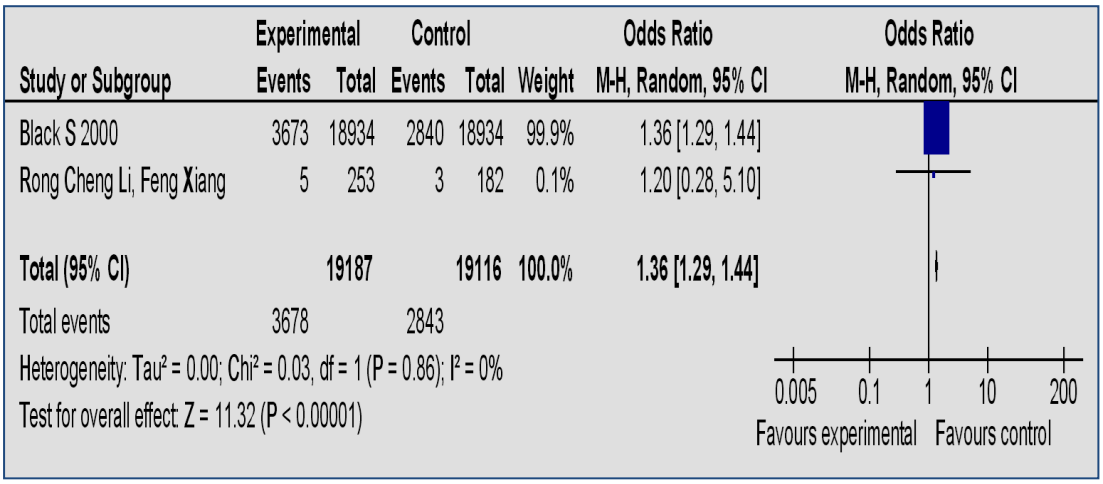
**Tenderness**

**Fig 1: Tenderness post dose1**




The first forest plot (Fig 1) describes the tenderness after first dose of PCV7. This includes a total of 19231 subjects with and odds ratio 1.52 [95% CI; 0.56, 4.15]. The *p* value of the Chi-squared test has evidence of statistical variability between the two studies, with the value showing considerable heterogeneity in the outcome variable ($I^2$=80%).

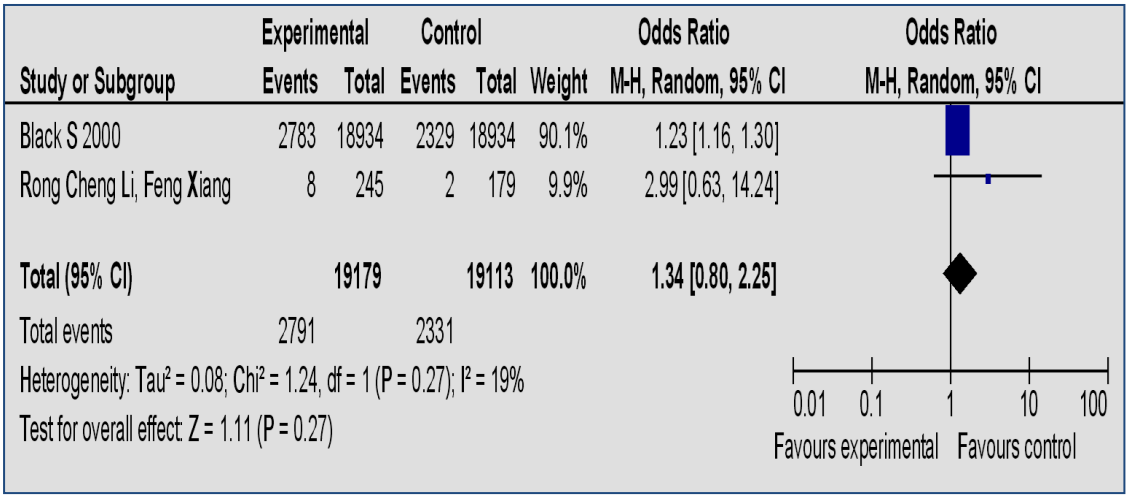
**Fig 2: Tenderness post dose 2**




Forest plot in this figure (Fig 2) has a total of 19 187 subjects and describes tenderness after the second dose of PCV7. The odds ratio in this plot is 1.36 [95% CI; 1.29, 1.44].

It also shows that the *p* value of the Chi-squared test has no evidence of statistical variability between the two studies, with the value showing no considerable heterogeneity in the outcome variable ($I^2$=0%).

**Fig 3: Tenderness post dose 3**



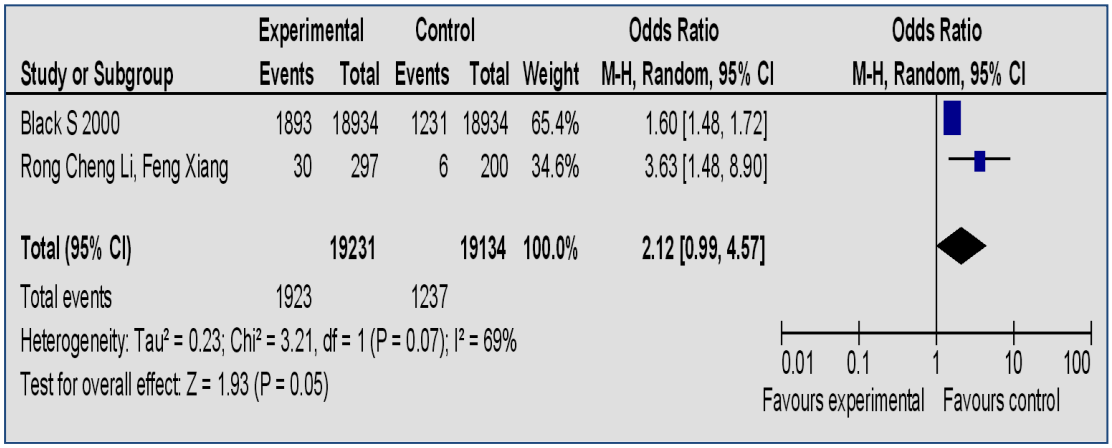

This figure describes tenderness after the third dose of PCV7. This includes a total of 19179 subjects with and odds ratio 1.34 [95% CI; 0.80, 2.25].

The *p* value of the Chi-squared test has no evidence of statistical variability between the two studies, with the value showing no considerable heterogeneity in the outcome variable ($I^2$=19%).

The following figures (4, 5 and 6) represent the forest plots for redness after first, second and third dose of PCV7 respectively.

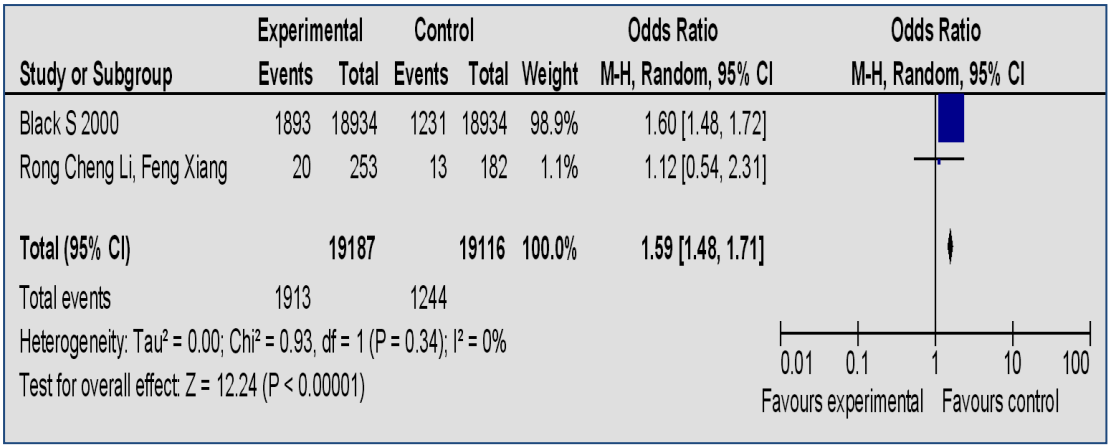
**Redness**

**Fig 4: Redness post dose 1**



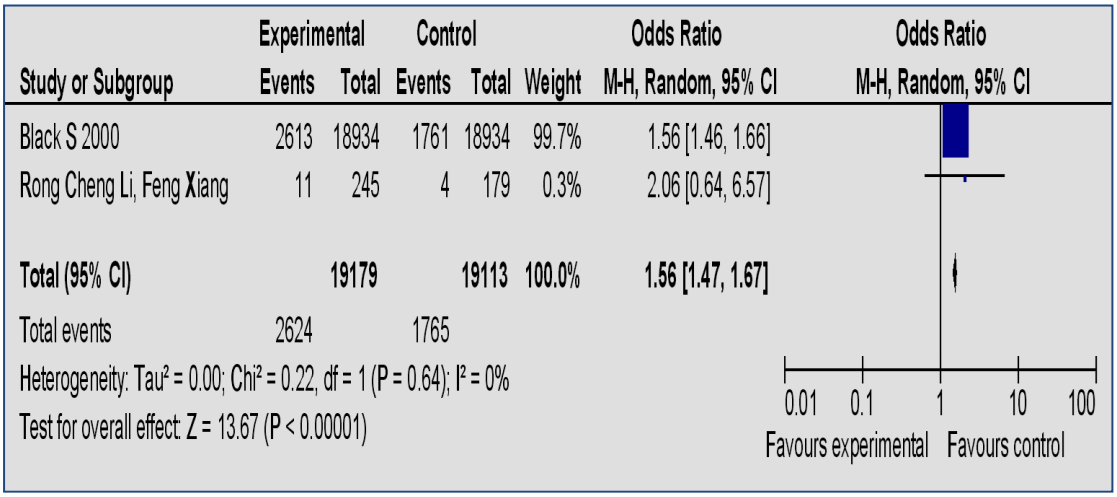

After the first dose, the total number of subjects is 19231; odds ratio 2.12[95% CI; 0.99, 4.57]. The Forest plot figure displays that the *p* value of the Chi-squared test shows evidence of statistical variability between the two studies, with the value showing considerable heterogeneity in the outcome variable (69%).

**Fig 5: Redness post dose 2**




After second dose, the total number of subjects was 19187; odds ratio 1.59 [95% CI; 1.48, 1.71], The Forest plot figure shows that the *p* value of the Chi-squared test has no evidence of statistical variability between the two studies, with the value showing no considerable heterogeneity in the outcome variable ($I^2$=0%).

**Fig 6: Redness post dose 3**

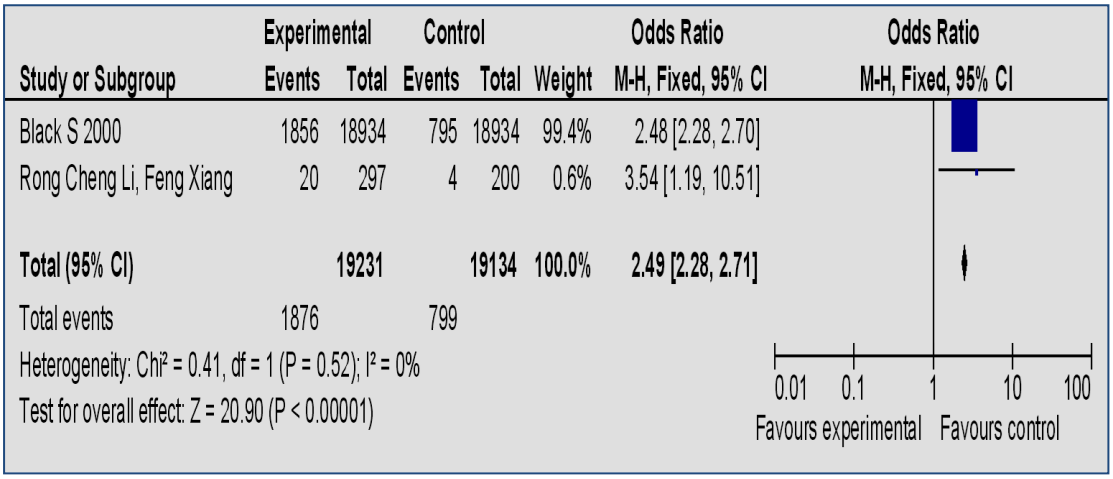



After the third does, the total number of subjects is 19179; odds ratio 1.56 [95% CI; 1.47, 1.67] .The Forest plot figure shows that the *p* value of the Chi-squared test has no evidence of statistical variability between the two studies, with the value showing no considerable heterogeneity in the outcome variable ($I^2$=0%).

Figure 7,8 & 9 represent the forest plots for swelling after the first, second and third dose of PCV7 respectively.

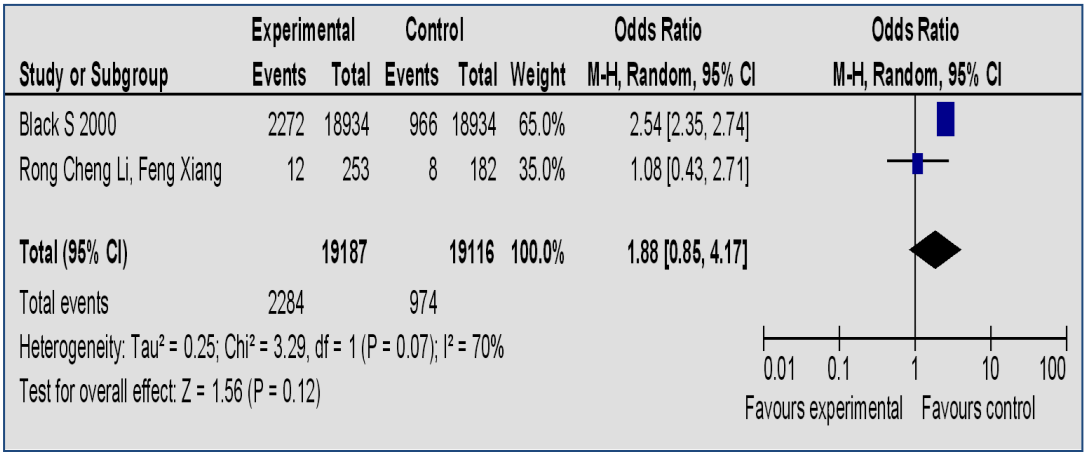
**Swelling**

**Fig 7: Swelling post dose 1**




After the first dose, total number of subject 19231 and odds ratio is 2.49 [95% CI; 2.28, 2.71]. The Forest plot figure shows that the *p* value of the Chi-squared test has no evidence of statistical variability between the two studies, with the value showing no considerable heterogeneity in the outcome variable ($I^2$=0%).

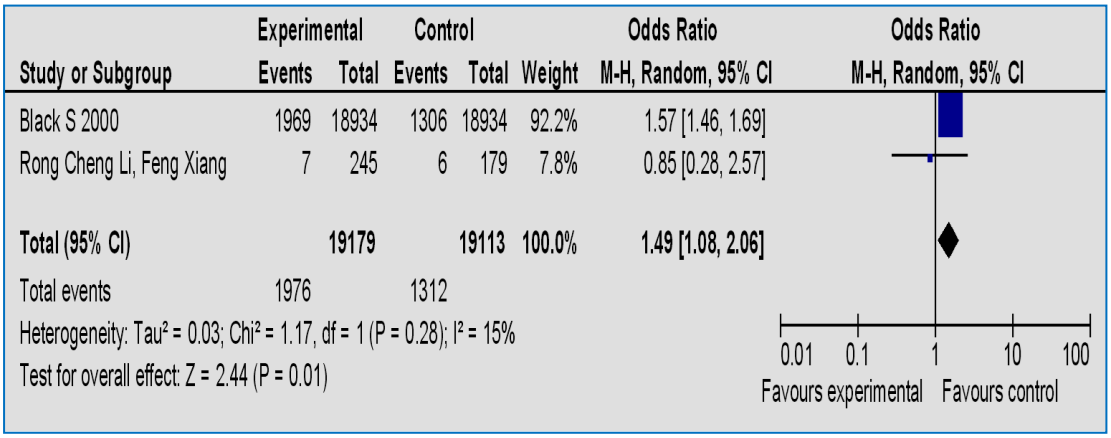
**Fig 8: Swelling post dose 2**




After the second dose, the total number of subjects is 19187 and odds ratio is 1.88 [95% CI; 0.85, 4.17].

The Forest plot figure shows that the *p* value of the Chi-squared test has no evidence of statistical variability between the two studies, with the value showing no considerable heterogeneity in the outcome variable ($I^2$=70%).

**Fig 9: Swelling post dose 3**

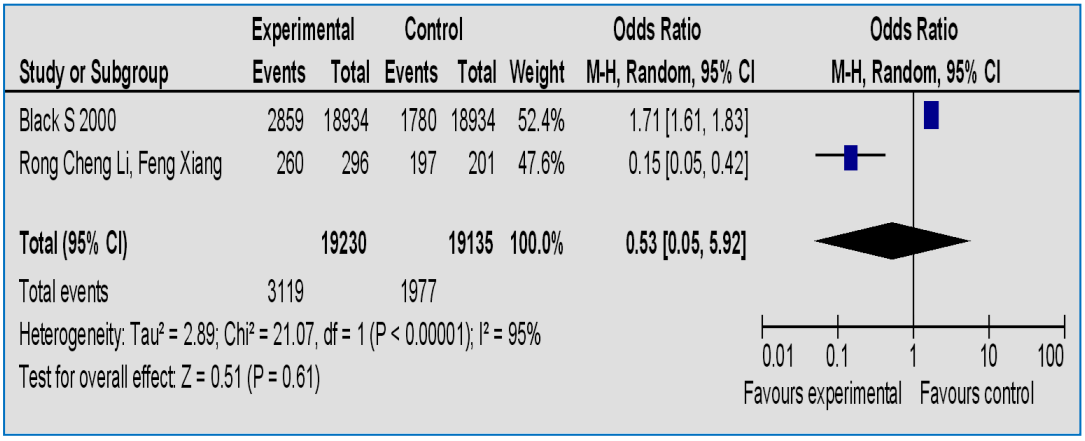



After the third dose the total number of subjects is 19179 and the odds ratio is 1.49 [95% CI; 1.08, 2.06]. The Forest plot figure shows that the *p* value of the Chi-squared test has no evidence of statistical variability between the two studies, with the value showing no considerable heterogeneity in the outcome variable ($I^2$=15%).

Figure 10, 11 & 12 represent the forest plot for the systematic ADR (fever) following the first, second and third dose of PCV7 respectively.

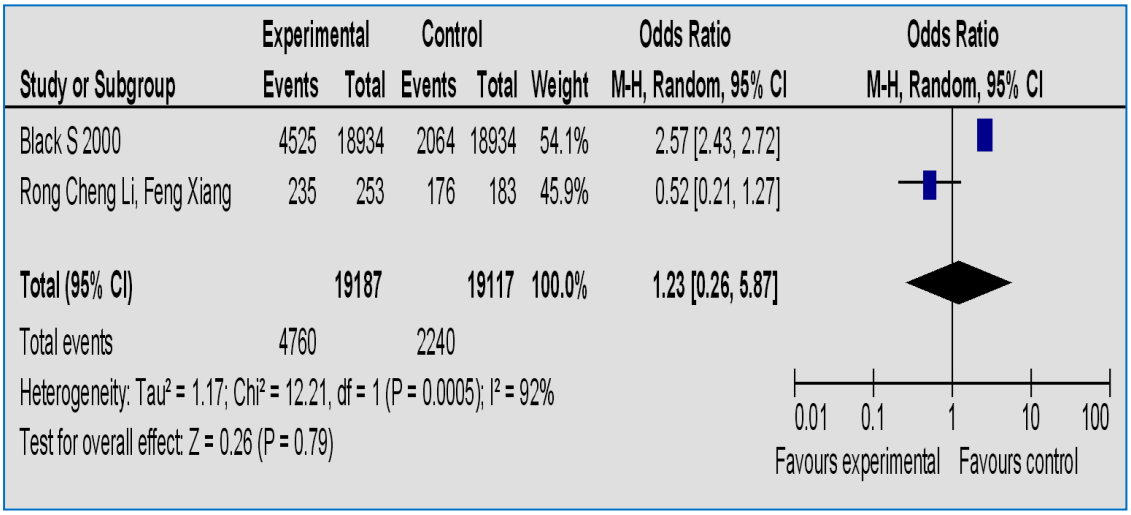
**Systematic ADR (Fever >38 °C)**

**Fig 10: Fever post dose 1**



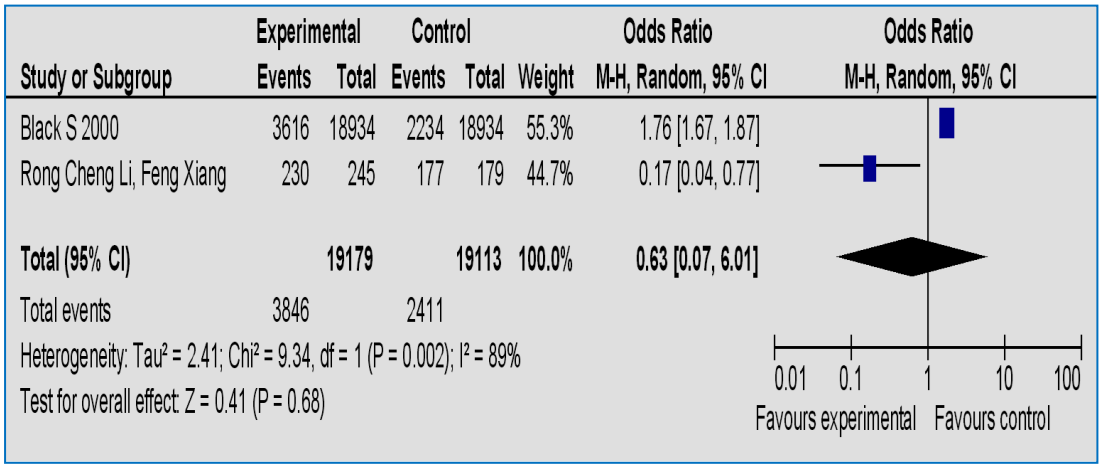

The total number subjects is 19230 and odds ratio is 0.53 [95% CI; 0.05, 5.92] after the first dose. The Forest plot figure shows that the *p* value of the Chi-squared test has evidence of statistical variability between the two studies, with the value showing considerable heterogeneity in the outcome variable ($I^2$=95%).

**Fig 11: Fever post dose 2**



After the second dose the numbers were 19187; 1.23 [95% CI; 0.26, 5.87]. The Forest plot figure shows that the *p* value of the Chi-squared test has evidence of statistical variability between the two studies, with the value showing considerable heterogeneity in the outcome variable ($I^2$=92%).

**Fig 12: Fever post dose 3**:




After the third dose the numbers where 19179; 0.63 [95% CI; 0.07, 6.01]. The Forest plot figure shows that the *p* value of the Chi-squared test has evidence of statistical variability between the two studies, with the value showing considerable heterogeneity in the outcome variable ($I^2$=89%).

### 3.2 DISCUSSION

The aim of this systematic review was to examine the efficacy of the heptavalent pneumococcal conjugate vaccine (PCV7) as a primary outcome. The secondary outcome was to investigate the ADRs related to PCV7. This was a systematic review of controlled clinical trials i.e., PCV7 groups were compared to a control group. The control group in the two included studies received a meningococcal conjugate vaccine.

As for the efficacy of the vaccine, this could unfortunately not be ascertained due to the lack of data for the control groups in the two respective studies. Attempts to contact authors have were made but data was not attainable.

It is problematic to evaluate the efficacy of the PCV7 since different methods were used in the included studies. Many articles have investigated the efficacy on the number of infection episodes that PCV7 has prevented compared to unvaccinated groups (control group). Eskola *et al*. (2001) states that the efficacy of PCV7 in preventing Otitis Media was relatively low, reducing cases of any cause by 6% "(95 percent confidence interval, -4 to 16 percent [the negative number indicates a possible increase in the number of episodes]), culture-confirmed pneumococcal episodes by 34 percent (95 percent confidence interval, 21 to 45 percent), and the number of episodes due to the serotypes contained in the vaccine by 57 percent (95 percent confidence interval, 44 to 67 percent). The number of episodes attributed to serotypes that are cross-reactive with those in the vaccine was reduced by 51 percent, whereas the number of episodes due to all other serotypes increased by 33 percent"(Eskola *et al.,* 2001, p 403).

Another way of assessing efficacy is to investigate the immunogenicity the vaccine provides for each serotype, as the incidence of different pneumococcal diseases varies according to the serotype it is caused by. The World Health Organisation has reported that the minimum concentration which is considered immunogenic is 0, 20 – 0, 35 µg/ml for children (Capeding *et al.,* 2008). Thus the levels of geometric mean concentration of an antibody can be another indicator to evaluate the efficacy of PCV7.

In addition, as mentioned earlier, the serotype 19A was the leading cause for invasive pneumococcal diseases in children less than 5 years of age. However, this cannot be evaluated due to the lack of sufficient data in this review.

The meta-analysis was successfully conducted on the ADRs of the vaccine. The ADRs of PCV7 in three doses prior to the booster were assessed. The results clearly demonstrated that the control group had more ADRs than PCV7 vaccinated children, indicating that the PCV7 is well tolerated with no serious ADRs. However due to the few articles included, it is difficult to draw a conclusion on the safety of PCV7 in children.

As for the systemic ADRs (e.g. fever), it is apparent that the PCV7 group (vaccinated children) reported more fever than the control group. This is an expected side-effect of the vaccine; however fever can be very abstract and it is difficult to evaluate the association with PCV7.

It is difficult to analyse the heterogeneity of only two studies; conclusions made cannot be generalised. For the local ADRs, there is a trend in the heterogeneity; there is a clear drop in heterogeneity ($\tau$). For all three ADRs: tenderness, redness and swelling, the $\tau$ is higher in the first dose but drops for the second and three doses. It is evident that there has been some sample attrition in the studies which may contribute to the heterogeneity being similar in the last two doses. The authors did not provide any information to why there was attrition in the studies.

The results for the systematic ADR of fever showed that the heterogeneity varied and was relatively higher than the local ADRs, this has also been seen at different

doses. This may be due to the different sampling and measurement of fever in each individual study.

A quality assessment of two included articles was carried out using the CONSORT statement (Appendix 9). The included articles were considered high quality to carry out the meta-analysis. The results needed for meta-analysis were reported, such as randomisation, allocation, intervention, inclusion criteria and population. There is some concealment of information, which may address the questions of bias, for example the article by Cheng *et al* (2008), did not report the number of patients who dropped out after first dose, as well as the reason for the withdrawal. In addition, both included articles did not report the data for the control group on the serotype specific GMCs which makes it difficult to carry out the comparison for this measurement.

Finally, publication bias could not be examined via a Funnel Plot (a statistical method used to detect publication bias in systematic reviews and meta-analyses, via plotting intervention effect estimates from individual studies against the size of each investigation – Cochrane, 2006), since this analysis needs at least 10 studies.

## 3.3 HYPOTHESIS, AIMS AND OBJECTIVES

Following the literature review and meta-analysis, the study hypothesis, aims and objectives were confirmed as follows:

### 3.3.1 HYPOTHESIS

The incidence rate of pneumococcal diseases and respective antibiotic prescribing post the introduction of the PCV7 in children and adolescents will be lower as compared to the rates observed prior to its introduction.

### 3.3.2 AIMS

To investigate whether the introduction of PCV7 has had an impact on the recorded occurred pneumococcal diseases (OM and Pneumonia) and the volume number of antibiotics prescribed to treat these conditions in children and adolescents.

### 3.3.3 OBJECTIVES

**Primary objective:**

To characterise the annual incidence rates of OM and pneumonia and antibiotic prescribing trends for these diseases in children and adolescents, between 2002 and 2010 in the UK primary care setting before and after the introduction of PCV7.

**Secondary objectives:**

1) To compare the percentage of children recorded as receiving PCV7 in the IMS DA with the national statistical data (COVER).
2) To validate the IMS DA immunisation records in children aged 0-2 years through questionnaires sent to GP.
3) To investigate the association between the vaccine consumption and the incidence of OM in children aged 0- 2 years old by using individual patient-analyses.

## CHAPTER FOUR: VALIDATION STUDY

This chapter presents the findings of the validation study performed to investigate PCV7 immunisation recording in children aged 0-2 years in general practice. This study strand compared the percentage of immunisation recording in general practice (recorded in IMS DA) with COVER data. To validate the study, firstly the percentage of PCV7 vaccinated children born in 2008, in the IMS DA database was calculated and compared with the COVER data. Secondly, children of the same age (0-2years) without a PCV7 record in the primary care setting, in IMS DA database, were validated through a questionnaire sent to their general practitioners.

### 4.1 RESULTS

In the IMS DA data, 12,740 vaccination records of PCV7 for children born in 2008 were identified, 2,497 children had no vaccination records. From those children without PCV7 vaccination record 173 children (7%) from 53 practices were randomly selected (the estimated overall number of questionnaires required for this study, chapter 2). The GP questionnaire was then sent to those practices. There were 2 practices unable to return the questionnaires as one practice had stopped contributing their data to IMS DA, and the other practice encountered a technical problem. A total of 117 questionnaires were returned (68%; 117/173) (Chart 4.1).

**Chart 4.1: Questionnaire Responses**

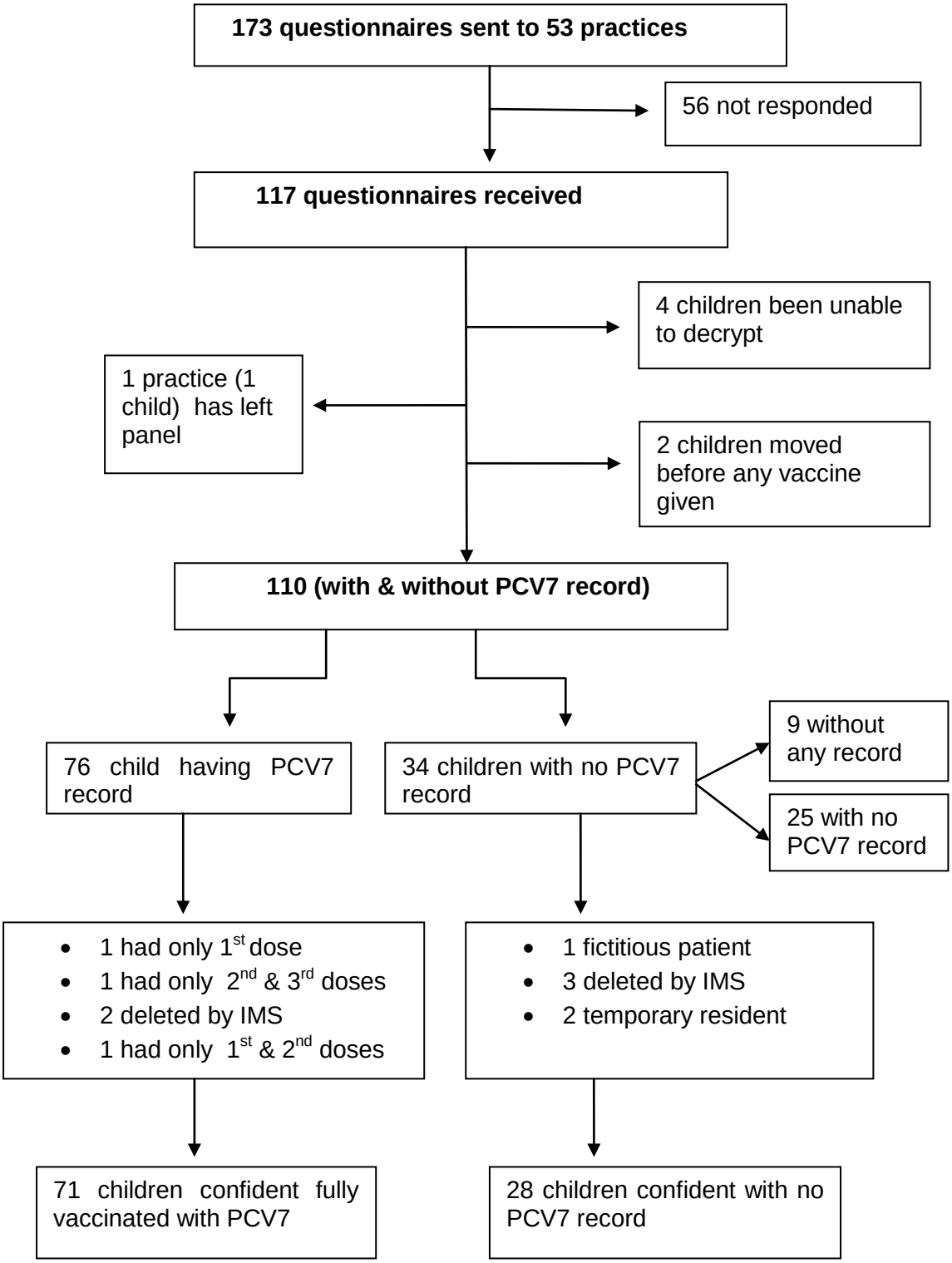


Table 4.1 displays the vaccination records of the 173 children by region. One hundred percent of children in Yorkshire region, 87.5% of children in Mersey region and 73% of children in North West Thames region had been vaccinated yet they had no vaccine records in the data. In contrast, in Wessex, the result shows that 78% of the children were truly un-vaccinated.

**Table 4.1: Vaccination records by region**

| Region | L P | CMBV | NPR | NGR | UD | Vac. | Unvac. | Total |
|---|---|---|---|---|---|---|---|---|
| East Anglian | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 2 |
| North Western | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 4 |
| Mersey | 0 | 0 | 0 | 2 | 0 | 21 | 3 | 26 |
| Northern | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 3 |
| Oxford | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 3 |
| North East Thames | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 |
| Wales | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| South Western | 0 | 0 | 0 | 17 | 2 | 5 | 5 | 29 |
| South West Thames | 0 | 0 | 2 | 9 | 1 | 4 | 4 | 20 |
| South East Thames | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Trent | 0 | 0 | 0 | 7 | 0 | 1 | 0 | 8 |
| Wessex | 0 | 0 | 0 | 1 | 0 | 2 | 7 | 10 |
| West Midlands | 1 | 2 | 0 | 9 | 1 | 8 | 1 | 22 |
| Yorkshire | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 8 |
| North West Thames | 0 | 0 | 7 | 1 | 0 | 24 | 2 | 34 |
| Overall | 1 | 2 | 9 | 56 | 4 | 76 | 25 | 173 |

**PL= Left Practice**
**CMBV= Children Moved Before Vaccination**
**NPR= No Patient Record, assumed not vaccinated**
**NGR= No GP reply**
**UD= IMS unable to decrypt**
**Vac. = Vaccinated with PCV7**
**Unvac. =Unvaccinated with PCV7, not included in other category**

## 4.2 DISCUSSION

Overall, the percentage of PCV7 vaccinated children in the IMS DA database is slightly lower as compared to that in the COVER data (83% and 90%-95%). However, out of the 117 children with no PCV7 record in the IMS selected data, 65% of these had in fact received the PCV7 but this had not been recorded in the IMS data set. This indicates that, the administration rate of PCV7 was higher than that reported by IMS. As can be seen from the table 4.2, most geographical regions need to improve their practices' vaccination records.

According to the percentage of the vaccination records in the data, there is a potential under-recording of the immunisation history of the children in the IMS database. This could be due to the fact that, healthcare professionals other than GPs can also administer the vaccine to children, and these professionals may not have direct access to the patients' electronic record. In addition, where the vaccine is given (irrespective of who it is given by) GPs may not always record the vaccination of the child as The Quality and Outcomes Framework (QOF) scheme does not include vaccination as an indicator (Dixon *et al.,* 2011).

There is therefore reason to conclude that health authorities and general practices need to develop strategies to improve their computerised vaccination records. One way of achieving this could be by assigning more clinicians read/write access to primary care IT systems and records. If all relevant health professionals were to have the facility to record their patients' immunisations, organisations like IMS would be able to offer more reliable databases to investigate the impact of vaccines on the incidence of related conditions.

This topic is considered further in chapter 7 of this thesis. But more immediately the evaluation reported here has established that individual patient-level data analyses based on IMS data cannot reliably be employed to investigate the association between the incidence of OM and PCV7 usage, due to the under-recording of childhood immunisation in current NHS GP records. A cohort study based design using Interrupted Time Series techniques was therefore employed in the work described in the next chapter. (See also chapter 2 for the underpinning methodology used).

### 4.3 CONCLUSION

This validation study has shown that it is not appropriate to use the recorded IMS patient-level data to analyse the effectiveness of PCV7. A cohort study based design using Interrupted Time Series techniques is the appropriate methodology.

# CHAPTER FIVE: THE IMPACT OF PCV7 ON THE INCIDENCE OF OM AND ANTIBIOTIC PRESCRIBING FOR OM IN CHILDREN AND ADOLESCENTS BETWEEN 2002 AND 2010

This chapter presents the results of the study strand that investigated the incidence rates of OM and antibiotic prescribing patterns in children and adolescents before and after the introduction of PCV7 between 2002 and 2010 in the UK primary care setting stratified by age and gender. As described in chapter 2 a retrospective cohort study was conducted on data between 2002 and 2010 taken from IMS Disease Analyzer (IMS DA) database.

## 5.1 RESULTS

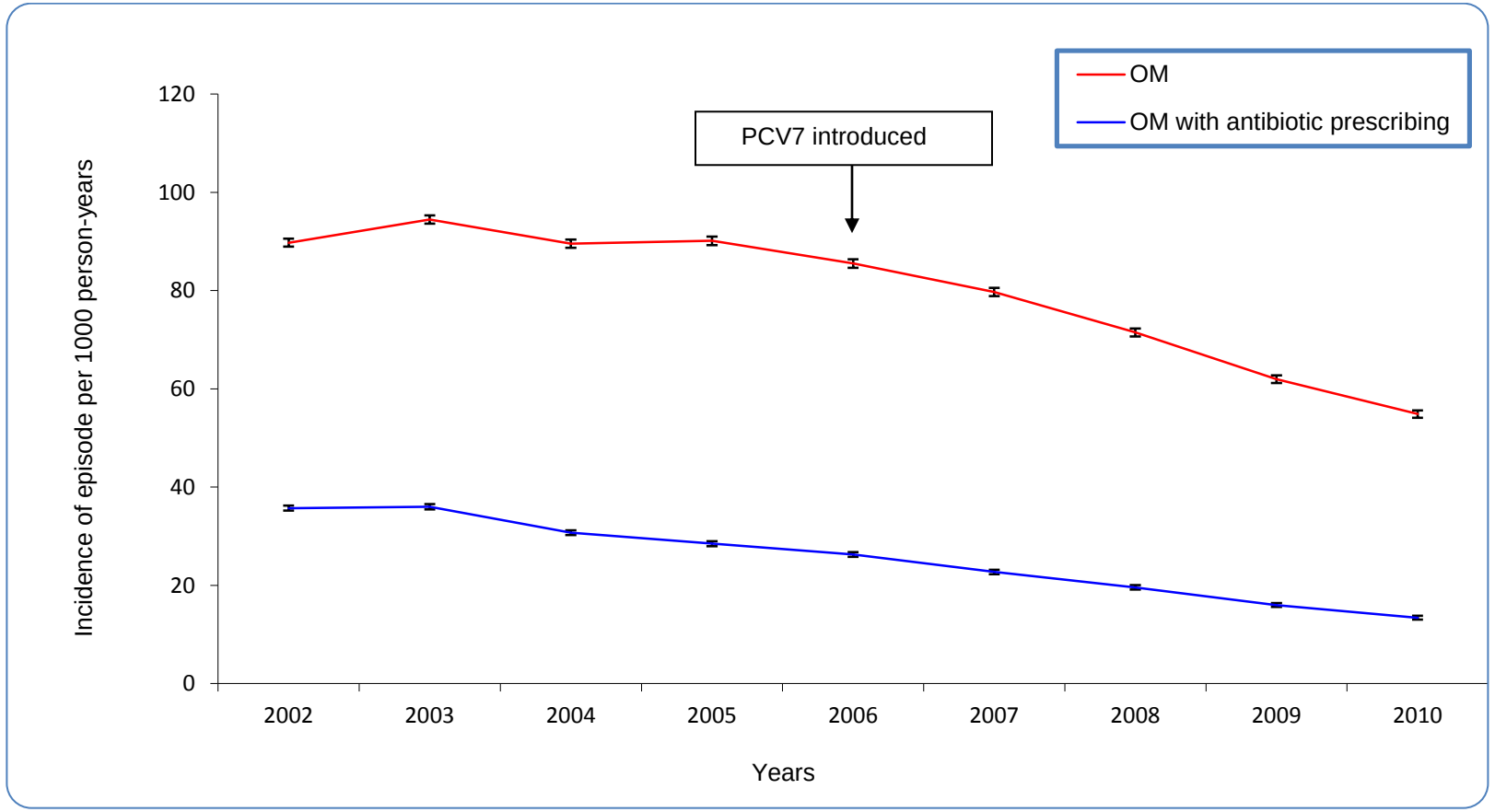
There were 799,126 (49% female; n=395,363) children and adolescents aged 0 to 18 years in the IMS DA contributing 4,020,777 person-years between January 2002 and December 2010. Of these, a total of 151,599 (19%; 151,599/799,126) had a diagnosis of OM. Half of them were female (51%; 77,102/151,599). Table 5.1, shows the demographic of children diagnosed with OM between 2002 and 2010.

Figure 5.1 shows that the number of OM episodes gradually declined over the years in both boys and girls. Amongst those children with an OM diagnosis, approximately 40% (n=59,950; 59,950/151,599) of them had received an antibiotic prescription. Overall, the incidence of OM episodes significantly decreased by 36% from 85.5 per1000 person-years (95% CI: 84.6-86.4) in 2006 to 54.9 per1000 person-years (95% CI: 54.1-55.6) in 2010 ($P<0.05$). A similar trend was seen in the incidence of antibiotic prescribing for OM. It also significantly decreased between 2006 and 2010, from 26.3/1000 person-years (95% CI: 25.8-26.8) to 13.4/1000 person-years (95% CI: 13.0-13.8) respectively ($P<0.05$). This represented a standardised decline of 49%.

**Table 5.1: Demographic of children and adolescents diagnosed with OM, aged 0-18 years in IMS DA, 2002-2010.**

| Year | Boys | | | Girls | | |
|---|---|---|---|---|---|---|
| | Number of patients | Number of episodes | Person-years | Number of patients | Number of episodes | Person-years |
| 2002 | 17,454 | 23,248 | 263777.9 | 17,749 | 23,247 | 254243 |
| 2003 | 17,930 | 24,041 | 258312.5 | 18,357 | 23,868 | 248746.9 |
| 2004 | 15,940 | 21,283 | 244468.2 | 16,505 | 21,657 | 235088.5 |
| 2005 | 15,197 | 20,399 | 233251.9 | 15,873 | 20,799 | 223886.7 |
| 2006 | 14,326 | 18,817 | 226924.2 | 14,930 | 19,225 | 218008.5 |
| 2007 | 12,669 | 16,614 | 219137 | 13,722 | 17,620 | 210379.6 |
| 2008 | 11,089 | 14,499 | 211939.1 | 11,767 | 15,175 | 203246.9 |
| 2009 | 9,228 | 12,047 | 201208.5 | 9,635 | 12,359 | 192740.3 |
| 2010 | 7,819 | 10,087 | 191773.4 | 8,253 | 10,514 | 183644.6 |

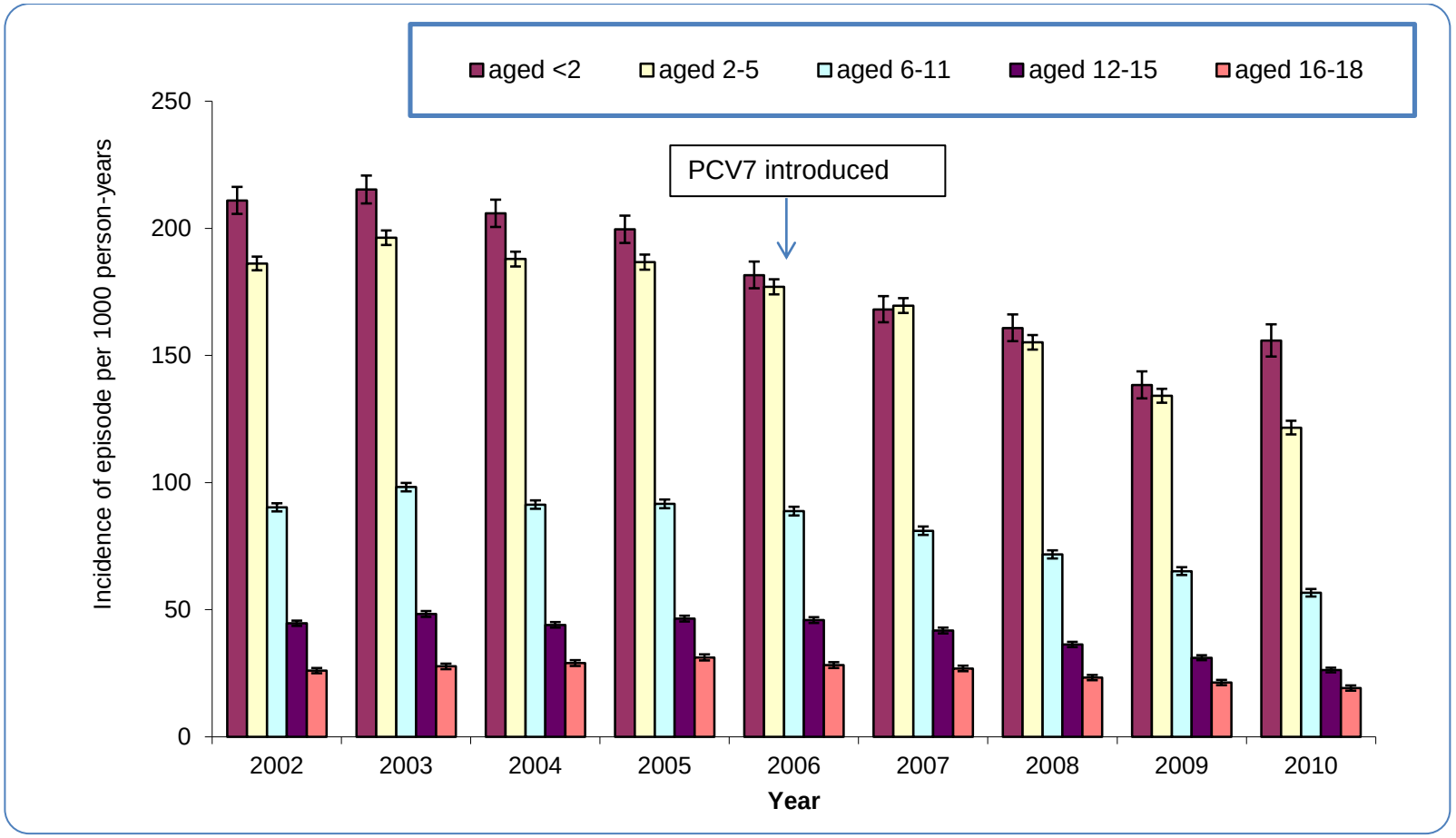
**Figure 5.1: Incidence of OM diagnosis and antibiotic episodes for the treatment of OM in children and adolescents aged 0-18 years, by year, derived from IMS DA**



Of the included children with OM episodes, diagnosis varied between each age group (Fig. 5.2). From 2002 onwards and up to the end of the study period, the incidence of OM reduced with age. The lowest recorded incidence was in adolescents/young adults aged 16-18 years. The highest incidence was in children aged less than 2 years, although this group experienced a 15% decline in the rate of OM diagnoses from 181.6/1000 person-year (CI: 176.4-186.9) to 155.8/1000 person-year (CI:149.6-162.3) between 2006 and 2010. It is of note that for the same age group there was between 2009 and 2010 a slight increase of 11% from 138.3/1000 person-year (95% CI:136.5-142.2) to 155.8/1000 person-year (CI:149.6-162.3) respectively.

For the other age groups, there was a notable decline observed in the incidence of OM diagnosis between 2006 and 2010. In children aged between 2 and 5 years old there was a 31% decrease, from 176.9/1000 person-years (95% CI: 174.0-179.9) to 121.6/1000 person-years (95% CI: 118.9-124.3). Likewise there was a 36% fall amongst those aged between 6 and 11 years old from 88.8/1000 person-years (95% CI: 87.1-90.5) to 56.7/1000 person-years (95% CI: 55.2-58.2); a 43% fall in those aged 12-15 years old from 45.9/1000 person-years (95% CI: 44.7-47.1) to 26.2/1000 person-years (95% CI: 25.3-27.2); and a 32% decline in those aged between 16 and 18 years. In the latter group the diagnosis rate declined 28.2/1000 person-years (95% CI: 27.1-29.4) to 19.2/1000 person-years (95% CI: 18.2-20.2).

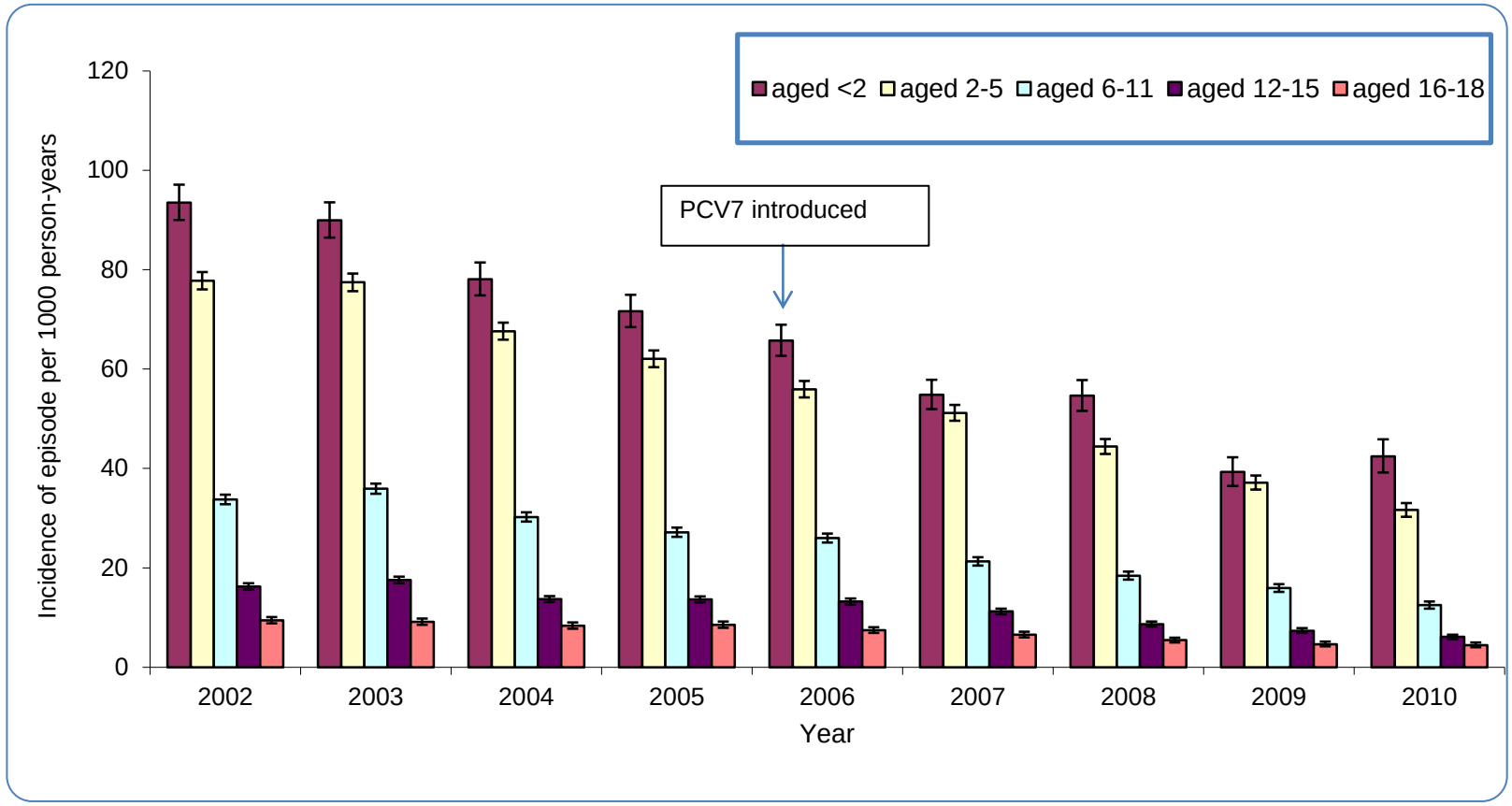
**Figure 5.2: Age group- specific incidence of OM diagnosis, by year, derived from IMS DA**



The annual incidence of antibiotic prescribing for the treatment of OM also varied between age groups during the study period (Fig. 5.3). In line with OM incidence the highest treatment incidence was also seen in children aged less than two years old, followed by children aged between 2 and 5 years old. Following the introduction of the PCV7 there was between 2006 and 2010 a 36% decline in the incidence of antibiotic prescribing for OM in children aged less than 2 years, from 65.7/1000 person-years (95% CI: 62.6-68.9) to 42.4/1000 person-years (95% CI: 39.2-45.8).

A 43% decrease was observed in children aged between 2 and 5 years old, from 55.9/1000 person-years (95% CI: 54.3-57.6) to 31.6/1000 person-years (95% CI: 30.2-45.8). In those aged between 6 and 11 years there was a 52% decline from 25.9/1000 person-years (95% CI: 25.1-26.9) to 12.5/1000 person-years (95% CI: 11.8-13.2) while in those aged 12-15 years it was 53%, from 13.2/1000 person-years (95% CI: 12.6-13.8) to 6.1/1000 person-years (95% CI: 5.7-6.6). Finally in young adults aged between 16 and 18 years there was a 40% drop, from 7.5/1000 person-years (95% CI: 6.9-8.1) to 4.5/1000 person-years (95% CI: 4.0-4.9) between 2006 and 2010.

**Figure 5.3: Incidence of antibiotic prescribing for OM for children and adolescent aged 0-18 years, by age group, derived from IMS DA**




.

With regards to gender the overall incidence of OM diagnosis was slightly higher in females compared to males (Fig. 5.4). Between 2002 and 2010 in females the incidence of OM decreased during the study period by 37% from 91.4/1000 person–years (95% CI: 90.3-92.6) to 57.3/1000 person-years (95% CI: 56.2-58.4). In males it fell by 40% from 88.1/1000 person–years (95% CI: 87.0-89.3) to 52.6/1000 person-years (95% CI: 51.6-53.6) in the same period.

Likewise between the years 2006 and 2010 the incidence of OM in females decreased by 35% from 88.2/1000 person–years (95% CI: 86.9-89.4) to 57.3/1000 person-years (95% CI: 56.2-58.4) respectively. In males it decreased by 37% from 82.9/1000 person–years (95% CI: 81.7-84.1) to 52.6/1000 person-years (95% CI: 51.6-53.6).

Antibiotic prescribing rates for the treatment of OM in children were similar between the two sexes throughout the study period (Fig 5.5). Between 2002 and 2010 the incidence of antibiotic prescription for females declined progressively, by a total of 63% from 35.9/1000 person–years (95% CI: 35.4-36.9) to 13.4/1000 person-years (95% CI: 12.8-13.9) Roughly the same percentage reduction was observed in males. Likewise, between 2006 and 2010, the incidence of antibiotic prescribing in females declined by about half from 26.8/1000 person–years (95% CI: 26.1-27.4) to 13.4/1000 person-years (95% CI: 12.8-13.9) and similar reduction was also observed in males.

**Figure 5.4: Incidence of OM episodes for children and adolescent aged 0-18 years, by gender, derived from IMS DA**

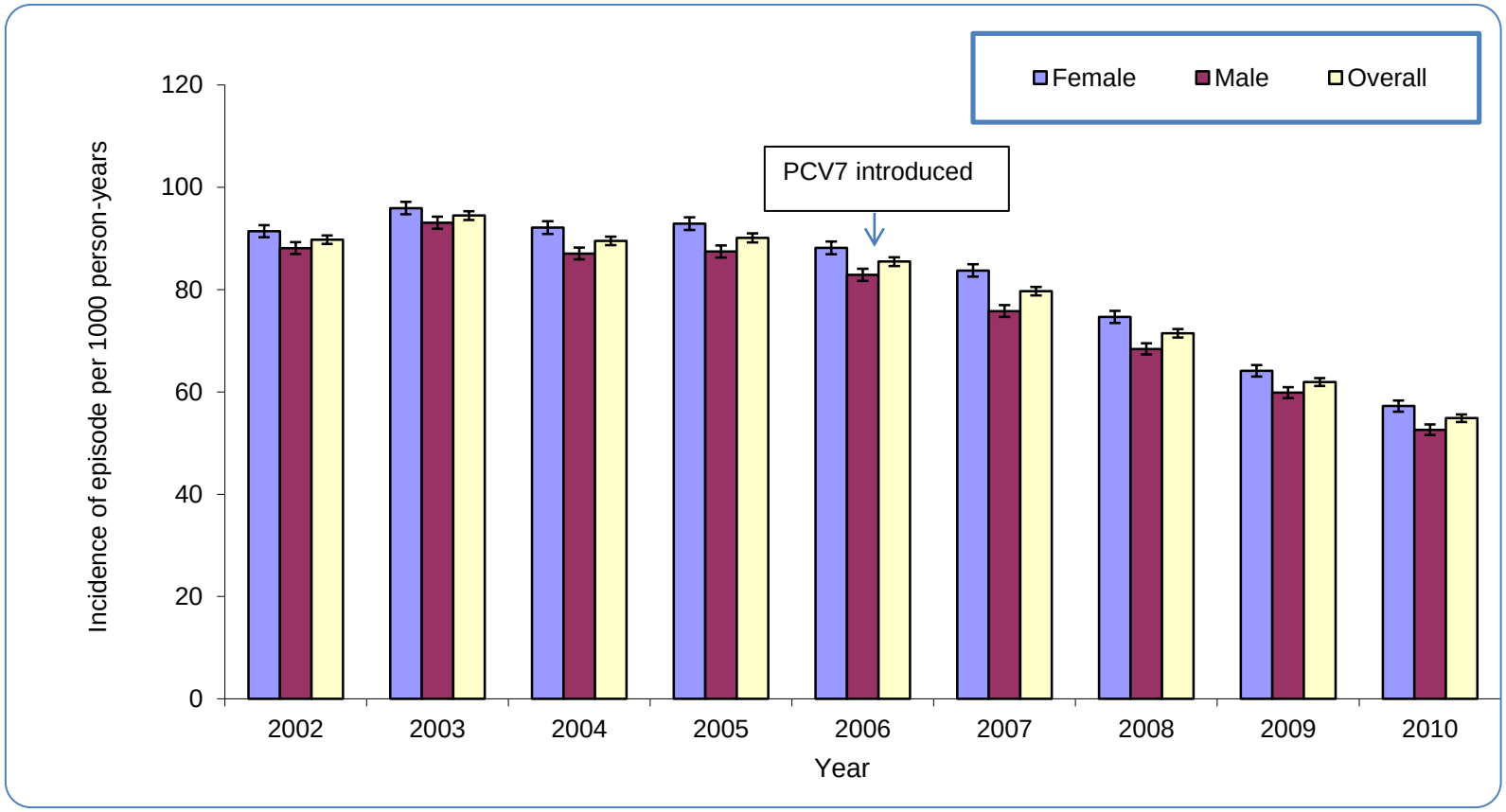


**Figure 5.5: Incidence of antibiotic prescribing for OM for children and adolescent aged 0-18 years, by gender, derived from IMS DA**

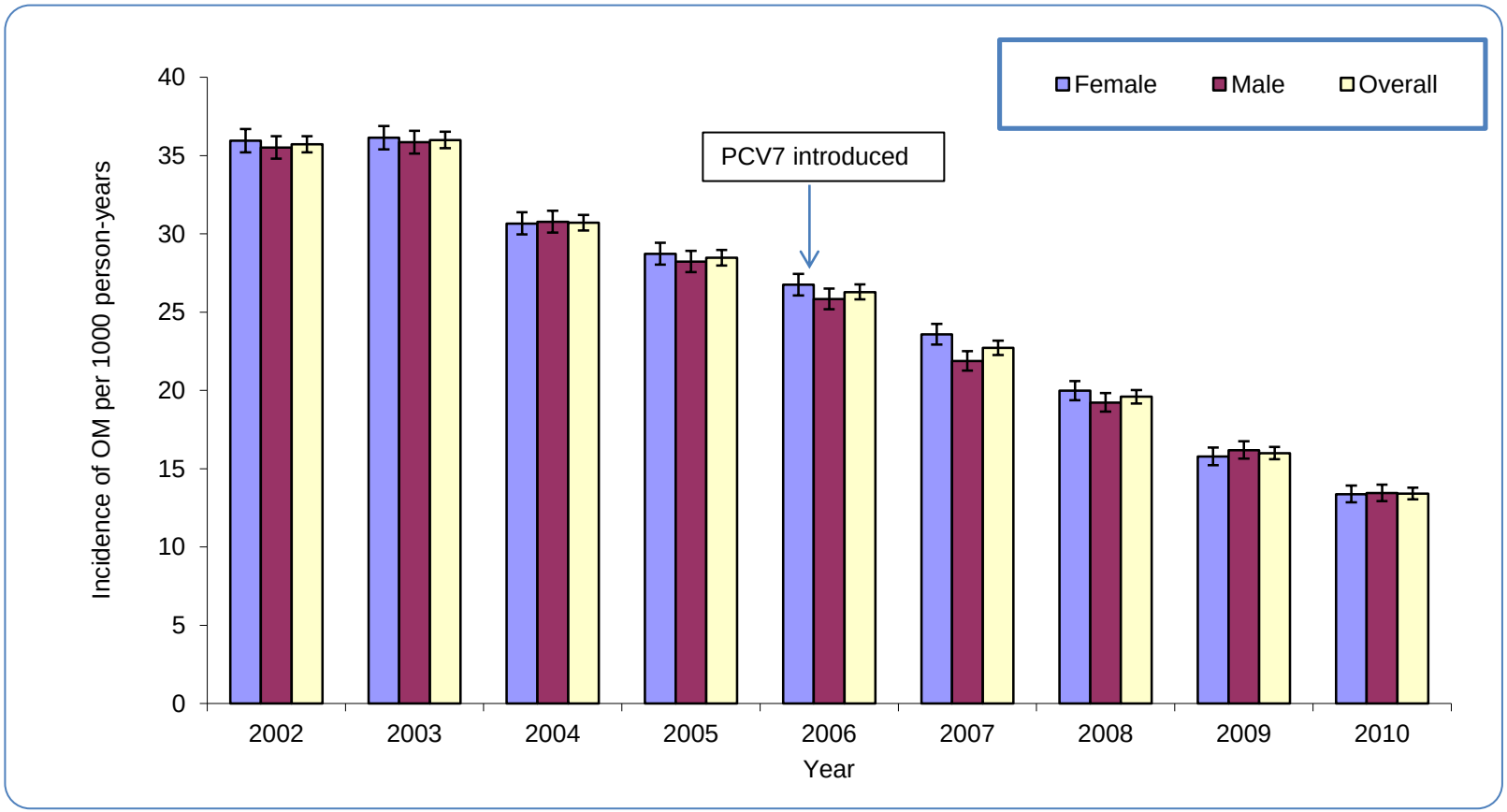


Figure 5.6 shows the quarterly incidence of OM diagnosis for all age groups. Overall, OM incidence peaked in the first quarter of each year. However, there was a significant decline of 31% from the 3rd quarter of 2006, when it stood at 54.2 per1000 person-years (95% CI:52.8-55.6), to 37.3 per 1000 person-years (95% CI: 36.1-38.6) in the 3rd quarter of 2010 (P<0.05).

Figure 5.7 shows that between 2006 and 2010 the 3rd quarter incidence of OM declined 17% for children aged less than two years old, from 129.14 per1000 person-years (95% CI:121.2-136.9) in 2006 to 106.83 per 1000 person-years (95% CI:97.5-116.1) in 2010. The equivalent decline was 26% for children aged between 2 and 5 years from 84.7 per1000 person-years (95% CI:80.9-88.6) in 2006 to 63.1 per1000 person-years (95% CI:59.4-66.8)in 2010 and 33% for children aged between 6 and 11 years. In this last age group OM incidence dropped from 56.7 per1000 person-years (95% CI:54.3-59.1) in 2006 to 38.2 per1000 person-years (95% CI:36.0-40.2) 2010. In addition a 35% decline was seen in children aged between 12 and 15 years, from 34.3 per1000 person-years (95% CI:32.3-36.6) to 22.2 per1000 person-years (95% CI:20.3-24.0). In subjects aged between 16 and 18 years old there was a 22% decline from 21.8 per1000 person-years (95% CI:19.8-23.7) in 2006 to 17.1 per1000 person-years (95% CI:15.3-18.9) 2010.

**Figure 5.6: Quarterly incidence of OM episodes in children and adolescents aged 0-18, derived from IMS DA**

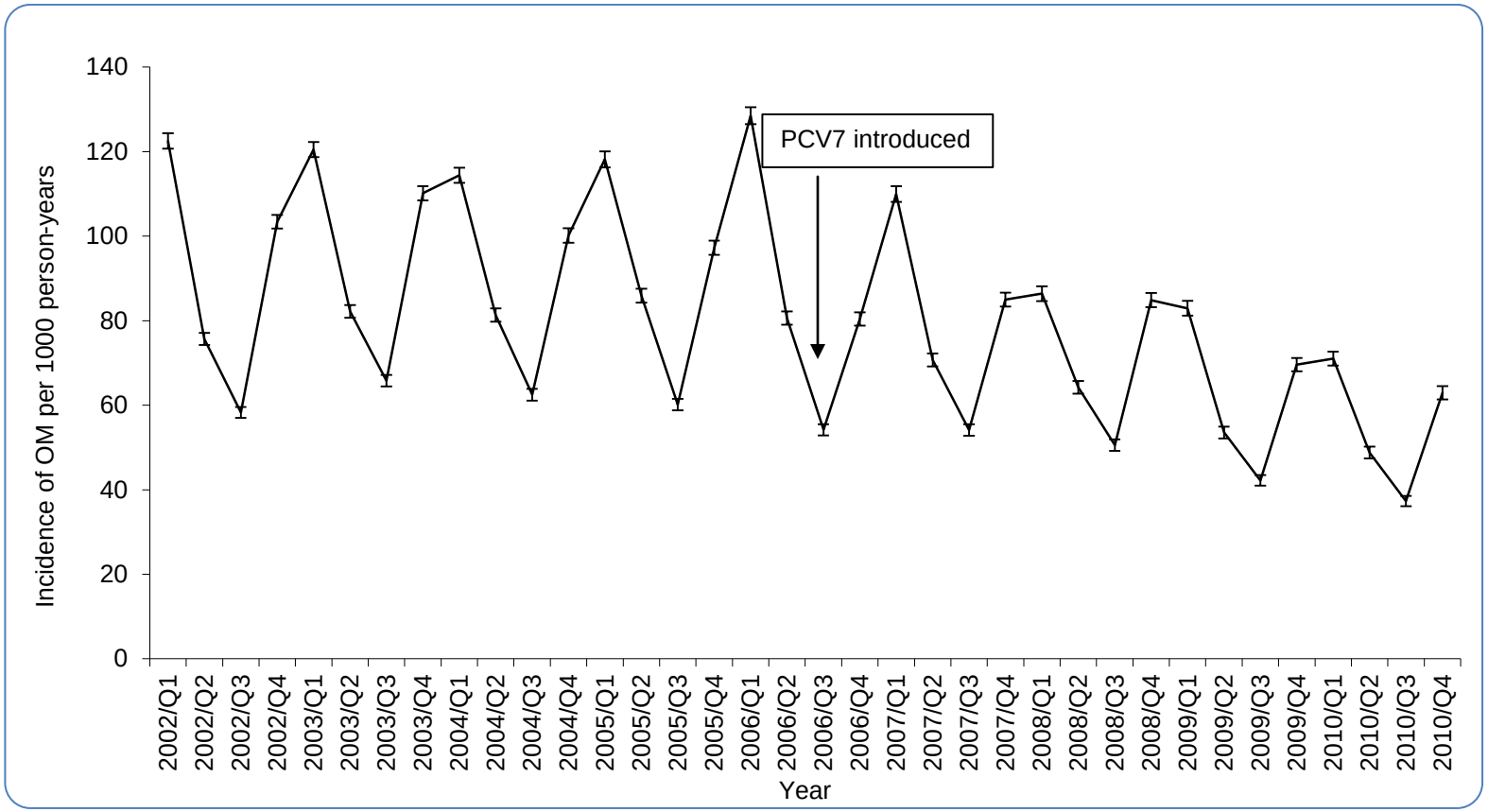
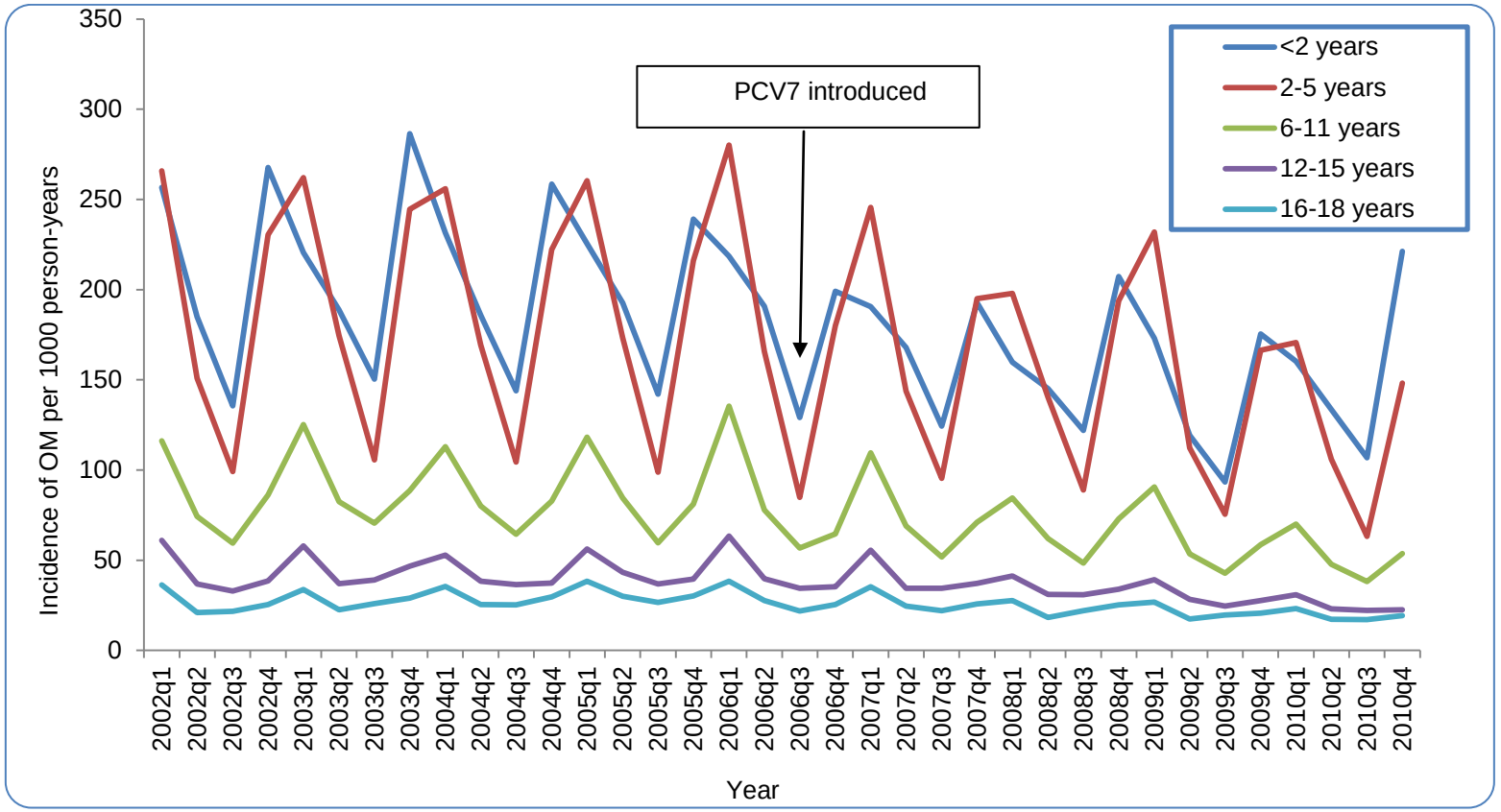


**Figure 5.7: Quarterly incidences of OM episodes in children and adolescents by age group, derived from IMS DA**



As mentioned earlier, to compare the quarterly change on OM episode in children aged less than 2 years old before and after the introduction of PCV7. ITS using segmented regression modeling found that for children aged <2 years old there was a significant decline in the level of OM incidence following the introduction of the heptavalent vaccine (P= 0.001). Yet despite this there was not a significant difference in the trend of incidence of OM following the introduction of the vaccine (P=0.727) (table 5.2). The 4$^{th}$ quarter was used as the reference group in these calculations, as in the UK OM incidence always peaks at this time of the year (Fig 5.7).

**Table 5.2: Segmented regression model for children with OM episodes age less than 2 years old**

| Parameter | IRR | IRR (95% Lower CI) | IRR (95% Upper CI) | p |
|---|---|---|---|---|
| baseline trend | 1.00 | 0.99 | 1.00 | 0.092 |
| level change after PCV7 intervention | **0.84** | **0.76** | **0.93** | **0.001** |
| trend change after PCV7 intervention | 1.00 | 0.99 | 1.01 | 0.727 |
| Quarter 1 vs. 4 | 0.86 | 0.81 | 0.92 | <0.001 |
| Quarter 2 vs. 4 | 0.71 | 0.67 | 0.76 | <0.001 |
| Quarter 3 vs. 4 | 0.55 | 0.51 | 0.59 | <0.001 |

**Key:**
**IRR =** Incidence Rate Ratio, which in this instance compares the condition incidence rates before and after the introduction of PCV7 at a given point in time.
**baseline trend**: original trend of the mean OM incidence, independently from all intervention
**level change after PCV7 intervention**: immediate impact of the intervention on the mean OM incidence
**trend change after PCV7 intervention:** change in trend of the mean OM incidence after the intervention

## 5.2 DISCUSSION

### 5.2.1 SUMMARY OF MAIN FINDINGS AND COMPARISON WITH OTHER STUDIES

This chapter has presented the findings of the first UK national study to investigate the impact of PCV7 on the incidence of OM and antibiotics prescribed for OM using a UK primary care database. Since the introduction of the vaccine in 2006 this research strand found a significant decline in the incidence of OM diagnoses (36%) and also in antibiotic prescribing (49%) for the treatment of OM in children and adolescents aged between 0-18 years old. Although initial reductions in reported OM cases predated the introduction of the vaccine, an accelerated trend was seen after the introduction of the vaccine – see, for instance, Table 5.2 above. The incidence of OM antibiotic treatment follows the same pattern as the incidence of OM episodes, but with much lower incidence. Overall, only a third of the children diagnosed with OM were prescribed antibiotics.

After the introduction of the PCV7 antibiotic prescribing for the treatment of OM in UK primary care fell to a much lower level than that found in a previous study that used GPRD data and was undertaken before the free mass availability of immunisation. Thompson *et al*. (2008) showed that between 1990 and 2006 in the GPRD 1,210,237 episodes of OM were identified amongst a population of 464,845 children. In two-thirds of these instances (68%) an antibiotic prescription was issued on the same day. Such indicates that PCV7 has had an impact on OM as well as on antibiotic prescribing for OM. This in theory at least should have decreased the incidence antibiotic resistance.

Despite clinical guidance to the contrary, a proportion of GPs may have continued habitually to prescribe antibiotics for children consulting with OM despite the fact that many cases are self-limiting and spontaneously resolve without antibiotic treatment (Glasziou *et al.*, 1997). Such higher than average usage of antibiotics could be due to several factors (Thompson *et al.,* 2008). For instance, some GPs may be more concerned than others to avoid the development of potential complications, which are more likely to occur in vulnerable populations (Kumar, Little and Britten, 2003). Also, articulate parental pressure for antibiotics may at times lead doctors to prescribe regardless of whether or not they believe antibiotic treatment is strictly necessary (Britten and Ukoumunne, 1997; MacFarlane *et al.*, 1997; Bauchner, Pelton and Klein, 1999; Mangione-Smith *et al.*, 1999; Kumar, Little and Britten, 2003; Coenen *et al.*, 2006).

Randomised controlled trials and observational studies have indicated the effectiveness of PCV7 in children of all ages. In the US, for instance, several studies have shown that PCV7 has reduced the incidence of OM as well as the level of antibiotic use in children (see Fireman *et al.*, 2003; Poehling *et al.,* 2007). Similarly, studies from continental Europe (Finland, Italy, and France) have reported decreases in AOM rates and antibiotic use in children who were administered PCV-7 (Eskola *et al.,* 2001; Cohen *et al.*, 2006). Following on from the above this study demonstrates a 15% decline in the incidence of OM in children aged <2 years old and a 31% fall in children aged between 2 and 5 years old in the UK primary care setting.

Such figures are encouraging for observers concerned with the reduction of *S. pneumonia* related morbidity. However, the reported levels of disease decline found in this study are not as great as those observed in some other studies. For instance, one retrospective cohort study evaluated the vaccine effectiveness in the US outpatient setting via analyses of two national health care surveys (NAMCS & NHAMCS) during the period 1994 to 2003. It was found that after the introduction of PCV7 in 2001, OM visit rates declined by 20% in children aged <2 years (Grijalva *et al*., 2006).

In 2009 another study by Grijalva *et al*. in the US assessed the annual visit rates for OM and antibiotic prescription rates for OM for children aged less than 5 years, between 1995 and 2006 using the same health care data sources. This study reported that the annual visit rate for OM had declined by 33%. This fall was accompanied by a corresponding 36% decrease in antibiotic prescribing for OM.

In this study the decline in incidence of antibiotic prescription for OM exceeds the effects reported in Grijalva *et al*., 2009. The results show that following the introduction of PCV7 antibiotic prescribing for OM has declined by 43% in the UK primary care. In the older age groups (ages 6-11, 12-15 &16-18), OM incidence decreased by 36%, 43% & 32% respectively. Additionally, the study shows marked reduction in OM episodes in older children, who were above age of vaccination. This suggests a reduction in the carriage of the infective agent.

Overall, when comparing age groups this study's results show that the burden of OM and the rate of antibiotic prescription for OM decreased significantly with increasing age. This could be related to the fact that younger children have immature immune systems and anatomically undeveloped Eustachian tubes, which before immunisation put them at particular risk of infection.

Although between 2006 and 2010 the burden of OM and the antibiotic prescribing for OM decreased in all age groups, in 2010 there was a significant increase in the incidence of OM and antibiotics prescribed for OM for children aged less than 2 years. It is possible that this increase in the incidence of OM at this point was due to serotype replacement. A non-vaccine *S. pneumoniae* serotype may have become active, increasing disease incidence specifically for those aged less than two years. Other authors have observed that following the introduction of PCV7 non-vaccine *S.pneumoniae* serotypes to a degree replace vaccine serotypes (Hendrickson *et al.,* 2008 & WHO, 2009). Indeed, the threat of serotype replacement disease in part led to the introduction of PCV13 into the UK childhood primary immunisation schedule in April 2010,

In terms of gender, although there were fluctuations in the incidence of the diagnosis and in antibiotic prescribing for OM before the introduction of the vaccine and a significant decline post introduction of the vaccine, the rates observed were consistently higher in females. One possible explanation for this is that females are at raised risk because of anatomical as opposed to immune system linked variables.

In addition, this study investigated the incidence of the disease on a quarterly basis. The results show that seasonal variation is one of the main factors affecting the incidence of OM.

The seasonal variation found was an increased incidence in the winter months, as is true for many other infectious diseases (e.g. measles, influenza, whooping cough) (Grassly & Fraser, 2006; Zielhuis *et al.,* 1990).

As already noted, ITS analyses were employed in this study, and segmented regression modelling was used to assess the impact of PCV7 and control for seasonal effect. There was a statistically significant drop in the level of mean OM incidence immediately after the introduction of PCV7, but no significant change in trend. As mentioned earlier, this apparently paradoxical finding was probably associated with a declining incidence of OM established before the introduction of the vaccine, coupled with contingent phenomena such as serotype replacement.

### 5.2.2 POSSIBLE REASONS FOR THE REDUCTION OF OM INCIDENCE PRIOR TO THE INTRODUCTION OF THE VACCINE

The findings presented in this chapter show that, before the introduction of the vaccine in 2006, there was unexpected decline in the incidence of OM diagnosis in general practice between 2003 and 2004, followed by another decline from 2005 to 2006. The reason behind these events is unknown. Apart from random variations in incidence they

could perhaps have been due to increased host immunity to infection, or they could reflect a true reduction in the nature of the disease itself.

There are consistent findings from other UK national studies to support this study's results. In as early as 1982 Quinn observed that over time the streptococcal infections that are the most common causes of OM appear to be becoming less virulent (Quinn, 1982).

A previous study by Fleming *et al* (2003) conducted a time-trend analysis of respiratory tract infection diagnoses (including OM) and antibiotic prescribing for patients of all ages between 1994 and 2000. Respiratory infection data was obtained from the Weekly Returns Service of the Royal College for General Practitioners, which are surveillance network covering approximately 600,000 patients from general practice in England and Wales. Antibiotic prescribing information was derived from Prescribing Analysis and Cost (PACT) data. The authors reported a reduction in respiratory tract infection diagnoses, including OM, from 1995 until 2000. Parallel trends were observed in total antibiotic prescribing (Royal Collage of General Practitioners, 2007). Moreover, evidence provided by the Health Protection Agency (2008), shows that since 1999 laboratory reports of Respiratory Syncytial virus have continually reduced.

As mentioned earlier, environmental factors could also be one of the risks influencing the pathogens that cause OM. Improvements in people's behaviour towards tobacco smoking, such as reducing smoking in confined areas, and improving basic hygiene could have contributed to the reduction of infections in children (Fleming *et al*., 2003).

In 2003 a Scottish Intercollegiate guideline Network stated that "…there is likely to be a causal relationship between parental smoking and both acute and chronic middle ear disease in children …" (Scottish Intercollegiate guideline Network, 2003, p3).

Another factor that could have influenced Otitis Media treatment trends is changes in healthcare-seeking behaviour. A Standing Medical Advisory Committee (SMAC, 1998) report recommended a Campaign on Antibiotic Treatment (CAT) in the NHS primary care setting. It advised, firstly, that antibiotic prescriptions should not be given for simple coughs and colds or for viral sore throats; secondly, prescribing over the phone should be limited; and, thirdly, that antibiotic prescribing for uncomplicated diseases should be limited to three days if the patient is fit.

These recommendations were combined with a National Advice to the Public (NAP) campaign, together forming the CATNAP campaign. The NAP campaign aimed to educate the public/parents. It discouraged them from unnecessarily consulting their GPs, sought to lower their expectations for antibiotic prescriptions for OM and advised them to seek out advice on symptomatic relief from their community pharmacists instead of visiting GP practices. Patients/parents may have therefore have become better informed with regard to the symptoms and treatment of OM, consequently resulting in fewer consulting their GP for OM incidents.

## 5.3 STRENGTHS AND LIMITATIONS OF THIS STUDY

It is believed that this study is the first paediatric population-based cohort study undertaken to assess the incidence of OM and antibiotic prescribed for OM in children and adolescents in the UK primary care.

The strengths of this study are that, firstly, the IMS DA contains robust data from primary care across the whole of the UK, so the overall estimate of OM incidence is likely to be representative of the UK paediatric population as a whole. Secondly, in the IMS database antibiotic prescriptions are directly linked to a Read Coded clinical indication by the GP at the time of consultation. This direct linking of therapy and indication data enables trends in antibiotic prescribing for OM to be investigated in relation to patterns of OM and for the appropriateness of the choice of antibiotic to be assessed.

The major limitation of the study, which is common in all studies based on routinely collected clinical data, is the inability to confirm diagnosis. The case categorisations used were based on the codes entered by the GPs. Not all data of interest may have been recorded in the IMS DA.

Furthermore, it is unknown whether a diagnostic code changes during the study time span contributed to the significant reduction in OM diagnosis and prescribing through under-recoding. Further work is needed in order to understand how GPs make the diagnosis and the decision to prescribe.

## 5.4 CONCLUSION

This study identified an overall fall of more than a third in OM diagnosis and antibiotic prescribing for the treatment of OM in children between 2006 (the date of introduction of the vaccine in this country) and 2010. However, some of this reduction predated the introduction of PCV7. Several factors appear to have influenced this finding. Interrupted Time Series analysis using segmented regression modelling shows that there was a significant decline in the incidence of OM at around the time vaccination commenced, but that the overall trend was unaffected. This is suggestive of several causal factors being at work being simultaneously. It is of note that ITS based calculations have not previously been used in studies of the impact of PCV7 immunisation on the incidence of OM.

# CHAPTER SIX: THE IMPACT OF PCV7 ON THE INCIDENCE OF PNEUMONIA AND RELATED ANTIBIOTIC PRESCRIBING IN CHILDREN BETWEEN 2002 AND 2010

Although the previous chapter's results have shown a reduction in both OM diagnoses and antibiotic prescribing following the introduction of PCV7 in UK general practice, the vaccines impacts on incidence and treatment of pneumonia remain unclear. Therefore, an observational cohort study based on THIN database was undertaken to assess the effects of the introduction of PCV7 on the burden of disease due to pneumonia and the associated antibiotic prescribing for children. This chapter reports its findings.

## 6.1 Results

For the period 2002 and 2010 there were a total of 1,410,663 children aged 0 to 15 years old (726,766 male/ 683,897 female) in the THIN database population, contributing 5,732,111 person-years of follow-up data. Table 6.1 shows the information relating to children diagnosed with pneumonia between 2002 and 2010. In this cohort, 5,261 (5,261/1,410,663; 0.4%) had a diagnosis of pneumonia. Of these nearly a half were female (n=2,383), and just over a quarter (27%; 1,425) received an antibiotic prescription.

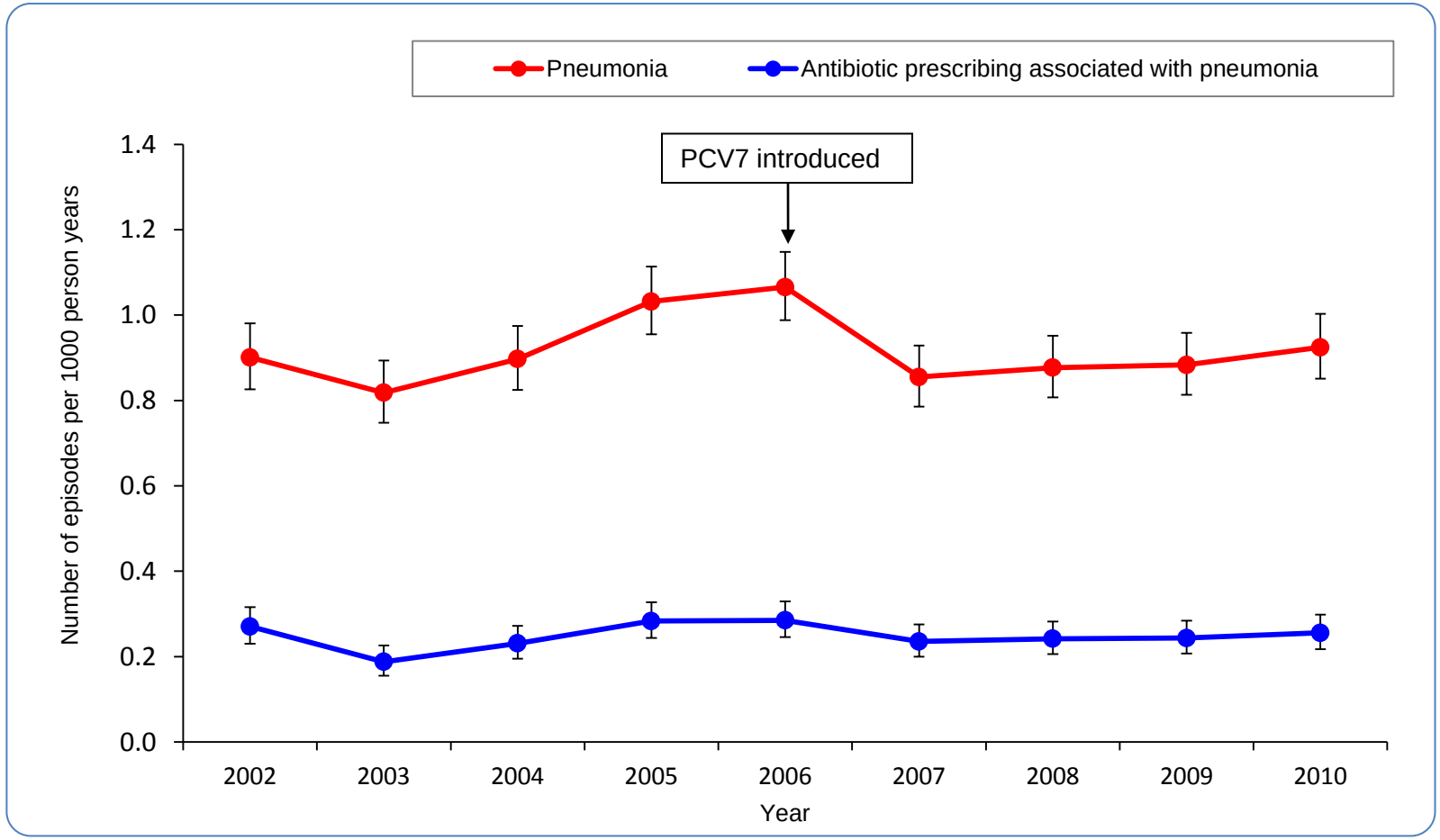
**Table 6.1: Children diagnosed with pneumonia, aged 0-15 years in THIN, 2002-2010 – episode numbers and person years of exposure**

| Year | Boys | | | Girls | | |
|---|---|---|---|---|---|---|
| | Number of patients | Number of episodes | Person-years | Number of patients | Number of episodes | Person-years |
| 2002 | 284 | 292 | 309260.6 | 236 | 244 | 285706.2 |
| 2003 | 267 | 282 | 314125.8 | 209 | 214 | 292113.1 |
| 2004 | 288 | 299 | 324136.2 | 261 | 264 | 303273 |
| 2005 | 365 | 376 | 332278 | 281 | 290 | 313148.3 |
| 2006 | 365 | 379 | 334845 | 291 | 316 | 317324.3 |
| 2007 | 296 | 306 | 337126.4 | 255 | 257 | 321457.9 |
| 2008 | 305 | 311 | 338076.7 | 263 | 269 | 323188.7 |
| 2009 | 305 | 311 | 335684.3 | 263 | 269 | 320812.6 |
| 2010 | 314 | 322 | 321889.7 | 258 | 260 | 307664.3 |

Between 2002 and 2010 the lowest incidence of pneumonia diagnosis amongst children was seen in 2003 with 0.82/1000 person-years (95% CI: 0.74-0.89) (Fig. 6.1). But it increased by 30% to 1.07 per 1000 person-years (95% CI: 0.98-1.14) in 2006. The incidence of pneumonia episodes then decreased by 21% between 2006 and 2007, from 1.07 per 1000 person-years (95% CI: 0.98-1.14) to 0.85 per 1000 person-years (95% CI: 0.78-0.92). Following this the rates then started to gradually climb to an incidence in 2010 of 0.92 per 1000 person-years (95% CI: 0.85-1.00). Overall, however, the number of pneumonia episodes recorded from 2006 onwards declined by 14% from 1.07 per 1000 person-years (95% CI: 0.98-1.14) in 2006 to 0.92 per 1000 person-years (95% CI: 0.85-1.00) in 2010 ($P<0.05$).

Similarly, the incidence of antibiotic prescribing for pneumonia treatment in subjects aged 0-15 years declined by 10% from 0.29 per 1000 person-years (95% CI: 0.25-0.33) in 2006 to 0.26 per 1000 person-years (95% CI: 0.22-0.29) in 2010 ($P<0.05$).

**Figure 6.1: Incidence of pneumonia diagnosis and antibiotic prescribing for pneumonia treatment in children aged 0-15years, derived from the THIN database.**

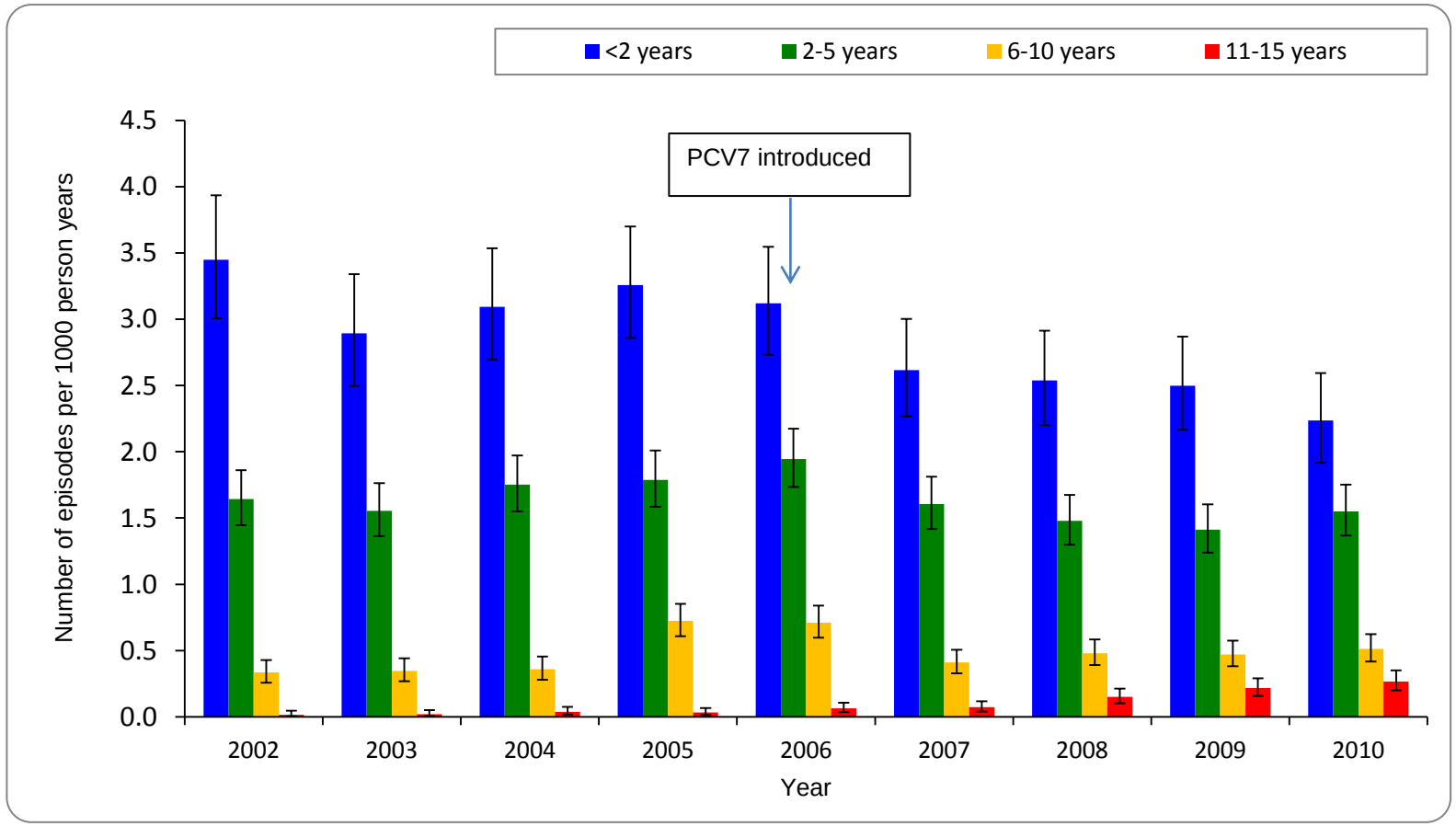


The number of pneumonia episodes varied between each age group (Fig. 6.2). From 2002 onwards and up to the end of the study period, the incidence of pneumonia episodes fluctuated by age group until it reached the lowest incidence for children aged between 11 and 15 years old. The highest age specific incidence was found in the youngest age group (under two). However, the incidence rate for children under 2 years old decreased 29% between 2006 and 2010, from 3.1 per 1000 person-years (95% CI: 2.7-3.5) in 2006 to 2.2 per 1000 person-years (95% CI: 1.9-2.6) in 2010.

In addition, between 2006 and 2010, a 16% decrease was observed in the incidence of pneumonia in children aged between 2 and 5 years old, from 1.9 per 1000 person-years (95% CI: 1.7- 2.2) to 1.6 per 1000 person-years (95% CI: 1.4-1.8). However, between 2009 and 2010 the incidence of pneumonia in the 2-5 year old group slightly increased, from 1.4 per 1000 person-years (95% CI: 1.2-1.6) to 1.6 per 1000 person-years (95% CI: 1.4-1.8).

The recorded incidence of pneumonia decreased in children aged 6-10 years old by 28% between 2006 and 2010, from 0.71 per 1000 person-years (95% CI: 0.6-0.8) in 2006 to 0.5 per 1000 person-years (95% CI: 0.4- 0.6) in 2010. Yet it increased in this age group by 8% between 2009 and 2010, from 0.47 per 1000 person-years (95% CI: 0.38-0.57) to 0.51 per 1000 person-years (95% CI: 0.42-0.62). Moreover, the incidence of pneumonia in those aged between 11 and 15 years increased by 77%, from 0.06 per 1000 person-years (95% CI: 0.03-0.11) in 2006 to 0.26 per 1000 person-years (95% CI: 0.19-0.35) in 2010.

**Figure 6.2: Age group- specific incidence of pneumonia diagnosis, by year, derived from the THIN database.**



The annual incidence of antibiotic prescribing for the treatment of pneumonia also varied between age groups during the study period (Fig. 6.3). From 2002 to 2009, it was highest in children aged less than two years old, followed by those aged between two and five years old. This is in line with the reported incidence rates for pneumonia itself. However, in 2010, the antibiotic prescribing rate was higher in children aged between two and five years than in all other groups.

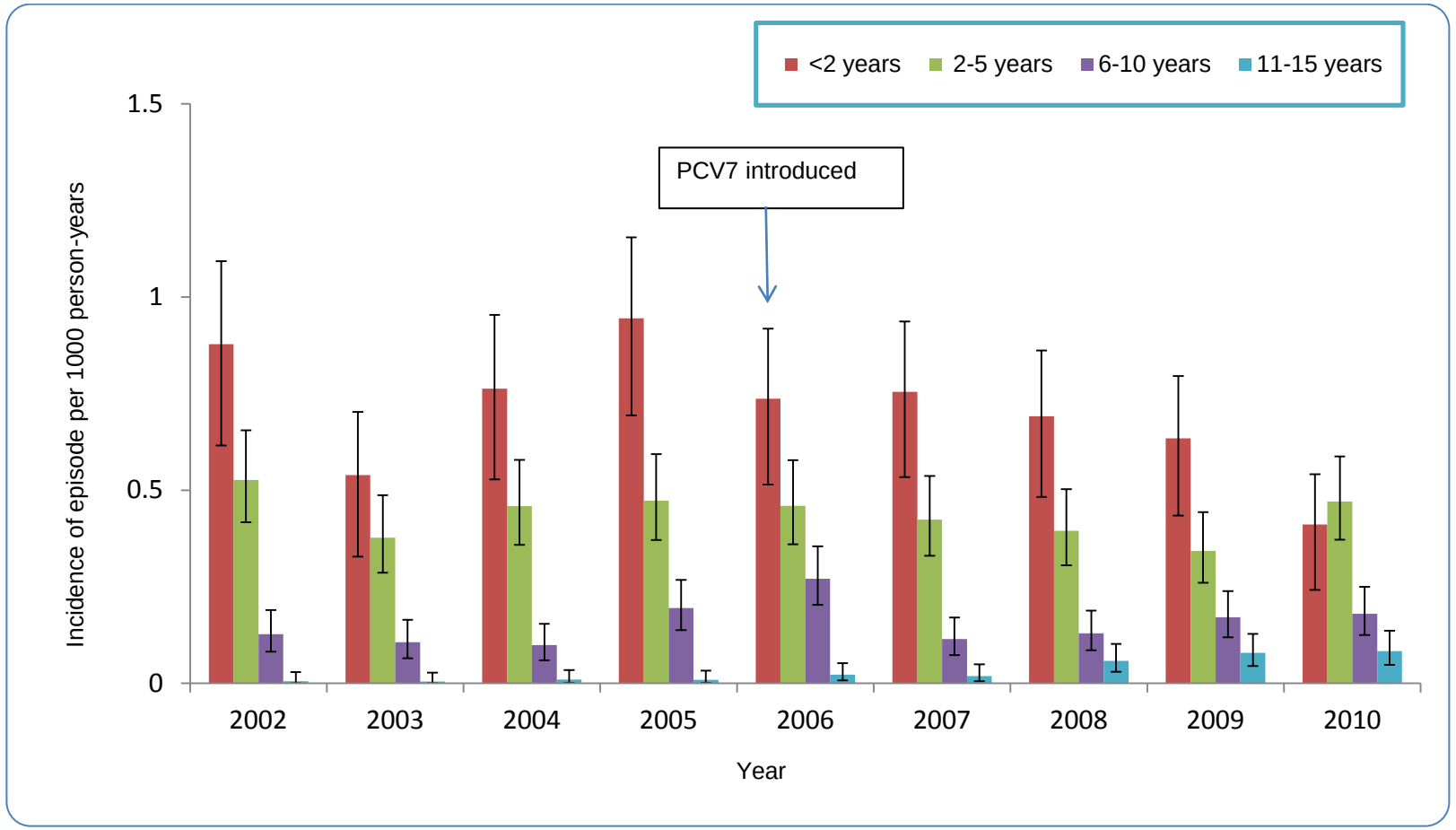
In children aged less than two years old, there was a 44% decline in the incidence of antibiotic prescribing for diagnosed pneumonia between 2006 and 2010, from 0.73 items per 1000 person-years (95% CI: 0.55-0.95) to 0.41 per 1000 person-years (95% CI: 0.28-0.58). However, in children aged between two and five years there was slight increase of 2% in the overall incidence of antibiotic prescribing for this condition between 2006 and 2010. It rose from 0.46 prescription items per 1000 person-years (95% CI: 0.36-0.58) to 0.47 per 1000 person-years (95% CI: 0.37-0.59). Against this, if the period 2006 to 2009 is taken there was a 26% decline in the incidence, from 0.46 per 1000 person-years (95% CI: 0.36-0.58) in 2006 to 0.34 per 1000 person-years (95% CI: 0.26-0.44) in 2009.

Since 2002 there has also been a fluctuating trend in antibiotic prescribing for children aged from 6-10 years old, with a peak in 2006 of 0.27 per 1000 person-years (95% CI: 0.20-0.35). There was then a decrease of 37% to 0.17 per 1000 person-years (95% CI: 0.12-0.24) in 2009. However, antibiotic prescribing for this group slightly increased (by 6%) to 0.18 per 1000 person-years in 2010 (95% CI: 0.13-0.25).

Interestingly, in children aged 11-15 years old, antibiotic prescribing for pneumonia increased substantially during the study period. Between 2006 and 2010, the incidence increased 75%, from 0.02 per 1000 person-years (95% CI: 0.007-0.05) to 0.08 per 1000 person-years (95% CI: 0.05-0.1).

In children aged 11-15 years old antibiotic prescribing for pneumonia also increased during the study period. Between 2006 and 2010 it increased by 75%, from 0.02 prescriptions per 1000 person-years (95% CI: 0.007-0.05) to 0.08 per 1000 person-years (95% CI: 0.05-0.1) respectively.

**Figure 6.3: Incidence of antibiotic prescribing for pneumonia for children aged 0-15 years, by age group, derived from the THIN database.**



With regard to gender, overall the incidence of pneumonia diagnosis was slightly higher in males compared to females (Fig. 6.4). From 2002 until 2010, the incidence in both genders fluctuated. The incidence in males peaked in 2006, falling by 19% from 1.13 antibiotic items per 1000 person-year (95% CI: 1.02-1.25) in 2006 to 0.92 per 1000 person-year (95% CI: 0.82-1.04) in 2009. However, there was a subsequent slight increase to 1.00 per 1000 person-year (95% CI: 0.9-1.1) in 2010. Similarly with females a peak was seen in 2006, then rates fell by 14% from 0.99 per 1000 person-year (95% CI: 0.88-1.1) to 0.85 per 1000 person-year (95% CI: 0.75-0.95) in 2010.

Additionally the annual incidence of antibiotic prescribing for the treatment of pneumonia was slightly higher in males compared to females during the study period (Fig. 6.5). Between 2006 and 2010, the incidence decreased by 7% in males from 0.29 per 1000 person-year (95% CI: 0.24-0.36) in 2006 to 0.27 per 1000 person-year (95% CI: 0.24-0.36) in 2010. In females the incidence of antibiotic prescribing decreased by 15% from 0.27 per 1000 person-year (95% CI: 0.22-0.34) in 2006 to 0.24 per 1000 person-year (95% CI: 0.18-0.30) in 2010.

**Figure 6.4: Incidence of pneumonia episodes by gender and year, aged 0-15 years, derived from the THIN database.**

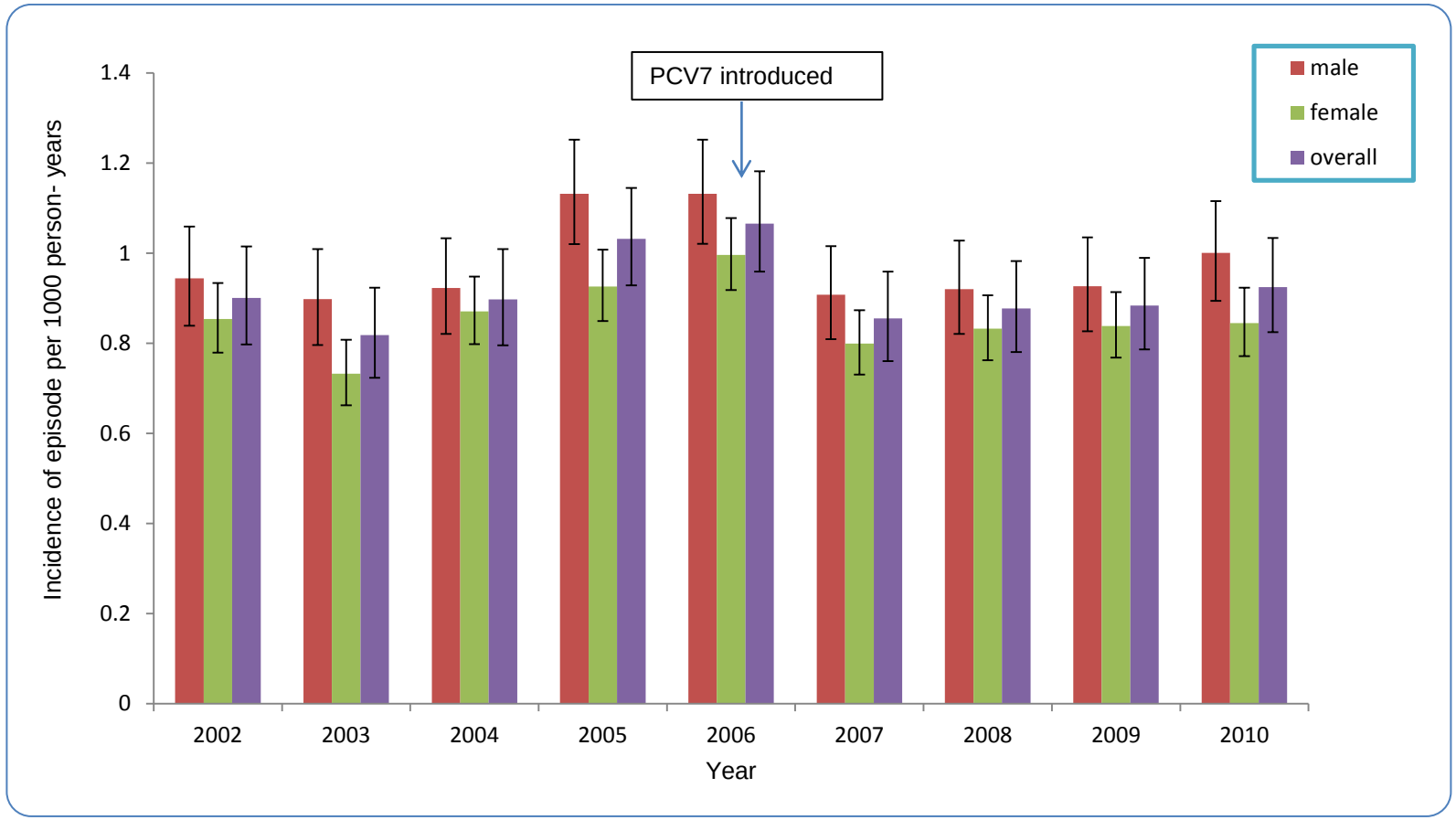


**Figure 6.5: Incidence of antibiotic prescribing for pneumonia for children aged 0-15 years, by gender, derived from the THIN database.**

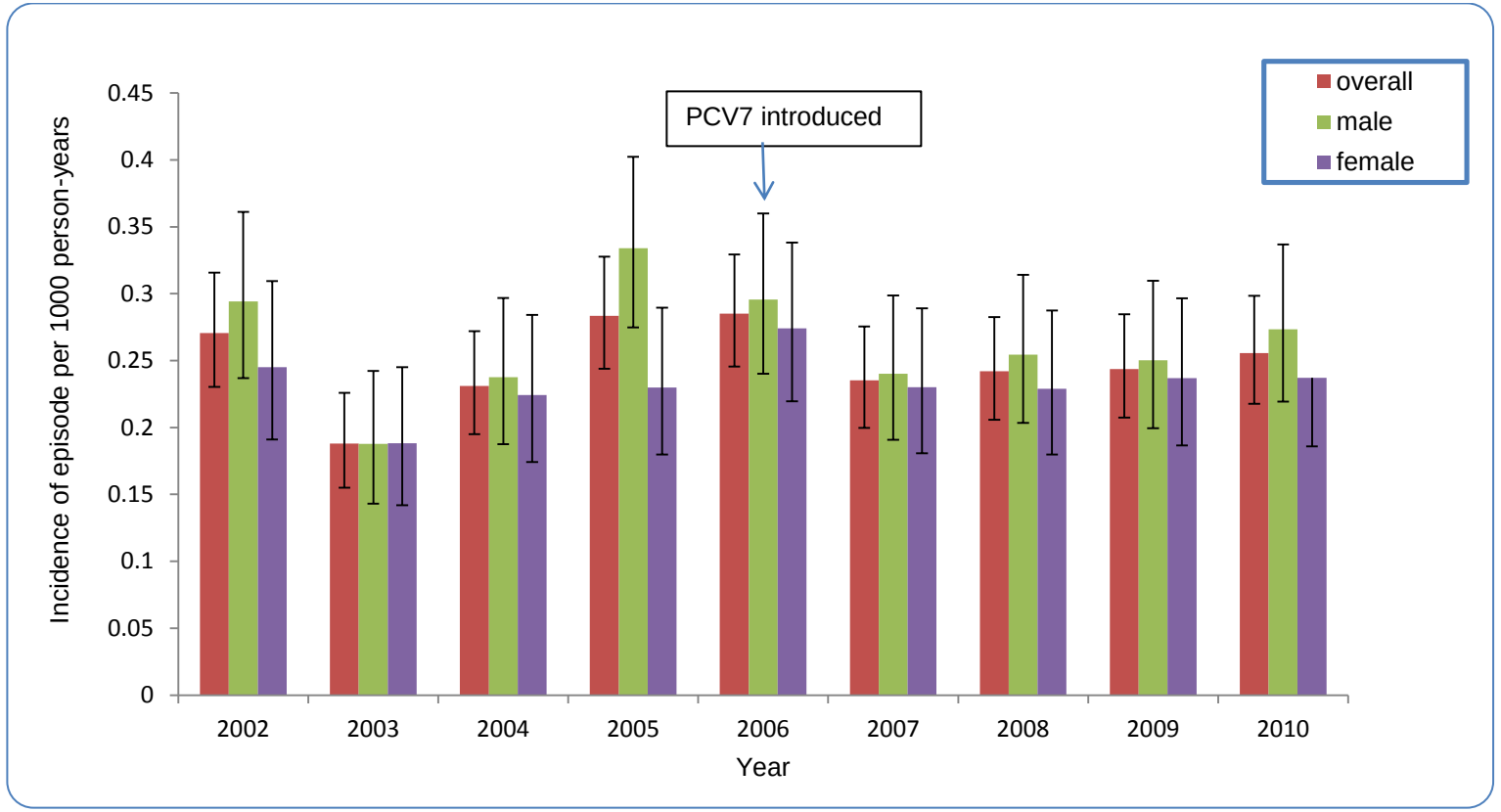


Figure 6.6 shows the quarterly incidence by year of pneumonia diagnoses for all age groups. Overall, the incidence of pneumonia increased in the first quarter of the year. However, there was a marked decline (20%) from the 3rd quarter of 2006 from 0.56/1000 person-years (95% CI: 0.53-0.79) to 0.45/1000 person-years (95% CI: 0.35-0.55) in 2010. Between 2006 and 2010 the 3rd quarter incidence of pneumonia declined 49% for children aged less than two years old, from 1.48/ 1000 person-years (95% CI: 0.98-2.15) in 2006 to 0.76/ 1000 person-years (95% CI: 0.43-1.26) in 2010 (Fig. 6.7).

The corresponding findings in the other age groups were 29% for children aged between 2 and 5 years old from 1.07/ 1000 person-years (95% CI: 0.77-1.45) in 2006 to 0.76/ 1000 person-years (95% CI: 0.52-1.08) in 2010; and 10% for children aged between 6 and 11 years old from 0.39/ 1000 person-years (95% CI: 0.24-0.61) in 2006 to 0.29/1000 person-years (95% CI: 0.16-0.48) in 2010. However, for children aged between 12 and 15 years old the 3rd quarter incidence increased by 77% from 0.05/ 1000 person-years (95% CI: 0.01-0.16) in 2006 to 0.22/1000 person-years (95% CI: 0.11-0.39) in 2010.

**Figure 6.6: Quarterly incidence of pneumonia episodes in children aged 0-15, derived from the THIN database.**

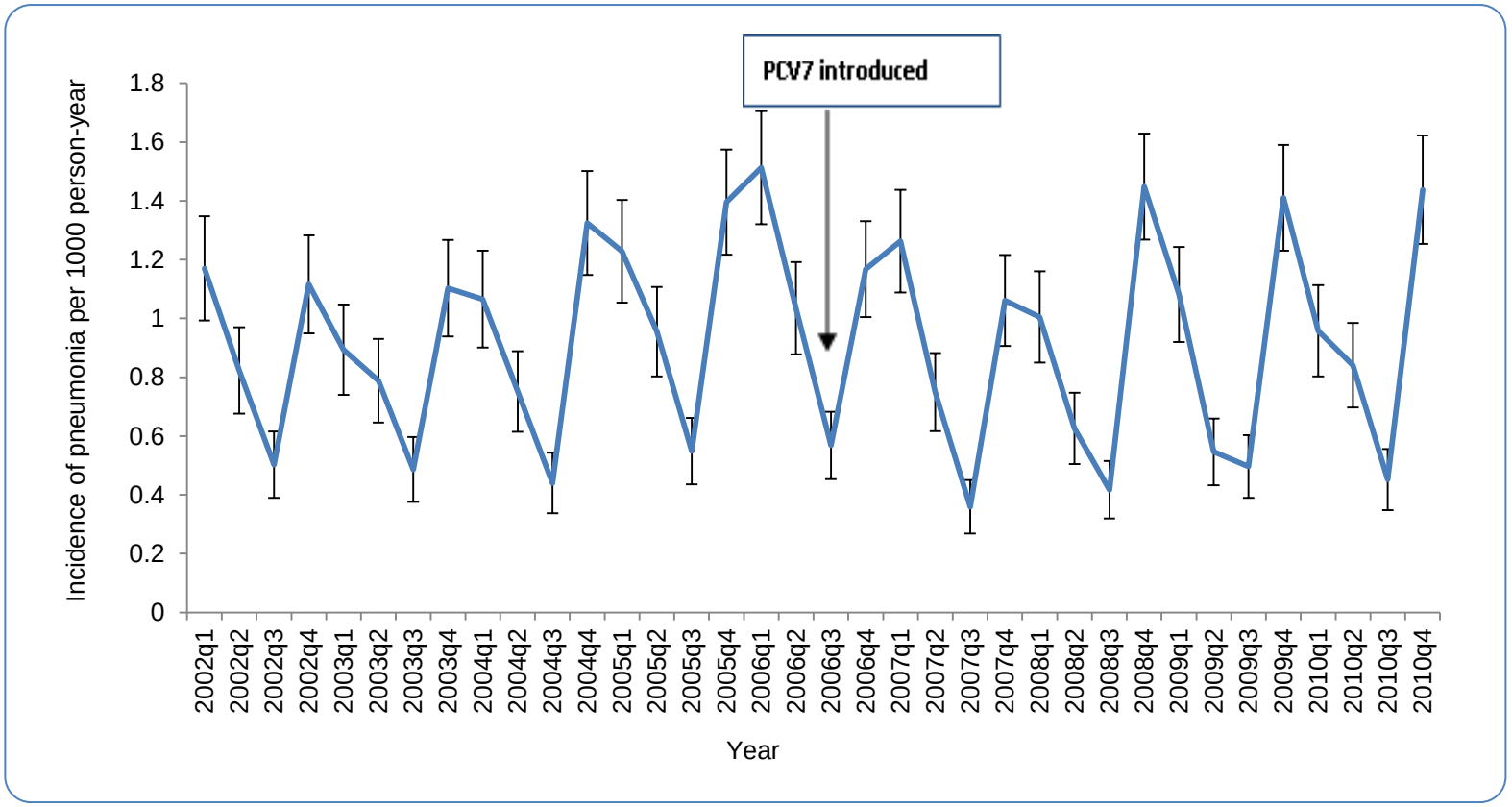
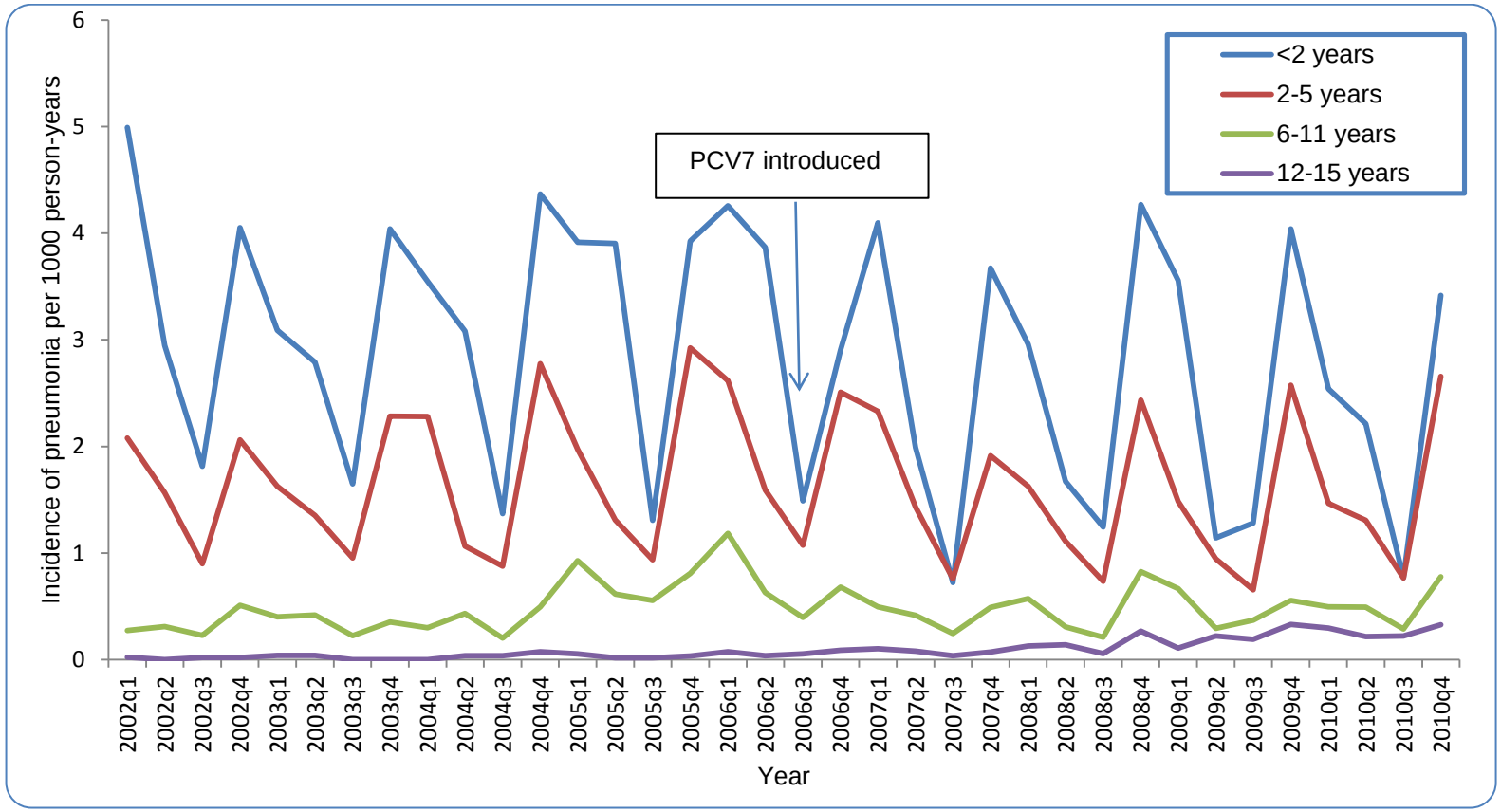


**Figure 6.7: Quarterly incidences of pneumonia episodes in children, by age group, derived from the THIN database.**



## 6.2 DISCUSSION

### 6.2.1 Summary of main findings and comparison with other studies

This chapter presents the findings of the research strand that investigated the impact of the PCV7 on the incidence of pneumonia and respective antibiotic prescribing using a UK primary care database. Overall the total number of children diagnosed with pneumonia in general practice was low (0.4%). This study's findings show that, year by year, the number of pneumonia episodes was slightly higher than the number of children affected. This indicates that a small number of the children will have experienced more than one recorded pneumonia episode within a year i.e. they suffered recurrent infections.

This study shows that between 2002 and 2010 the greatest fall in the incidence of pneumonia diagnosis was seen in 2003. This predated the introduction of PCV7. Such a trend might have been due to decreased disease virulence (Fleming *et al*., 2003). However, it is also of note that in 2003 a *Haemophilus influenza b* (Hib) booster vaccine was introduced for younger children to increase their immunity against Hib infection (HPA, 2012). *Haemophilus influenzae* and *S. pneumoniae* can both be found in the upper respiratory tract (Pettigrew *et al.*, 2008). It may be that the Hib booster vaccine could have decreased the rate of respiratory tract infections, including those classified by GPs as pneumonias.

Nevertheless, the overall incidence of pneumonia diagnosis gradually increased by 30% between 2003 and 2006 (prior the introduction of PCV7) but then declined by 21% in 2007 (post the introduction of PCV7).

The incidence rate for pneumonia diagnosis in the research described here is comparable to a recent study in the UK reported in 2010 by Koshy *et al*. This used the Hospital Episode Statistic (HES) database to identify the impact of PCV7 on childhood hospital admissions for bacterial pneumonia and empyema in England during a 12 year period (1997- 2008).

According to this source the hospital admission rate for children aged <15 years old with bacterial pneumonia increased by 31% from 1997 to 2005 and by 19% from 2004 to 2006. However, it declined by 19% following the addition of PCV7 in 2006 to the national vaccination programme. The authors suggested that the sharper increases prior the introduction of the vaccine in the incidence of bacterial pneumonia admission rates were unlikely to be an indication of the true rises of the disease itself but were more likely due to other factors such as changes in health-seeking behaviour. Furthermore, they noted, the HPA reported that prior to 2006, the number of isolated pneumonia cases were stable (Koshy *et al*., 2010).

This study shows that from 2007 the incidence of pneumonia diagnosis has gradually increased, peaking in 2010. The interpretation offered here is that it is unlikely that this has been due to serotype replacement, and more likely that it is due to low herd immunity in older children/young adults. The results presented in this thesis show that between 2006 and 2010 the incidence of pneumonia diagnoses in the primary care setting appears to have gradually declined in children aged less than 2 years old (see Figure 6.2). This finding is consistent with the available HPA/PHE data on vaccine serotype infection, as shown in Fig. 6.8.

However, with the non-vaccine serotypes the picture is less clear cut (Fig 6.9). It can be concluded that in overall terms PCV7 (and its successor PCV13) has reduced the incidence of pneumonia amongst infants aged less than 2 years old, the target population of the programme. However, this was not true in the older unvaccinated age groups.

**Figure 6.8: Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the seven serotypes in Prevenar 7™: Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2005- To Date) (HPA, 2013a).**

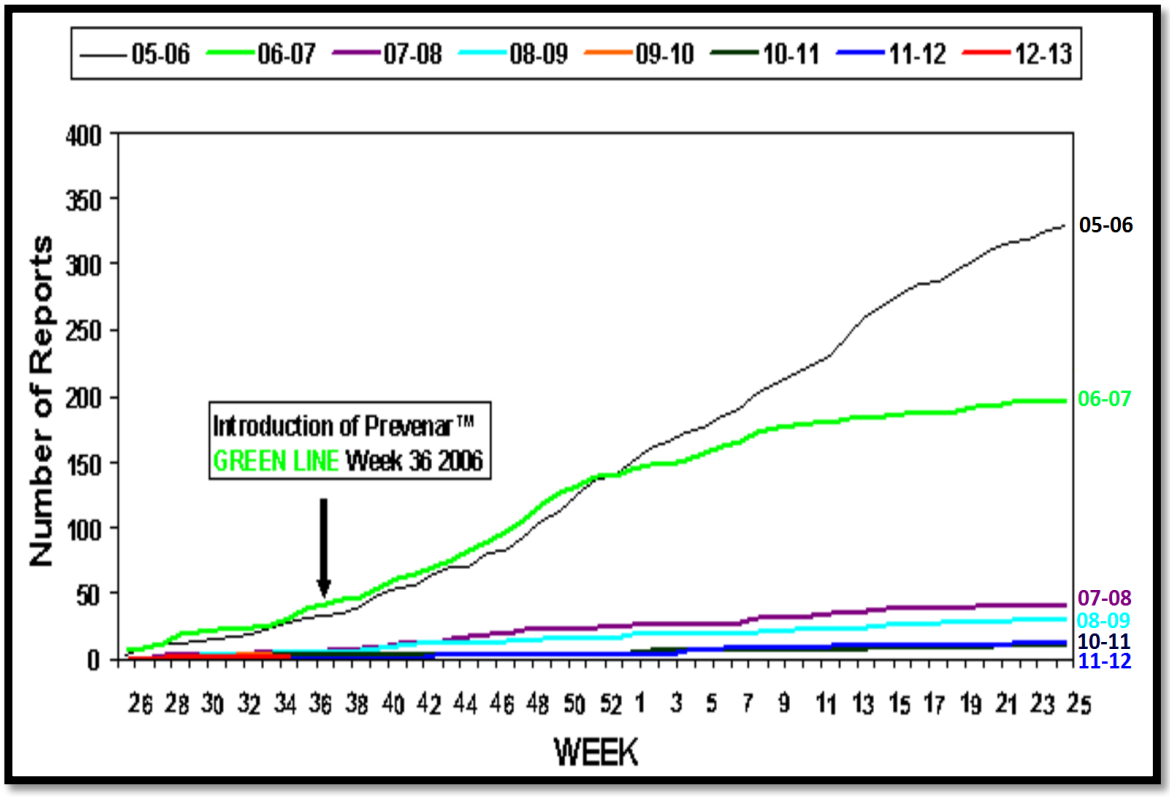
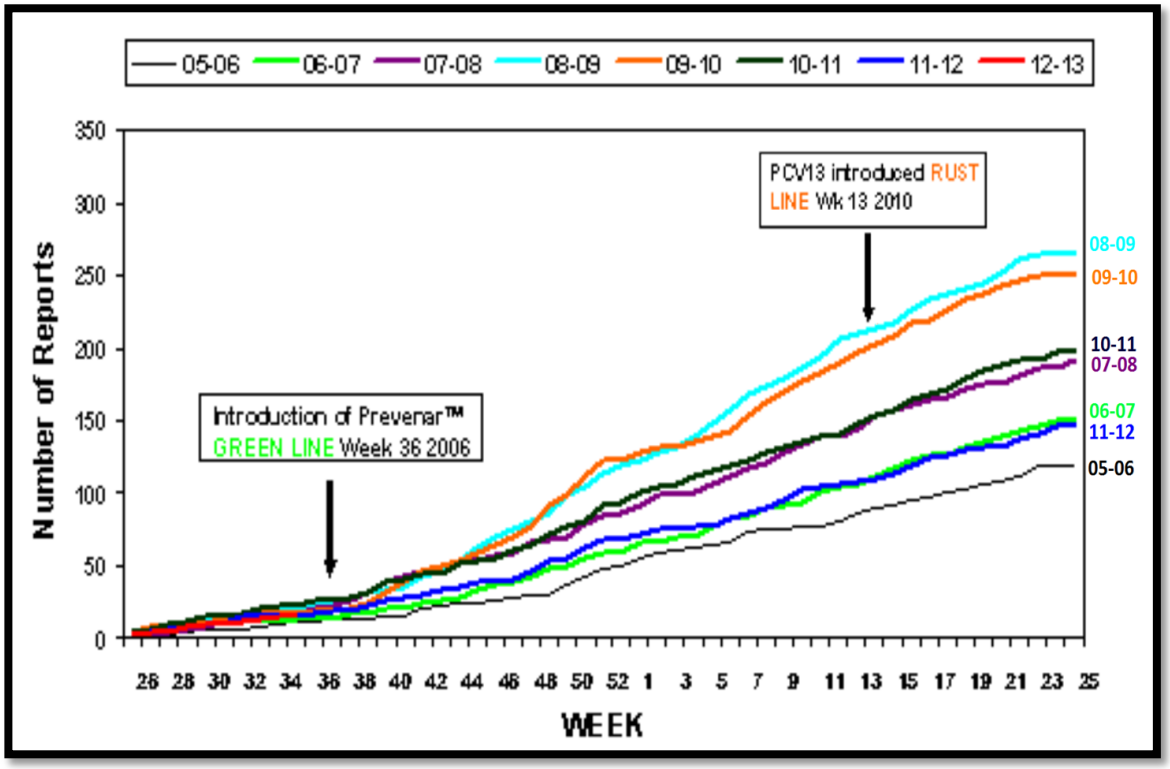


**Figure 6.9: Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the seven serotypes NOT in Prevenar 7™: Persons aged under 2 years in England and Wales by Epidemiological Year: July-June (2005-To Date) (HPA, 2013b).**




Other studies offer similar but more significant results. As already highlighted, in the US it has been reported that a 39% decline in pneumonia admission rates for children aged <2 years old occurred between 2001 and 2004 (National Inpatient Sample data were used – Grijalva *et al.,* 2007). Also, the HPA (now PHE) reported in this country a marked reduction in the rate of IPD cases caused by the seven serotypes in PCV7 since the introduction of the vaccine. Moreover, in 2013, a study by Ladhani *et al.,* using enhanced national surveillance data in England and Wales, reported that even infants aged less than 3 months have derived benefit from PCV7's introduction.

In addition, for those ages between 2-5 years old, 6-10 years and 11-15 years, the incidence of pneumonia apparently declined from 2007 to 2009, but slightly increased in the next year. The older age group was expected to be protected from pneumonia through herd immunity. A recent study found that although hospitalisation rates for childhood pneumococcal pneumonia substantially decreased between 2001 and 2007 (by 61% in children aged less than 2 years and 26% in those aged 2-4 years old) the rate of pneumonia complicated by empyema increased two-fold in children aged <2 years. It rose from 3.5 cases per 100,000 children between 1996-1998 to 7.0 per 100,000 between 2005-2007. It also increased by 2.8 times in children aged 2-4 years old (from 3.7 per 100,000 children in 1996-1998 to 10.3 per 100,000 in 2005- 2007 – Grijalva *et al.,* 2010). Such trends may help explain the increased incidence of pneumonia in the older age groups in this study's data.

Overall, when comparing the various age groups, the results of this analysis show that the burden of pneumonia and antibiotic prescription for pneumonia apparently decreased with increasing age. The highest incidence was seen in children aged less than 2 years old. In general, the incidence of antibiotic treatment follows the same trend as the incidence of pneumonia itself.

Pneumonia has always been one of the primary causes of antibiotic prescribing in children, so it was postulated at the start of the study that the incidence of antibiotic prescribing for pneumonia would correlate closely with the incidence of pneumonia itself.

However, the low incidence of antibiotic prescription in the data could be due to GPs becoming increasingly likely to refer children to hospitals for treatment, particularly if there are concerns relating to factors like the development of complications. They may also seek hospital care if there are uncertainties over the choice of antibiotic at the initiation of treatment as the infecting organism is almost never known at this point. It may also be relevant to note that if there as a need for intravenous antibiotic treatment this is only available in hospitals (British Thoracic Society Standards of Care Committee, 2002 & 2010).

In terms of gender, allthough, there was a fluctuation in the incidence of diagnosis and antibiotic prescribing for pneumonia before the introduction of the vaccine and apparent decline one year post its introduction, incidence rates were consistently higher in males than females. A recent study in the UK also found that males with bacterial pneumonia have higher hospital admission rates than females in all age groups (Koshy *et al.,* 2010).

In addition, this study investigated the incidence of the disease on a quarterly basis. The results underline the fact that seasonal variations are one of the key factors affecting the incidence of pneumonia. Despite the availability of antibiotics and vaccines, invasive pneumococcal diseases in the UK are more prevalent during the winter months (Clarke *et al.,* 2006; Zielhuis *et al.*, 1990).

This pattern of seasonal variation is also mirrored in other infectious diseases (e.g. measles, influenza and whooping cough) (Grassly and Fraser, 2006). Because in this study the overall incidence of pneumonia did not significantly decline it was not possible to use ITS analysis in the same way that it was employed in the previous chapter on OM to analyse the impact of the vaccine in the pneumonia context.

## 6.3 CONCLUSION

This study strand identified that the overall number of pneumonia episodes and level of antibiotic prescribing for pneumonia declined by 14% and 10% respectively in the UK between 2006 and 2010. Nevertheless, the Health Protection Agency (now Public Health England) has recognised that since the introduction of the initial vaccine the incidence of disease due to non-vaccine serotypes has been increasing and that serotype replacement is therefore a concern.

The cumulative incidence of serotypes 7F, 19A and 22F in particular led the HPA and its advisors to recommend the introduction PCV13 into the national childhood vaccination programme in 2010. Taken in its totality this thesis has increased knowledge of the impact of PCV7 on the incidence of OM and pneumonia and related antibiotic prescribing for children and adolescents in the primary care setting in the UK. This work has also systematically evaluated the efficacy of the vaccine by investigating the serotype specific antibody concentrations, geometric mean concentration (GMC) and the local and systemic adverse drug events associated with PCV7 from published RCTs, utilising a systematic review and meta-analysis methodology (see Chapter 3).

In addition, a pharmaco-epidemiological study was performed utilising two large health care databases (The Health Improvement Network database and IMS Disease Analyzer). IMS DA was utilised to investigate immunisation recording in children aged 0-2 years in general practice (Chapter 4) and it was also employed for a retrospective cohort study to evaluate the annual incidence of OM diagnosed in the primary care setting and the antibiotic prescribing patterns associated with OM in both children and adolescents (Chapter 5). The THIN database was used to conduct a retrospective cohort study to estimate the incidence of pneumonia and associated antibiotics in children in the primary care setting.

The final chapter below builds on this body of work to consider the clinical and wider health policy implications of its findings and to provide recommendations for future research.

# CHAPTER SEVEN: OVERALL DISCUSSION

## Overview

The findings presented in this thesis can be taken to confirm the effectiveness of the PCV7 in preventing vaccine serotype related childhood pneumococcal diseases in the UK context. The vaccine is beneficial in preventing invasive pneumococcal disease and it has also played an important role in reducing rates of non-invasive conditions associated with *S. pneumoniae*, most notably Otitis Media in children. The original research reported here found that the overall number of (all cause) pneumonia episodes and antibiotics prescribed by GPs for pneumonia in children and young adults declined by 14% and 10% respectively between 2006 (the year of introduction of the PCV7) and 2010. In addition, the study identified an overall fall of more than a third in OM diagnosis and antibiotic prescribing for the treatment of OM in children between 2006 and 2010.

Given that the PCV7 has now been replaced by the PCV13 (which may in turn – in part because of possible increases in the incidence of currently non-vaccine serotype disease – be superseded by further vaccine changes in the future) this discussion seeks to raise a series of important practice and policy related issues that are as yet unanswered. It will also make comparisons with other studies conducted in this area, both globally and regionally. The impact and value of the collation of routine surveillance data will in addition be considered, and a focus placed on the actual and possible pathogenic (serotype) changes that may in part have led to the need for the PCV13 vaccine's introduction.

Examples of the types of question addressed include 'if currently more prevalent serotypes are effectively eliminated due to vaccine use, what happens to the incidence and virulence of illness caused by other remaining *S. pneumoniae* serotypes?' and 'what are the implications of vaccine use in the very young and young for the health of the older (near or post retirement) population?' People over 65 are more at risk of not only death but also prolonged morbidity because of *S. pneumoniae* infection than any other section of the adult population.

### 7.1 Comparisons with other studies and settings

This study's findings are similar to those of other studies undertaken in the UK and Western Europe. However, it is known that in countries such as the United States much higher rates of IPD incidence have been recorded. In America the reported IPD incidence in children under 2 years of age prior to PCV7 introduction was, for example, far higher (160-180 per 100,000 children) than in the UK (35.7 per 100,000) or in Western Europe overall (20-35 per 100,000) (Poehling *et al.,* 2006; Ladhani *et al.,* 2013b). Such data imply differences in the health gain related value of vaccination programmes in different settings.

It is possible that the higher observed US incidence has been due to a higher proportion of relatively deprived 'at risk' populations (e.g. in the Alaskan Native, American Indian and black/African American communities) coupled with a lower threshold for performing blood cultures in febrile children, especially in the out-patient setting.

It is of note that Ladhani *et al* (2013b) found that in infants under 90 days old the IPD incidence in England was comparable to the US population figures (13.0 per 100,000 compared to 11.8 in the US study). They speculated that this is because infants are more likely to develop severe IPD, to be admitted to hospital, and to have lower thresholds for having blood cultures taken both here and in the US.

Furthermore, in the US study PCV7 serotypes initially accounted for 71% of IPD in young infants. PCV7 introduction in 2000 led to a 39% ($P$ <0.001) overall and 67% ($P$=.004) PCV7 serotype specific IPD reduction within 3 years compared with reductions of 25% and 83% respectively in the Ladhani et al (2013b) study, where the pre-vaccine proportion of PCV7 IPD infections was 44%.

Importantly, the US study cohort had a higher proportion of black/African American infants (34%, compared to only 6% in the Ladhani et al work) who are said to be at a raised risk of IPD. The fall in infant IPD in the US study occurred primarily among black Africans (from 17.1 to 5.2 per 100,000 live births, $P$=0.001) with a far smaller impact among white infants (from 9.6 to 6.8 per 100,000 live births, $P$=0.11) (Poehling *et al.,* 2006).

**7.2 Are there regional variations within the UK?**

Aspects of this question demand further research. Clarke *et al* (2006) reported higher rates of IPD in Scotland and serotype variations across the UK. In Scotland the overall reported incidence of IPD is 11 cases per 100,000 populations in subjects aged up to 1 year and 45 cases per 100,000 in those aged over 65 years. By contrast in England

and Wales the overall incidence of IPD is 8.6 per 100,000 populations, with the highest reported burden among the very young and older people, in whom it is in excess of 30 per 100,000.

The 10 most common pneumococcal serotypes associated with IPD in England and Wales are 14, 9, 6, 19, 23, 8, 1, 4, 18, and 7. The most common serotypes in Scotland are 14, 8, 9V, 1, 3, 22F, 23F, 6B, 18C and 19F (Clarke *et al*., 2006). Such differences suggest that in the future it may be beneficial to tailor *S. pneumoniae* vaccines more to specific regional, national or sub-regional/local protection needs.

### 7.3 The value of routine surveillance and GP record data sets

Microbiology laboratories in England and Wales voluntarily report all clinically significant pneumococcal isolates to what is now the PHE Centre for Infections via a computerised surveillance system called CoSurv. Laboratories are also encouraged to send serotypes to the Respiratory and Systemic Infection Laboratory (RSIL) for serotyping. Yet currently reporting is not required by law and the system remains a voluntary one. Therefore not all pneumococcal isolates are sent to RSIL and CoSurv, and some isolates may be sent to one reporting stream and not the other. In an uncertain number of other cases GPs treat CAP cases on the basis of clinical signs and symptoms alone, without the causal agent ever being clearly identified.

In Scotland, however, reporting of *S. pneumoniae* bacterium infections is mandatory under the Part 2 of the Public Health Act (Scotland) of 2008. This part of the Act came into effect on 1 January 2010. To support notifications, clinicians send reports electronically via SCI Gateway. But although reporting of *S. pneumoniae* is a statutory requirement, IPD itself is not a statutorily notifiable disease. Surveillance is therefore based on local laboratory reports of *S. pneumoniae* from invasive body sites (i.e. mainly blood and cerebral spinal fluid).

In 1999, an enhanced surveillance scheme was introduced, which is jointly managed by HPS and the Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL). Data gathered in this part of the UK are posted to the website http://www.hps.scot.nhs.uk/resp/pneumococcaldisease.aspx (last accessed 16.7.13), enabling researchers and interested clinicians to view the number of cases of IPD per year by quarter and by age group.

Since 1996, a dataset for all invasive pneumococcal infections reported in England and Wales has also been in existence. This links computerised reports sent to the HPA and isolates referred to RSIL for serotyping. It consists of cases where *S. pneumoniae* has been identified by culture or more rarely by antigen detection or polymerase chain reaction (PCR) in a normally sterile site. From January 2006 PCR facilitated diagnosis has been performed by the HPA on cerebrospinal fluid and pleural fluid samples from patients with suspected meningitis or empyema, with serotyping performed via a pneumococcal polysaccharide antigen assay that detects 14 serotypes.

After the introduction of PCV7 in September 2006 all patients with IPD were followed up for vaccination history and clinical presentation, improving diagnosis of cases (Miller *et al.,* 2011). Serotypes 6A and 6C were routinely distinguished from one another from May 2009 onwards. The value of such routine surveillance data is considerable. Relevant datasets have enabled researchers to ascertain the impact and efficacy of the PCV7, particularly in the context of more serious disease (Miller *et al.,* 2011; Ladhani *et al*., 2013a; Ladhani *et al*., 2013b).

Miller *et al* (2011) found that 5,809 cases of IPD were reported in 2009-2010 in England and Wales, giving an overall incidence of 106 per 100,000 populations. This when compared with the adjusted average annual incidence of 16.1 in 2000-2006 gives an overall reduction of 34% (95% CI 28-39). Vaccine type (VT) disease decreased in all age groups, with reductions of 98% in individuals younger than 2 years and by 81% in those aged 65 years or older.

Non-vaccine type (NVT) disease increased by 68% in individuals younger than 2 years and by 48% in those aged 65 years or older, giving an overall reduction in IPD of 56% in those younger than 2 years and 19% in those aged 65 years or older. Using HPA data Ladhani *et al* (2013a) calculated that between September 2006 and March 2010 a total of 1,342 IPD episodes occurred in 1,332 children. In a further study Ladhani *et al* (2013b) also found that prior to PCV7 introduction IPD incidence in infants aged less than 90 days was 13.0 (95% CI, 12.0-14.0) per 100,000 live births and PCV7 serotypes accounted for 44% (154/349) of serotyped isolates.

These data indicated that PCV7 introduction resulted in an 83% (95% CI, 66-91%, P <.001) reduction in PCV7 IPD and a declining trend in overall IPD by 2009-2010. Taken with the results presented in Chapters 5 and 6 of this thesis, such figures mean that there can be little doubt as to the efficacy of the conjugate PCV vaccines in preventing relevant serotype illness in children and others in the UK, albeit that the overall picture in general practice is complicated by a variety of factors.

Robust surveillance data will continue to be needed to assess the epidemiological effect of multivalent pneumococcal disease vaccines. A recommendation for the future would be to fully enshrine the reporting of IPD into a regulatory framework across the whole UK in order to create complete data sets, and prevent the underreporting of cases. Such a measures could also curb non-diagnosis, incomplete diagnosis and potential condition mismanagement in primary care as well as in hospital care.

Nevertheless, a note of caution is required. Miller *et al* (2011) highlighted the complexity of interpreting disease trends in changing clinical, diagnostic and surveillance environments. They have drawn attention to the difficulty of interpreting IPD data from different countries, and of comparing the effect of programmes at different stages of maturity and with surveillance systems targeting different sets of patients. For example, they argue that the extent to which findings from surveillance studies in the UK can be extrapolated to populations such as those in developing countries where bacterial carriage and IPD incidence rates are much higher than in Europe and the US, and where the coverage of prevalent serotypes by PCV7 is lower, is far from clear.

Understanding the full effects of higher valency vaccines will also arguably require robust surveillance systems and good knowledge of the invasiveness potential of non-PCV serotypes (see below), highlighting their prevalence in carriage as well as their prevalence in IPD. This distinction appears to have been overlooked in surveillance systems to date (Miller *et al*., 2011). Additionally Clarke *et al* (2006) raised another issue that has been overlooked in surveillance to date, namely the possibility of simultaneous carriage of more than one pneumococcal serotype. The extent to which simultaneous carriage of different serotypes occurs is unknown and there is arguably a need for future systems to identify all the causative serotypes involved in individual cases of IPD.

A final point to emphasise under this heading is that although aggregated GP record based data sets such as the IMS DA and THIN products used in this research clearly have some utility, their value in relation to detailed research and/or disease surveillance should not be over-stated. Their strengths and weakness reflect those of general medical practice itself. Although they can provide robust overall measures of volumes of activity and drugs prescribed in response to broad categories of symptomatic illness they do not necessarily provide deep insight as to exactly what is being treated, or indeed whether or not prescribed items such as antibiotics are actually dispensed or taken by those for whom they were intended (see further remarks below).

### 7.4 Pathogenic changes over time

There are presently some open questions as to the extent to which, as some previously successful serotype strains are eliminated via vaccine use, others will become more infectious or virulent (or both) in order to exploit the new opportunities available. It is, however, already known that serotype replacement disease does occur in response to vaccination programme roll-outs. As referred to earlier, Miller *et al* (2011) found that after the PCV7 vaccine's introduction more NVT serotypes increased in frequency than decreased. This is entirely consistent with vaccine induced serotype replacement.

Worryingly, in certain countries – including Spain, the Netherlands, France in the EU – and in some indigenous populations in the US and Australia, increases in NVT infections appear largely to have offset the reduction in VT infections following the introduction of PCV7 (Weinberger *et al*., 2011). In the Miller *et al* (2011) study, which examined the effects of the vaccine in England and Wales, the key serotypes showing replacement were 7F, 19A and 22F. Yet they found that increased NVT IPD was not associated with antimicrobial resistance. It may be therefore being argued that as yet at least serotype replacement disease in the UK has not been strengthened through antibiotic resistance.

In addition, Ladhani *et al* (2013a) have observed that compared with IPD caused by PCV7 serotypes (44/248; 17.7%), co-morbidities were less common for the extra 3 serotypes in the 10-valent vaccine (15/2999; 5.0%) but similar to the 3 additional PCV13 serotypes (45/336; 13.4%).

Further, they increased for the 11 extra serotypes in the 23-valent polysaccharide vaccine (PPV23) (38/138; 27.5%). Some 52 (3.9%) cases resulted from PCV7 failure. Furthermore, co-morbidities were more prevalent in children with IPD caused by non-PCV13 serotypes, and were associated with an increased case fatality level.

The overall case fatality rate was 4.4%, but this rose to 9.1% in children with co-morbidities. It may therefore be hypothesised that serotype replacement disease caused by the various vaccines available does not in overall terms increase the risks associated with IPD. That is, to date at least disease potency cannot generally be shown to have increased. Nonetheless, serotype replacement disease is complicated by the fact that those who contract NVT disease may have additional co-morbidities that might affect outcomes.

Ladhani *et al* (2013a) found that in their study cohort the 3 extra PCV10 serotypes were more likely to affect healthy children. They argued that serotypes 1, 5 and 7 (which are included in both PCV10 and PCV13) are known to be highly invasive and to mainly affect previously healthy persons. But they appear to cause less severe disease, as determined by clinical severity and requirement for intensive care. Furthermore, a meta-analysis of 7 different datasets in children found that serotypes 1, 5 and 7 were infrequently isolated among carriage strains but had the highest potential for invasive disease, whereas serotypes that were more likely to be carried (e.g. 6B, 19F and 23F) were less likely to be invasive (Brueggemann *et al* 2004).

Similarly in a study examining the epidemiology of IPD in the pre-conjugate vaccine era (1996-2006) in England and Wales (Trotter *et al*., 2010) it was found that carrier ratios varied substantially by serotype. As might logically be expected, the higher the case:carrier ratio the greater the invasive potential of the serotype. For some serotypes, they found differences in the case:carrier ratio by age (e.g. serotype 18C was more invasive in younger children) but for others this ratio was similar (e.g. serotype 9V). The most common serotypes over the time period in children aged less than 5 years were serotypes 14, 6B and 19F, whereas serotypes 14, 9V, 1 and 8 were most common in those aged 5 years or more. Additionally, there was greater diversity of serotypes in those aged 5 years or more as compared to younger children.

Importantly, Trotter *et al* (2010) also noted that serotype distribution can change over time without vaccine involvement (i.e. through natural secular changes). They observed increases and decreases in major serotypes, predominantly a decrease in the percentage due to serotype 14 and an increase in serotype 1. Such changes over time were also observed in the work of Miller *et al* (2011). The reasons for such shifts are not known, although it has been postulated that factors related to changes in population immunity through natural exposure may be responsible (Trotter *et al*., 2010). The key point to emphasise from the perspective of this thesis and sustained child and public health improvement generally is that the situation is dynamic. Regardless of past events and achievements, continuing adaptations in immunisation and treatment strategies aimed at minimising the harm caused by *S. pneumoniae* infections may from time to time be necessary.

### 7.5 Implications for the very young and older populations

In relation to the very young Ladhani *et al* (2013b) noted a reduction in PCV7 serotype IPDs achieved through indirect protection in neonates and infants starting from birth. Prior to routine pneumococcal vaccination, IPD incidence in infants aged less than 90 days in England and Wales was 13.0 per 100,000 live births, and PCV7 serotypes contributed to 44% of cases. The introduction of PCV7 led to a significant reduction in PCV7 IPD in young infants, most of whom could not (because of the schedule used) have directly benefited from vaccination. Indeed, almost 40% of cases occurred in the first week of life, a third of which were in the first 48 hours of life. The authors state that they believe this indirect protection indicates complex interactions between infants, siblings, parents and other household contacts, in line with the full range of risk factors known to be associated with IPD.

There is evidence that pre-PCV7 neonates who contracted IPD were more likely to be infected with a PCV7 serotype if there were at least 2 siblings in the household and/or if their siblings attended childcare (Hoffman *et al*., 2003). It is concluded here that more work needs to be undertaken on the risk factors for IPD in pregnancy and strategies to prevent mother to child transmission, not least because (like other neonatal pathogens) *S. pneumoniae* is often acquired via the maternal genital tract during the birth process (Hoffman *et al*., 2003).

Questions also remain with regard to the implications of childhood protection for pneumococcal disease incidence in elderly populations. A study by Andrews *et al*. (2012) that evaluated the impact and effectiveness of the 23-valent pneumococcal

polysaccharide vaccine (PPV-23) against IPD in older people in England and Wales found that IPD caused by the serotypes covered by PCV7 declined in those aged 65 or above after 2006, following its introduction in this country. Yet this gain was largely offset by an increase in non-PCV7 serotypes. Furthermore, following the introduction of the PPV23 for all 65 and above year olds in England and Wales (in 2003) they found "…*no discernible impact…*" on IPD incidence or PCV7 induced serotype replacement (Andrews *et al*., 2012, p6802).

This is in contrast to the introduction of PCV7 for children, which these authors found had produced a "…*modest reduction…*" in overall IPD in the elderly and large reductions in PCV7 serotypes through herd protection (Andrews *et al*., 2012, p 6805). They concluded that the impact on overall IPD incidence in the older population from the indirect effects of vaccinating children with PCV7 is more effective than the specific PPV23 programme for the over 65s. Furthermore, they argue that – with the use of higher valency conjugate vaccines for child protection, that by definition cover more serotypes – additional reductions in IPD in older age groups can be anticipated.

The interpretation of such data offered here is that because those older people most at risk from harm due to IPD are likely to have impaired immune responses they are more likely to benefit from population wide herd protection effects than from programmes targeted specifically at their own age group.

However, this does not mean to say that immunisation for the immuno-competent population aged over 50 or 60 using the 23 valent polysaccharide or indeed even more

comprehensive vaccines, necessarily lacks – now or in the future –sufficient value to justify its costs. More research on the interactions between child and older adult pneumococcal diseases is needed to guide policy decisions in this area, alongside work designed to verify the hypothesis expressed above and/or to determine whether or not the relative immuno-competence of older people can cost effectively be determined in primary care or other settings.

### 7.6 Implications for practice

The findings reported in this thesis and discussed in this chapter carry with them a series of implications for medical, nursing and pharmacy practice. Firstly, it is arguably imperative, given that it is unusual in practice for general practitioners to administer vaccines to children, that practice nurses (and where relevant health visitors and school nurses) who provide the national childhood vaccination programme should have direct access to all appropriate levels of electronic patient record. This would enable them to update both immunisation records and where relevant GP based research databases, such as the IMS DA. The validation study offered in Chapter 4 highlights the need for improvement in this context. In addition, when vaccines are administered in the private system to children registered with NHS GPs then the relevant general practices should be informed, and their records updated accordingly.

Second, there is an associated problem in current practice, which is that prescribed medications are recorded as being issued with no check as to whether or not they have in fact been dispensed, let alone taken. It may never be possible accurately to confirm the latter in the community (as opposed to the hospital) setting, but it would be of value

for pharmacists and GP dispensers to be able to record whether items such as antibiotics have been supplied as opposed to, for instance, prescriptions being held on a contingency basis.

This last is of particular importance, given that the current good practice guidelines for OM recommend writing an antibiotic prescription for children with OM symptoms but advising parents and careers not to administer the medication unless the symptoms fail spontaneously to resolve (see Chapters 1 and 5).

Following on from the above, it is thirdly crucial that GPs are aware of the current guidance in this area in order to educate and enable parents to protect their children by ensuring that antibiotics are not administered unnecessarily. The latter can increase individual risks, as well as the long term collective threat of antibiotic resistance.

Fourth, it may be argued that recognition of IPD within the UK would be aided by more blood cultures being performed in children with fevers, in line with other European countries and the US (See Chapter 6 and Trotter *et al*., 2010). Blood cultures and allied tests are currently routinely taken and recorded only when children are being cared for as hospital in-patients.

There is a case for believing that such tests ought in contexts such as IPD management to be performed more frequently in community (GP and linked) settings, albeit this would have some cost implications. A good case exists for saying that if and when

improvements in the available diagnostic technologies occur they should be employed in as timely manner as possible.

Fifth, it may in addition be seen as crucial in both community and hospital care that blood cultures and bacterial sensitivity tests are repeated where there is recurrent pneumonia, in case of alterations in the causative pathogen(s). Lastly, as already addressed, it is also important for in-practice surveillance data that all hospital laboratories across the UK routinely report and submit clinical isolates to the relevant authorities.

### 7.7 Limitations

The main limitations of the linked original studies reported here include their focus on OM and pneumonia alone; the dominance of England and Wales in the sampled data; the under-recording of vaccination in the IMS DA; and the non-utilisation of HPA/Public Health England and Health Protection Scotland surveillance data for comparative purposes. A wider reaching study series might ideally examine additional childhood pneumococcal diseases, not just single diseases from the IPD and NIPD categories, with more extensive national sampling.

Although the recording of vaccination within the IMS DA was validated in this study, using COVER data for comparison and employing supplementary GP questionnaires to confirm whether individual children had been fully vaccinated or not, substantial questions remain over the use of retrospectively completed GP databases. These may in fact (despite payments for record completion) be far from comprehensive in the

immunisation context for the reasons alluded to earlier in this Chapter, and have both missing and non-validated data.

Furthermore, in relation to medicines administration studies, although databases like the IMS DA can inform researchers whether or not a particular medicine has been prescribed, it cannot at present reveal whether the prescription has been dispensed or taken. This limits their value as detailed research tools, albeit they are of value on areas like monitoring broad disease and disease management trends.

**7.8 Implications for future research**

It may be contended that in future a similar research approach to that employed in this analysis would be of use in examining the impact of the PCV13 on OM and pneumonia incidence in children and related antibiotic prescribing. However, if it is accepted on the basis of the findings of this study that vaccine administration is of proven value in preventing OM cases then a more pragmatic way forward could be designed utilising national surveillance data to examine IPD cases in more specific ways.

One important question that presently remains unanswered is 'how can new strategies and vaccines be developed that are better able to prevent pneumonia in children who are most susceptible to harm and reduce further the associated death and disability burden?' Continued surveillance and analysis of comprehensive, adequately specified, data sets will be essential for monitoring the efficacy of on-going and future vaccines, associated serotype replacement disease, and sensitivity to antibiotic treatment and trends in related antibiotic resistance.

Future studies could also examine further in parallel risk factors in the very young (pre-vaccination age), in women of child bearing age and in older populations living in the community and in residential and nursing care facilities. Questions relating to maternal carriage have not been examined in this thesis, but an additional research question for the future might be 'in what if any circumstances should vaccination against *S. pneumoniae* infections be given in or before pregnancy, in order to prevent mother to infant transmission?

**7.9 Originality**

The original contributions of this study can be seen as two-fold. The first was through the methodological approach based on utilising general practice based records. This was in part of value because it allowed cross-comparison between the administration of the vaccine, the occurrence of OM and pneumonia episodes and the prescribing of antibiotic therapy. A second original contribution was made through the focus of this work upon both invasive and non-invasive pneumococcal disease.

Looking at the occurrence and treatment of OM as well as pneumonia was important because it has shown the value of vaccination in preventing non-invasive pneumococcal disease and the associated use of antibiotic medicines, not just IPD.

### 7.10 Final conclusion

In the nineteenth century the work of individuals such as Edward Jenner and Louis Pasteur began to unlock the potential of immunising techniques to protect individuals and populations from infections. This scientific progress is continuing today with further improvements in understanding of the detailed mechanisms of the immune system and the ways in which it can be manipulated to benefit subjects. In the context of protecting children from conditions such as otitis media and pneumococcal pneumonia the recent introduction of conjugate techniques - which in the case of *S. pneumoniae* enable infants' immune systems to respond to weakly immunogenic polysaccharides as they do towards more strongly immunogenic proteins – promises important global opportunities for health improvement.

The evidence presented in this thesis shows that the introduction of Prevnar 7 in the UK reduced the incidence of OM in infants and children, and was also associated with reductions in antibiotic prescribing by GPs for this condition. The research reported here, together with information from sources such as Public Health England, also indicates similar if less pronounced benefits in the context of pneumonia/IPD have been derived from the use of Prevnar 7 and its 13 valent successor Prevnar 13.

Employed effectively such vaccines offer the prospect of further national and international reductions in not only infant and childhood morbidity and mortality, but also contributions to the 21$^{st}$ century task of promoting healthy ageing. However, concerns relating to the issues such as serotype replacement exist and have a degree of validity.

There is a need for the continued and where possible improved monitoring of pneumococcal vaccine effectiveness and the overall consequences of its administration on health outcomes and medicines usage.

The key contribution of this thesis is to further confirm the existence and extent of the health gains to date achieved via vaccination against *S. pneumoniae* infection in children. Challenges such as the emergence of non-vaccine serotype forms of disease may well have to be overcome in future decades, along with in England (and elsewhere) problems in areas such as diagnostic and record keeping precision in the community setting. But in the final analysis the demonstrated capacity of vaccines such as Prevnar 7 and 13 to help further reduce reliance on antibiotics and enhance human welfare is of major importance. It deserves informed recognition, and justifies further future investment in areas such as immunisation schedule evaluation and development.

# APPENDICES

## APPENDIX 1A: GP COVERING LETTER AND QUESTIONNAIRE

Impact of Prevnar® on the burden of disease due to Otitis Media in children in the UK

Dear GP,

At the Centre for Paediatric Pharmacy Research we are investigating the impact of 7-valent Pneumococcal Conjugate Vaccine (Prevnar®) in children. In September 2006, Prevnar® was introduced into the UK routine childhood immunisation programme. Our project aims to characterise the incidence rates of Otitis Media and antibiotic prescribing patterns for Otitis Media (OM) in children before and after the introduction of Prevnar®. The IMS Disease Analyser (IMS DA) database will be used to investigate the impact of Prevnar® on both OM and antibiotic drug prescribing in children aged 0-18 years. Different healthcare professionals such as practice nurses, health visitors and school nurses can also administer vaccine to children. However, as not all health professionals have direct access to the patients' electronic record, this potentially leads to under-recording of the immunisation history. Thus, we would like to validate the immunisation record of children aged 0-2 years in the primary care setting, in the IMS DA database through questionnaires sent to their GP.

We have identified a cohort of patients in 2009 on the IMS DA database that did not have any immunisation record. We would be grateful if you would complete this questionnaire to aid us in this important research. All data received is anonymised and will be treated with the utmost confidence and no individual cases will be reported.

This project is funded by the Libyan Government for a PhD student and a research grant from St. George's Hospital which is indirectly funded by the Wyeth (manufacturer of Prevnar®) to employ a research fellow. As questionnaire may take about few minutes to complete, we will offer you £15 for your assistance in this validation study.

As this is an epidemiological project, it is important that we receive all the information requested as this is necessary for meaningful results.

Your cooperation will be very much appreciated.

Many thanks in advance.

Professor Ian Wong
Centre for Paediatric Pharmacy Research
(A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street Hospital for Children)
Level 1, BMA House
Tavistock Square
London WC1H 9JP

**Impact of Prevnar® on the burden of disease due to Otitis Media in children in the UK-Questionnaire:**

Has this child had Prevnar® vaccine? (Please tick boxes)

| Practice ID | Patient ID | Age | Sex | Year of birth |
|---|---|---|---|---|
| | | | | |

☐ Yes ☐ No

## APPENDIX 1B: AMENDMENT GP COVERING LETTER

The School of Pharmacy
University of London
1st Floor, BMA House
Tavistock Square
London WC1H 9JP
T 020 7874 1530
F 020 7378 5693
www.pharmacy.ac.uk

Dear ISEAC members,

Re: protocol: "Impact of Prevenar on the burden of disease due to Otitis Media in children in the UK" (No: 2009/ISEAC/001)
I would be grateful if the ISEAC would consider and approve the following amendments of the above study.

1. Validation study

The ISEAC has already approved that a questionnaire would be sent to the GPs to confirm immunisation records of selected patients.

However, after further investigation of the immunisation records in the IMS DA, we have concluded that it is necessary to defer the questionnaire study.

Prevenar vaccine is given at two months, four months of age and 15months of age. A catch-up programme is recommended for those aged <2 years who were not vaccinated.

To identify all vaccinated/ unvaccinated children born in 2008, it is necessary to follow up for at least 2 years and 2010 data are needed. Hence we propose to postpone the questionnaire until mid 2011 when the 2010 data are available and fully analysed.
Many thanks in advance.

Professor Ian Wong
Centre for Paediatric Pharmacy Research
(A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street
Hospital for Children)
Level 1, BMA House
Tavistock Square
London WC1H 9JP

## APPENDIX 2: PCV7 NOTEREAD44OR5CODE

| READ_4or5_CODE | READ_4or5_TEXT |
|---|---|
| **65720** | Pneumococcal vaccination given |
| **.9Oo.** | Pneumococcal vaccination admin |
| **.6572** | Pneumococcal vaccination |
| **.n4b.** | PNEUMOCOCCAL VACCINE |
| **.68Ne** | Consent pneumococcal vaccine |
| **.657K** | Booster pneumococcal vaccinatn |
| **.Q5AC** | Adv reac: pneumococcal vaccine |
| **.657N** | 3rd pneumococcal conjug vaccine |
| **.657M** | 2nd pneumococcal conjug vaccine |
| **.657L** | 1st pneumococcal conjug vaccine |

## APPENDIX 3: ETHICAL APROVAL FROM IMS DA

10 October 2008

Professor Ian Wong
Centre for Paediatric Pharmacy Research
The School of Pharmacy, University of London,
First Floor , BMA House,
Tavistock Square,
London,
WC1H 9JP

Dear Ian,

I am writing to confirm that the Centre for Paediatric Pharmacy Research has submitted a protocol to the Independent Scientific and Ethics Committee established to review uses of the IMS Disease Analyzer database. The Committee approved the use of the database for drug utilisation studies in children as described in that protocol.

Yours sincerely

[redacted]

**Peter Stephens**
**VP Public Health Affairs Europe, Middle East & Africa,**
**IMS Co-ordinator for ISEAC**
IMS Health®
7 Harewood Avenue
London, NW1 6JB, UK
Tel: +44 207 393 5323 Mobile: +44 (0)7711 148653
email: pstephens@uk.imshealth.com
www.imshealth.com

**IMS HEALTH**
7 Harewood Avenue
London NW1 6JB
United Kingdom

Tel +44(0)20 7393 5300
Fax +44(0)20 7393 5900
www.imshealth.com

## APPENDIX 4: ANTIBIOTICS LISTED UNDER THE ATC THERAPEUTIC MAIN GROUP J01: FOR ANTIBACTERIAL SYSTEMIC USE

| atc4_code | Substance |
|---|---|
| J01A0 | DOXYCYCLINE |
| J01A0 | LYMECYCLINE |
| J01A0 | OXYTETRACYCLINE |
| J01A0 | TETRACYCLINE |
| J01B0 | CHLORAMPHENICOL |
| J01C1 | AMOXICILLIN |
| J01C1 | AMPICILLIN |
| J01C1 | AMPICILLIN + FLUCLOXACILLIN |
| J01C1 | CLAVULANIC ACID + AMOXICILLIN |
| J01D1 | CEFACLOR |
| J01D1 | CEFADROXIL |
| J01D1 | CEFALEXIN |
| J01D1 | CEFIXIME |
| J01D1 | CEFPODOXIME PROXETIL |
| J01D1 | CEFRADINE |
| J01D1 | CEFUROXIME AXETIL |
| J01E0 | SULFAMETHOXAZOLE + TRIMETHOPRIM |
| J01E0 | TRIMETHOPRIM |
| J01F0 | AZITHROMYCIN |
| J01F0 | CLARITHROMYCIN |
| J01F0 | CLINDAMYCIN |
| J01F0 | ERYTHROMYCIN |
| J01G1 | CIPROFLOXACIN |
| J01G1 | LEVOFLOXACIN |
| J01H1 | FLUCLOXACILLIN |
| J01H1 | PENICILLIN G |
| J01H1 | PENICILLIN V |
| J01X9 | FUSIDIC ACID |

## APPENDIX 5: OTITIS MEDIA READ-CODES

| read_4or5_code | read_4or5_text |
|---|---|
| 0.1492 | H/O: chronic ear infection |
| .1C3. | Earache symptoms |
| .1C32 | Unilateral earache |
| .1C33 | Bilateral earache |
| .1C3Z | Earache symptom NOS |
| .2D6. | O/E - discharge from ear |
| .2D7. | O/E - painful ear |
| .2D7Z | O/E - painful ear NOS |
| .2D92 | O/E-otoscopy:dull light reflex |
| .2D93 | O/E - otoscopy:no light reflex |
| .2D94 | O/E - tympanic membrane pink |
| .2D95 | O/E - tympanic membrane red |
| .2D96 | O/E -tympanic membrane bulging |
| .2D97 | O/E-otoscopy:central perforat. |
| .2D98 | O/E - otoscopy:posterior perf. |
| .2D99 | O/E - tympanic membrane tear |
| .2D9A | O/E -otoscopy:fluid-middle ear |
| .2D9B | O/E - tympanic membr retracted |
| 0.3145 | Magnifying otoscopy |
| 0.7434 | Myringoplasty |
| .F62. | Nonsuppurative Otitis Media |
| .F621 | Acute nonsupp. Otitis Media |
| .F622 | Chronic serous Otitis Media |
| .F623 | Chronic mucoid Otitis Media |
| .F625 | Otitis Media NOS |
| .F62Z | Chr. nonsupp. Otitis Media NOS |
| .F63. | Suppurative Otitis Media |
| .F631 | Acute suppurative Otitis Media |
| .F633 | Chronic purulent Otitis Media |
| .F63Z | Purulent Otitis Media NOS |
| .F671 | Perforation of ear drum |
| .F679 | Otalgia - earache |
| .I6.. | *OTITIS MEDIA [no drugs here] |
| 7312 | Repair of tympanic membrane |
| 73120 | Myringoplasty with fat/gelatin |
| 73121 | Revision of myringoplasty |

| *read_4or5_code* | read_4or5_text |
|---|---|
| 73122 | Myringoplasty using biol graft |
| 73123 | Excsn retract pocket tymp memb |
| 73124 | Myringoplasty nec |
| 73125 | Combined appr tympanoplasty |
| 7312y | Repair of eardrum (TM) OS |
| 7312z | Repair of eardrum (TM) NOS |
| 73133 | T-tube insertion tympanic memb |
| 73160 | Tympanoplasty-biological graft |
| 73161 | Tympanoplasty-artif prosthesis |
| 73162 | Revision of tympanoplasty |
| 73163 | Tympanoplasty nec |
| 73173 | Removal tymp membr vent tube |
| 73175 | Incision of eardrum NEC |
| 73177 | Maintenance vent tube eardrum |
| 73178 | Unblocking vent tube tymp memb |
| 7317A | Replace vent tube tymp memb |
| 7317B | Replace grommet tymp membrane |
| 7K344 | Arthroscpc tot med meniscectmy |
| A552. | Postmeasles Otitis Media |
| F5019 | Other acute ext.ear infections |
| F51.. | Nonsupp Otitis Media + eustach |
| F510. | Acute non supp Otitis Media |
| F5101 | Acute serous Otitis Media |
| F5102 | Acute mucoid Otitis Media |
| F5103 | Acute sanguinous Otitis Media |
| F5104 | Acute allerg.serous otit.media |
| F5105 | Acute allerg.mucoid otit.media |
| F510z | Acute nonsup.Otitis Media NOS |
| F511. | Chron ot media with eff-serous |
| F511z | Chronic serous otit.media NOS |
| F512. | Chron ot med with eff-mucoid |
| F5120 | Glue ear, unspecified |
| F5121 | Mucosanguinous chr.otit.media |
| F512z | Chronic mucoid otitis med. NOS |
| F513. | Chron ot med with eff-other |
| F5130 | Chronic allergic Otitis Media |
| F5131 | Chron ot med with eff-purulent |

| *read_4or5_code* | read_4or5_text |
|---|---|
| F514. | Nonsupp. Otitis Media unspec. |
| F5141 | Serous Otitis Media NOS |
| F5140 | Allergic Otitis Media NOS |
| F5142 | Catarrhal Otitis Media NOS |
| F5143 | Mucoid Otitis Media NOS |
| F514z | Nonsuppurat. Otitis Media NOS |
| F518. | Chron ot med with eff-unspec |
| F52.. | Suppurative Otitis Media |
| F520. | Acute suppurative Otitis Media |
| F5200 | Acute supp.otit.media-drum OK |
| F520z | Acute supp. Otitis Media NOS |
| F521. | Chron supp ot med-tubotympanic |
| F523. | Chronic supp.Otitis Media NOS |
| F524. | Purulent Otitis Media NOS |
| F5240 | Bilateral supp Otitis Media |
| F525. | Recurrent acute Otitis Media |
| F526. | Acute left Otitis Media |
| F527. | Acute right Otitis Media |
| F528. | Acute bilateral Otitis Media |
| F52z. | Otitis Media NOS |
| F54.. | Other tympanic membrane disord |
| F540. | Acute myringitis-no otitis med |
| F542. | Tympanic membrane perforation |
| F5420 | Tympanic membrane perf.unspec. |
| F5421 | Tympanic membrane-central perf |
| F5422 | Tympanic membrane-attic perf. |
| F5423 | Other marginal tymp.membr.perf |
| F5424 | Tympanic membr.multiple perfs. |
| F5425 | Tympanic membr perf > 50% |
| F5426 | Tympanic memb perf < 50% |
| F542z | Tympanic membrane perf. NOS |
| F54y. | Other tympanic membrane disord |
| F54y0 | Healed tympanic membrane perf. |
| F54y1 | Atrophic flaccid tymp.memb.NOS |
| F54y2 | Atrophic nonflaccid tymp membr |
| F54y3 | Retraction tympanic membrane |
| F54yz | Other tympanic membr.dis.NOS |

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| *read_4or5_code* | read_4or5_text |
|---|---|
| F54z. | Tympanic membrane disorder NOS |
| F5501 | Tympanoscler.-tymp.membr.only |
| F5614 | Otogenic vertigo |
| F587. | Otalgia |
| F5870 | Otalgia, unspecified |
| F5502 | Tympanoscl.-tymp.membr.+ossicl |
| F5871 | Otogenic pain |
| F587z | Otalgia NOS |
| F5902 | Cond.hearing loss-tymp.membr. |
| FyuP0 | [X]O ac nonsuppurtv otitis med |
| FyuP2 | [X]O chrn suppurtve otitis med |
| FyuP3 | [X]Otitis med/bact disease CE |
| FyuP4 | [X]Otitis Media/viral dis CE |
| FyuP5 | [X]Otitis Media/oth disease CE |
| FyuP8 | [X]O margn perfortn/tymp membr |
| FyuP9 | [X]Oth perfortn/tympanic membr |
| FyuPA | [X]O spcf disor/tympanic membr |

## APPENDIX 6: ANTIBIOTIC LISTED UNDER THE BNF-C HEADER :ANTIBACTERIAL DRUGS

| Drug Substance Name | BNF-C Code | BNF-C Header |
|---|---|---|
| Benzylpenicillin | 5010101 | Benzylpenicillin & phenoxymethylpenicillin |
| Phenethicillin | 5010101 | Benzylpenicillin & phenoxymethylpenicillin |
| Phenoxymethylpenicillin | 5010101 | Benzylpenicillin & phenoxymethylpenicillin |
| Flucloxacillin | 5010102 | Penicillinase-resistant penicillins |
| Temocillin | 5010102 | Penicillinase-resistant penicillins |
| Amoxicillin | 5010103 | Broad-spectrum penicillins |
| Ampicillin | 5010103 | Broad-spectrum penicillins |
| Bacampicillin | 5010103 | Broad-spectrum penicillins |
| Ciclacillin | 5010103 | Broad-spectrum penicillins |
| Clavulanic acid | 5010103 | Broad-spectrum penicillins |
| Cloxacillin | 5010103 | Broad-spectrum penicillins |
| Lansoprazole | 5010103 | Broad-spectrum penicillins |
| Pivampicillin | 5010103 | Broad-spectrum penicillins |
| Pivmecillinam | 5010103 | Broad-spectrum penicillins |
| Sultamicillin | 5010103 | Broad-spectrum penicillins |
| Talampicillin | 5010103 | Broad-spectrum penicillins |
| Carfecillin | 5010104 | Antipseudomonal penicillins |
| Pivmecillinam | 5010105 | Mecillinams |
| Cefaclor | 5010200 | Cephalosporins and other beta-lactams |
| Cefadroxil | 5010200 | Cephalosporins and other beta-lactams |
| Cefixime | 5010200 | Cephalosporins and other beta-lactams |
| Cefpodoxime | 5010200 | Cephalosporins and other beta-lactams |
| Cefprozil | 5010200 | Cephalosporins and other beta-lactams |
| Ceftibuten | 5010200 | Cephalosporins and other beta-lactams |
| Cefuroxime | 5010200 | Cephalosporins and other beta-lactams |
| Cephalexin | 5010200 | Cephalosporins and other beta-lactams |
| Cephradine | 5010200 | Cephalosporins and other beta-lactams |
| Bromhexine hydrochloride | 5010300 | Tetracyclines |
| Chlortetracycline | 5010300 | Tetracyclines |
| Clomocycline | 5010300 | Tetracyclines |
| Demeclocycline | 5010300 | Tetracyclines |
| Doxycycline | 5010300 | Tetracyclines |
| Lymecycline | 5010300 | Tetracyclines |
| Minocycline | 5010300 | Tetracyclines |
| Nystatin | 5010300 | Tetracyclines |
| Oxytetracycline | 5010300 | Tetracyclines |
| Tetracycline | 5010300 | Tetracyclines |
| Framycetin | 5010400 | Aminoglycosides |
| Neomycin | 5010400 | Aminoglycosides |
| Azithromycin | 5010500 | Macrolides |
| Clarithromycin | 5010500 | Macrolides |

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| Drug Substance Name | BNF-C Code | BNF-C Header |
|---|---|---|
| Erythromycin | 5010500 | Macrolides |
| Telithromycin | 5010500 | Macrolides |
| Clindamycin | 5010600 | Clindamycin |
| Lincomycin | 5010600 | Clindamycin |
| Chloramphenicol | 5010700 | Some other antibacterials |
| Colistin sulphate | 5010700 | Some other antibacterials |
| Fusidic acid | 5010700 | Some other antibacterials |
| Linezolid | 5010700 | Some other antibacterials |
| Vancomycin | 5010700 | Some other antibacterials |
| Calcium sulphaloxate | 5010800 | Sulphonamides & trimethoprim |
| Phenazopyridine | 5010800 | Sulphonamides & trimethoprim |
| Phthalylsulfathiazole | 5010800 | Sulphonamides & trimethoprim |
| Sulfametopyrazine | 5010800 | Sulphonamides & trimethoprim |
| Sulphamethoxazole | 5010800 | Sulphonamides & trimethoprim |
| Sulphaurea | 5010800 | Sulphonamides & trimethoprim |
| Trimethoprim | 5010800 | Sulphonamides & trimethoprim |
| Metronidazole | 5011100 | Metronidazole and tinidazole |
| Tinidazole | 5011100 | Metronidazole and tinidazole |
| Acrosoxacin | 5011200 | Quinolones |
| Cinoxacin | 5011200 | Quinolones |
| Ciprofloxacin | 5011200 | Quinolones |
| Citric acid | 5011200 | Quinolones |
| Enoxacin | 5011200 | Quinolones |
| Grepafloxacin | 5011200 | Quinolones |
| Levofloxacin | 5011200 | Quinolones |
| Moxifloxacin | 5011200 | Quinolones |
| Nalidixic acid | 5011200 | Quinolones |
| Norfloxacin | 5011200 | Quinolones |
| Ofloxacin | 5011200 | Quinolones |
| Sodium bicarbonate | 5011200 | Quinolones |
| Sodium citrate | 5011200 | Quinolones |
| Sparfloxacin | 5011200 | Quinolones |
| Temafloxacin | 5011200 | Quinolones |
| Amoxycillin | 5011300 | Urinary-tract infections |
| Fosfomycin | 5011300 | Urinary-tract infections |
| Methenamine | 5011300 | Urinary-tract infections |
| Nitrofurantoin | 5011300 | Urinary-tract infections |
| Pivmecillinam | 5011300 | Urinary-tract infections |

## APPENDIX 7: READ-CODE FOR PNEUMONIA

| read_4or5_code | read_4or5_text |
|---|---|
| **H062.** | Acute low respitract infection |
| **H06z1** | Lower resp tract infection |
| **H2...** | Pneumonia and influenza |
| **H21..** | Lobar (pneumococcal) pneumonia |
| **H22..** | Other bacterial pneumonia |
| **H220.** | Pneumonia - klebsiella pneum. |
| **H221.** | Pneumonia - pseudomonas |
| **H222.** | Pneumonia - H.influenzae |
| **H223.** | Pneumonia - streptococcal |
| **H2230** | Pneumonia due/streptococc,gp B |
| **H224.** | Pneumonia - staphylococcal |
| **H22y.** | Pneumonia - other specif.bact. |
| **H22y2** | Pneumonia - Legionella |
| **H22yz** | Pneumonia - bacteria NOS |
| **H22z.** | Bacterial pneumonia NOS |
| **H23..** | Pneumonia - specif.organisms |
| **H231.** | Pneumonia - mycoplasma pneumon |
| **H233.** | Chlamydial pneumonia |
| **H23z.** | Pneumonia - spec.organism NOS |
| **H24..** | Pneumonia + Infect.disease EC |
| **H240.** | Pneumonia + measles |
| **H243.** | Pneumonia + whooping cough |
| **H246.** | Pneumonia + aspergillosis |
| **H24y.** | Pneumonia+other infect.dis.EC |
| **H24y2** | Pneumonia + pneumocyst.carinii |
| **H24y7** | Pneumonia + varicella |
| **H25..** | Bronchopneumonia,organism unsp |
| **H26..** | Pneumonia, organism unspecif. |
| **H260.** | Lobar pneumon-unspec organism |
| **H261.** | Basal pneumon-unspec organism |
| **H262.** | Postoperative pneumonia |
| **H270.** | Influenza + pneumonia |
| **H2700** | Influenza + bronchopneumonia |
| **H28..** | Atypical pneumonia |
| **H2y..** | Pneumonia or influenza OS |
| **H2z..** | Pneumonia or influenza NOS |
| **H5303** | Abscess of lung with pneumonia |

| read_4or5_code | read_4or5_text |
|---|---|
| **H5400** | Hypostatic pneumonia |
| **H564.** | Bronchioliti oblit organ pneum |
| **H56y1** | Interstitial pneumonia |

## APPENDIX 8: ETHICAL APPROVAL LETTER FROM THIN (SRC)

# SRC Feedback

**Researcher Name:** Dr Macey Murray
**Organisation:** London school of Pharmacy
**SRC Reference Number:** 11-031
**Date:** 19/10/2011
**Study title:** A single Integrated Study of the Impact of Pneumococcal Conjugate Vaccination (PCV-7 and PCV13) on childhood pneumococcal diseases in both the community and hospital setting in the UK
**Committee opinion:** Approved

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**The following feedback has been supplied by the SRC.**
*The chair has approved this study with the following advice:*
*"A caution in terms of ensuring that they are clear about their exposures and outcomes and appropriate analyses to address their question -they need to seek further understanding of this. In particular their answer to Q4. Is "Following our discussion with our statistical advisor, we agreed to use Linear Regression for the analysis." – as their outcome is incidence it is not clear how this is appropriate – more careful consideration is needed in how they plan to do this analysis. I trust that they will seek this out doing the course of the study, however."*

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We are pleased to inform that you can proceed with the study as this is now approved.
Once the study has been completed and published, you must let CSD Medical Research know in order for your reference number to be closed.
CSD Medical Research will let the relevant Ethics committee know this study has been approved by the SRC and will inform them of study completion (when known) on your behalf.
I wish you and your team all the best with the study progression.
Kind Regards,
Mustafa Dungarwalla

Research Associate

## APPENDIX 9: QUALITY CHECK OF THE TWO STUDIES INCLUDED IN META-ANALYSIS VIA CONSORT STATEMENT 2001 – CHECKLIST

Article: Cheng Li, R *et al,* Safety and immunogenicity of a 7-valent pneumococcal conjugate vaccine (PCV7): primary dosing series in healthy Chinese infants, Vaccine 26, 2260-2269 (2008)

| PAPER SECTION And topic | Item | Descriptor | Reported on Page # |
|---|---|---|---|
| TITLE & ABSTRACT | 1 | How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned"). | 2260 |
| INTRODUCTION Background | 2 | Scientific background and explanation of rationale. | 2260,2261 |
| METHODS Participants | 3 | Eligibility criteria for participants and the settings and locations where the data were collected. | 2261 |
| Interventions | 4 | Precise details of the interventions intended for each group and how and when they were actually administered. | 2261 |
| Objectives | 5 | Specific objectives and hypotheses. | 2261 |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). | 2261 |
| Sample size | 7 | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules. | 2262 |
| Randomization -- Sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification) | N/A |
| Randomization -- Allocation concealment | 9 | Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were | N/A |

| | | | |
|---|---|---|---|
| | | assigned. | |
| Randomization -- Implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. | N/A |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. | N/A |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses. | 2263 |
| RESULTS Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. | 2262 |
| Recruitment | 14 | Dates defining the periods of recruitment and follow-up. | 2261 |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group. | 2263 |
| Numbers analyzed | 16 | Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%). | 2263 |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval). | 2263,2264, 2265 |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating | N/A |

| | | | |
|---|---|---|---|
| | | those pre-specified and those exploratory. | |
| Adverse events | 19 | All important adverse events or side effects in each intervention group. | 2267,2268,2269 |
| DISCUSSION Interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes. | 2268 |
| Generalizability | 21 | Generalizability (external validity) of the trial findings. | N/A |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence. | N/A |

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Article: Black,S et al, Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children, The Pediatric Infectious Diseases Journal, 187-195 (2000)

| PAPER SECTION And topic | Item | Descriptor | Reported on Page # |
|---|---|---|---|
| TITLE & ABSTRACT | 1 | How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned"). | 187 |
| INTRODUCTION Background | 2 | Scientific background and explanation of rationale. | 187 |
| METHODS Participants | 3 | Eligibility criteria for participants and the settings and locations where the data were collected. | 188 |
| Interventions | 4 | Precise details of the interventions intended for each group and how and when they were actually administered. | 188 |
| Objectives | 5 | Specific objectives and hypotheses. | 187 |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). | N/A |
| Sample size | 7 | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules. | N/A |
| Randomization -- Sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification) | 188 |
| Randomization -- Allocation concealment | 9 | Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. | N/A |
| Randomization -- | 10 | Who generated the allocation sequence, who enrolled | N/A |

| | | | |
|---|---|---|---|
| Implementation | | participants, and who assigned participants to their groups. | |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. | 189 |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses. | 190 |
| RESULTS<br>Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. | 189,190 |
| Recruitment | 14 | Dates defining the periods of recruitment and follow-up. | |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group. | |
| Numbers analyzed | 16 | Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%). | 189,190 |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval). | 193 |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory. | N/A |
| Adverse events | 19 | All important adverse events or side effects in each | 192 |

| | | | |
|---|---|---|---|
| | | intervention group. | |
| DISCUSSION<br>Interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes. | 194,195 |
| Generalizability | 21 | Generalizability (external validity) of the trial findings. | N/A |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence. | 194,195 |

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## APPENDIX 10: POSTER PRESENTATION (DRUG UTILISATION RESEARCH GROUP)

Impact of 7-valent Pneumococcal Conjugate Vaccine (PCV-7) on Otitis Media and Antibiotic Prescribing for Otitis Media on children and adolescent aged 0-18 years in United Kingdom

A.A. Elturki[1], Y.F. Hsia[1], P.F.Long[2], M. Sharland[3]and I.C.K.Wong[1].

[1]Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London

[2]Department of Pharmaceutics and Centre for Paediatric Pharmacy Research, The School of Pharmacy

[3]Paediatric Infectious Disease Unit, St. George's Hospital

**ABSTRACT**

Background: In 2006, the 7-valent pneumococcal conjugate vaccine (PCV-7) was introduced to the childhood immunization schedule in the UK. Studies from the USA and continental Europe have shown that PCV-7 reduced the incidence of Otitis Media (OM) and antibiotic prescribing in children. Our previous study reported a similar decline in OM diagnosis and antibiotic prescribing for OM treatment that may be related to the introduction of UK guidance in 1997 to restrict the use of antibiotic for OM treatment. However, it still remains unclear if there has been any change in OM management since the introduction of PCV-7 into UK General Practice.

**Objectives:** To investigate the incidence rate of OM and antibiotic prescribing for OM treatment before and after the introduction of PCV-7 in children and adolescents.

**Methods:** A retrospective cohort study was conducted using the UK Integrated Medical Systems Disease Analyzer (IMS DA) database. The cohort comprised all children and adolescents aged 0-18 years between 1 January 2001 and 31 December 2008.

**Results:** The IMS DA study population was composed of 270,092 children and adolescents. Of these, 35,184 had a diagnosis of OM, of which 30,703 (87%) received a prescription.
The incidence rate of OM significantly declined from 76 per 1000 person-years (95% CI: 75-78) in 2001 to 47 per 1000 person-years (95% CI: 46-48) in 2008. During the same time period, antibiotic prescribing for OM treatment also declined from 54 per 1000 person-year (95% CI: 53-55) in 2001 to 31 per 1000 person-year (95% CI: 30-31) in 2008.

**Conclusion:** The incidence of OM and antibiotic prescribing has significantly declined in the past 8 years. This decline, however, predated the introduction of PCV-7. The data will now be analyzed using an interrupted time series (ITS).

## APPENDIX 11: ORAL PRESENTATION (ROYAL COLLEGE OF PAEDIATRICS AND CHILD HEALTH)

Impact of 7-valent Pneumococcal Conjugate Vaccine (PVC-7) on the incidence and treatment of Pneumonia diagnosed in primary care in children and adolescents in United Kingdom

A.A. Elturki[1], Y.F. Hsia[1], S Saxena [2], P.F.Long[3], I.C.K.Wong[1]and M. Sharland[4]

[1]Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London
[2] Departments of Primary Care and Public Health, Imperial College London
[3]Pharmaceutical Science Institute, King's College London
[4]Paediatric Infectious Disease Unit, St. George's Hospital

**ABSTRACT**

**Background:** It has been estimated that over 2 million children under 5 years of age die from pneumonia each year worldwide. *Streptococcus pneumonia* is the main cause of pneumonia in children. In September 2006, 7-valent Pneumococcal Conjugate Vaccine (PCV7) vaccine was introduced into the childhood immunisation schedule. A study from USA has noted that PCV7 vaccine reduced the incidence of pneumococcal pneumonia diagnoses in children under- 5 years of age by 18%. However, the impact of PCV7 on the diagnosis and antibiotic treatment of all cause pneumonia in primary care in the UK is unclear.

**Objective:** To investigate the incidence rate of pneumonia and antibiotic prescription for pneumonia treatment in children aged 0-18 years in the UK primary care between 2002 and 2009.

**Methods:** A retrospective cohort study was conducted using the UK IMS Disease Analyzer (IMS DA) database. The cohort comprised all children and adolescents aged 0-18 years between 1 January 2002 and 31 December 2009 (study period). Broad Read Codes of all cause pneumonia were used and the impact of PCV7 was determined by comparing different age groups over time.

**Results:** 302,781 children and adolescents aged 0 to 18 years within the IMS DA study population between 2002 and 2009 were identified. There were 813 patients (0.3%) with a diagnosis of pneumonia, and 51% of these (417/813) received an antibiotic prescription.
Overall pneumonia diagnoses were stable, but there was a significant decline in pneumonia diagnoses in the under 2 year age group from 2.8/1000 person-years (95% CI: 2.6-3.1) in 2006 to 1.8/1000 person-years (95%CI: 1.6-2.0) in 2009, a 35.7 % reduction.
Antibiotic prescribing for pneumonia in children aged under 2 years had also declined from 2007 from 8.7/1000 person-years (95% CI: 7.2-10.2) to 0.9/1000 person-years (95% CI: 0.4-1.5) in 2009, with no similar change noted in other age groups.

**Conclusion:** Following the introduction of PCV7 into UK childhood immunization programme, there was a reduction in the diagnosis of all cause primary care diagnoses and antibiotic treatment of pneumonia in children under 2 in the UK that was not seen in older.

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