EXAMINING THE INTER-RELATIONSHIPS BETWEEN ANTIBIOTIC PRESCRIBING, COMPLICATIONS AND RESISTANCE IN ACUTE RESPIRATORY TRACT INFECTIONS

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

by

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Summary

The threat to public health from antibiotic resistance has increased, with growing evidence that antibiotic use is a major driver of resistance. This has led to campaigns to reduce prescribing of antibiotics by GPs, particular for respiratory tract infections (RTIs). These are among the most common reasons for prescribing antibiotics in primary care, in spite of the fact that there is evidence that most RTIs recover at a similar rate without antibiotic treatment, rarely resulting in complications if untreated. There are concerns, that a 'blanket' reduction in prescribing may occur, with reductions in prescribing that may benefit patients, leading to an increase in complications that can arise from untreated RTIs. The aim of this thesis was to explore the relationships between community antibiotic dispensing, complications from RTIs and resistance. We showed that decreasing rates of antibiotic dispensing in Wales coincided with increases in hospital diagnosed complications such as pneumonia and septicaemia from 1996-2006. At a practice level, there was evidence of a negative association between dispensing and complications. While a positive association was found between lagged dispensing and resistance, no clear pattern was found between change in dispensing and resistance for any of the organism/ antibiotic combinations examined possibly due to a lack of power. At an individual patient level, antibiotics are not justified to reduce the risk of a complication in those diagnosed with an acute RTI or sore throat. However, for patients presenting with a chest infection, the risk of developing a complication is higher and antibiotics appear to reduce the risk of complications; GPs should therefore consider prescribing for these patients. Further research is required to examine different lag periods of dispensing and their association with resistance and also to identify subgroups of patients at high risk of complications to help GPs target their prescribing of antibiotics.

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Glossary of abbreviations

BNF	British National Formulary
BSP	Broad spectrum penicillin
CI	Confidence interval
(AE) COPD	(Acute Exacerbations of) Chronic obstructive pulmonary disease
CV	Coefficient of variation
DIC	Deviance Information Criterion
DOH	Department of Health
ENT	Ear, nose and throat
GP	General Practitioner
GPMD	General Practice Morbidity Database
GPRD	General Practice Research Database
HA	Health Authority
ICC	Intra-class correlation
ICD10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} revision
IQR	Interquartile range
LHB	Local Health Board
LRTI	Lower respiratory tract infection
MCMC	Markov Chain Monte Carlo
MIC	Minimum Inhibitory Concentration
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NNT	Number needed to treat
NNTB/NNTH	Number needed to treat for benefit / harm
NPHS	National Public Health Service
NWIS	NHS Wales Informatics Service
OM	Otitis media
OPCS	Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures
OR	Odds ratio
PEDW	Patient Episode Database for Wales
PACT	Prescribing Analysis and Cost
PSU	Prescribing Services Unit
RIGLS	Restricted iterative generalized least squares
RR	Relative risk
RTI	Respiratory tract infection
SD	Standard deviation
SE	Standard error
SMAC	Standing Medical Advisory Committee
UTS	Up-to-standard
URTI	Upper respiratory tract infections

Chapter 1 Background

The History of Medicine

- 2000 B.C. – Here, eat this root.
- 1000 A.D. – That root is heathen. Here, say this prayer.
- 1850 A.D. – That prayer is superstition. Here, drink this potion.
- 1920 A.D. – That potion is snake oil. Here, swallow this pill.
- 1945 A.D. – That pill is ineffective. Here, take this penicillin.
- 1955 A.D. – Oops...bugs mutated. Here, take this tetracycline.
- 1960-1999 – 39 more "oops"…Here, take this more powerful antibiotic.
- 2000 A.D. – The bugs have won! Here, eat this root.

Anonymous (World Health Organisation (WHO) infectious disease report)

1.1 The discovery of antibiotics and their role in disease management

The development of antibiotics in the 20th century, spurred on by the landmark discovery of penicillin by Sir Alexander Fleming in 1928, revolutionised modern medicine. Antibiotics have a vital role in treating infectious bacteria and in maintaining health and, alongside improvements in the social determinants of health such as diet, housing and sanitary water have helped the decline of both morbidity and mortality from infectious diseases (Cosby *et al*. 2007).

General practitioners (GPs) immediately noticed a profound effect of antibiotics on outcomes for their patients and were given access to life-saving drugs. Complications and deaths from common infections such as pneumonia and acute rheumatic fever, which had previously been relatively common, became rarer. A study examining the mortality of respiratory illnesses in children in England and Wales between 1968 and 2000 found that pneumonia deaths fell over all age groups, with the most striking decrease of 96% found in post-neonatal infants (from 165 per 100,000 in 1968 to 27 in 1985 and 6.8 in 2000) (Panickar *et al*. 2005). The authors concluded that this was partly due to improvements in primary and secondary care, and immunisation, but mainly to the use of antimicrobial agents. The use of antibiotics has grown

substantially over the past 50 years and antibiotic prescribing continued to rise steadily throughout the 1980s and early 1990s. For example, between 1980 and 1993 the overall increase in the number of prescriptions for antibiotics in England was 45.8% (Davey 1996) while increases were greater for many European countries over a similar period (e.g. in West Germany an increase of 78% and France 65%) (Taboulet 1990).

1.2 The emergence of resistance

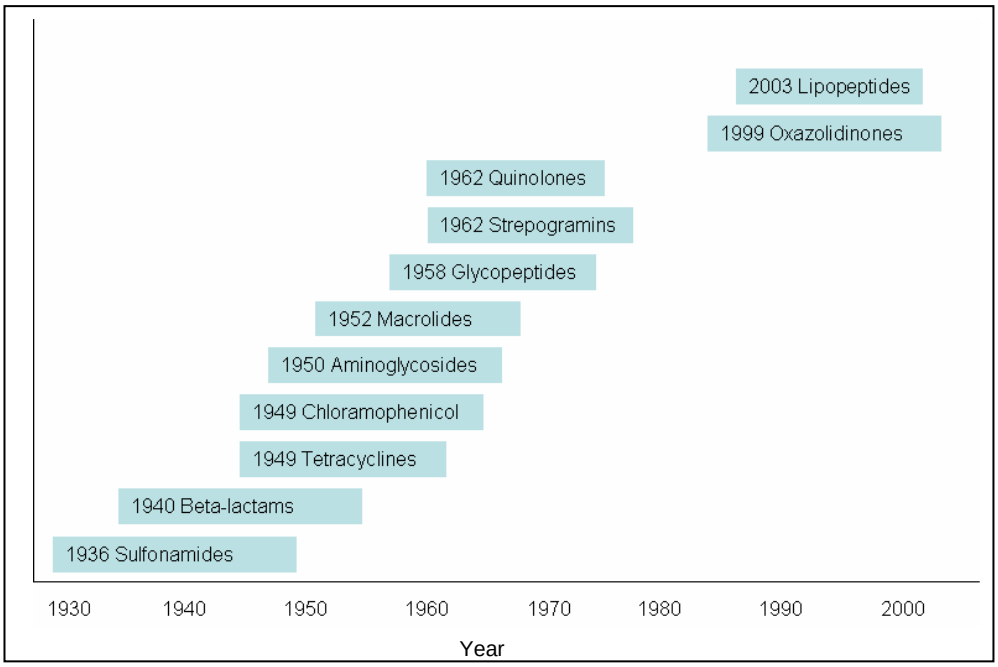
One drawback to this widespread increase in antibiotic use has been the rise of resistance to antibiotics in many bacteria. Antibiotic resistance occurs when bacteria lose their susceptibility to the antibiotic, usually to cheap and effective "first-line" drugs (WHO fact sheet no. 194). The bacterial infections that contribute most to human disease are also those in which emerging microbial resistance is most evident: diarrhoeal diseases, respiratory tract infections (RTIs), meningitis, sexually transmitted infections, and hospital-acquired infections. Some important examples include penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, multi-resistant salmonellae, and multi-resistant *Mycobacterium tuberculosis.* The problem is not confined to bacterial infections. The development of resistance to drugs commonly used to treat protozoal infections such as malaria is of particular concern, as is the emerging resistance to anti-retroviral drugs.

Antibiotic resistance is a threat to public health especially for immunocompromised, debilitated and elderly patients. Resistance, however, also presents a threat in the arena of common infections in primary care (Butler *et al*. 2006). Resistance can increase the length and severity of illness, contribute to the spread of disease, increase the use of antibiotic therapy and reconsultations, and finally increase the financial costs of treatment and care (National Prescribing Centre, MeReC Briefing Issue 21 2003; Alam *et al*. 2008). The concept of resistance was recognised as early as 1945, when, during his Nobel Prize Lecture, Fleming stated

> "*It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body."* (Nobel Prize website).

The first documented clinically serious consequence of antibiotic resistance was in the early 1950s with a case involving a penicillin-resistant strain of *Staphylococcus aureus* (WHO Bulletin 2001). The immediate response to this was to develop new antibiotics able to kill the bacteria and, as an antibiotic became less useful and resistance emerged, another antibiotic was generally developed that solved the problem. However, by the late 1990s the development of new antibiotics had slowed down and new classes of antibiotics have been harder to identify (Figure 1.1). Many existing classes of antibiotics, such as beta-lactams and quinolones, are effectively 'exhausted', or near exhaustion, for treating certain infections. No new truly novel class of antibiotics for treating gram negative organisms is likely to come to market in the short to medium term (Wellcome focus 2005). An additional concern is that major pharmaceutical companies are devoting fewer and fewer resources to antibiotic discovery because of the high associated costs, low chances of success and cautious profit projections (Wise 2004; Norrby *et al*. 2005). In light of the lack of new antibiotics, and increasingly limited options of other therapeutic agents to control infections, some experts have forecast a return to pre-antibiotic days (Wise *et al*. 1998). Measures must therefore be taken to either stop or delay the growth of resistance.

Figure 1.1 Development and discovery of antibiotics over time (Norrby SR *et al*. 2005)



1.3 Mechanisms of resistance

Susceptible bacteria can acquire resistance to antibiotics by either genetic mutation or by accepting antibiotic resistant genes from other bacteria. This usually occurs through one of several biochemical mechanisms: mutation, destruction or inactivation, and efflux. Mutation is a change in the DNA that can sometimes cause a change in the gene product, which is the target of the antibiotic. Antibiotics can no longer bind efficiently (usually leading to cell death) allowing the bacterium with the mutated DNA to continue DNA replication. Many bacteria possess genes which produce enzymes that chemically degrade or deactivate the antibiotic (destruction), rendering them ineffective against the bacterium. Lastly, certain bacteria can often become resistant to antibiotics through a mechanism known as efflux. An efflux pump is a channel that actively exports antimicrobial and other compounds out of the cell. The antibiotic enters the bacterium through a channel, and then is pumped back out of the bacterium by the efflux pump preventing the antibiotic from attacking the bacteria.

In addition to genetic material being passed down through successive generations, genetic material can be transferred between bacteria by several means, most often by conjugation, transduction and transformation. During conjugation bacteria coming into physical contact with each other are able to share extra-chromosomal genetic material. This may either be in the form of plasmids (circular segments of self-replicating DNA of varying size) or transposons (short segments of DNA that can insert into chromosomes or plasmids). This enables susceptible bacteria to acquire resistance to a particular antimicrobial agent. Transduction involves the sharing of extra chromosomal DNA passed between bacteria by bacteriophages (viruses that infect bacteria). Transformation involves the take up of exogenous DNA from the environment. Conjugation is the predominant mechanism by which bacteria share resistance mechanisms. This ability to share genetic material between different species of bacteria is a key part of their evolutionary success, enabling them to accumulate a wide genetic armoury which allows them to adapt to environmental pressures.

In any large population of bacteria, a few cells will be present that have undergone

genetic changes which means that they possess traits that enable them to survive in the presence of a noxious substance, such as being able to fend off the action of an antibiotic. This indicates that susceptible organisms, those lacking the advantageous trait, will be destroyed, leaving the remaining resistant populations behind. With long-term antibiotic use in a given environment, the bacterial communities will change dramatically, with an increase in the proportion of more resistant organisms. This can result in a situation where the next time an antibiotic is needed it may no longer be effective to treat what was previously an easily treatable infection.

1.4 Drivers of resistance

The causes of antibiotic resistance have been categorised into two factors: the spread of resistance genes in bacteria (as detailed above) and antibiotic use, and (Levy and Marshall 2004). An association has been shown, in both ecological and individual studies, between antibiotic prescribing in the community and resistance for a number of organism-drug combinations. There is somewhat less evidence for an association in secondary care, primarily because it is much harder to measure usage (Goossens *et al*. 2005; Goossens 2009; Berrington 2010). It is not only human antibiotic consumption that contributes to resistance levels; veterinary, agricultural and other industries may play a role in the growth of antibiotic resistance, as there is concern that antimicrobial-resistant bacteria in animals may transfer to humans, in particular through food (Inter-Agency Report 2004).

With no completely new class of antibiotic expected on the market in the short term, what can be done to at least slow down the progress of increasing resistance? Three strategies were suggested by Wise (2007): firstly, attempt to prevent the spread of organisms, secondly develop vaccines to restrict pathogens and thirdly reduce selective pressure on organisms to become resistant through reducing antibiotic use.

1.5 Minimising resistance by reducing antibiotic use

In the mid 1990s, before the publication of large scale studies demonstrating the link between antibiotic use and resistance, numerous influential bodies raised concerns, through reports and strategies, regarding the problem of continuously rising

resistance rates (American Society for Microbiology 1994, House of Lords 1998, Standing Medical Advisory Committee (SMAC) 1998). These national strategies aimed to improve surveillance of resistance and contain resistance through promoting more prudent antibiotic prescribing by education of both GPs and patients, thus preserving the possibility of effective antibacterial treatment for present and future generations. To reduce inappropriate antibiotic prescribing it was important to identify where the majority of antibiotic usage occurred, for example in which healthcare setting, for which patient populations, and for which infections.

1.5.1 Antibiotic use in primary care

In the United Kingdom (UK), around half of antibiotic use occurs in humans and half in agriculture (Inter Agency Report 2007). Around 80% of human use is in the community, attributable to GP prescribing (SMAC 1998). Based on data collected in the Fourth General Practices Morbidity Survey (between September 1991 and August 1992), it was estimated that 41% of the population consulted to general practice each year with an infection; RTIs accounted for half of these (Wilson and Bhopal 1998; Fleming *et al*. 2002). Approximately half of all antibiotic prescriptions are for respiratory symptoms (Davey *et al*. 1996) and more recent figures show that RTIs account for more than 50% of all antibiotic prescribing in primary care in the UK (Ashworth *et al*. 2004; Petersen and Hayward 2007). Additionally, studies have shown that antibiotic prescribing between RTI groups varies greatly; over 82% of those with chest infection are prescribed an antibiotic, over 60% with sore throat, but only 44% with upper RTIs (Petersen and Hayward 2007).

RTIs range from the common cold to life-threatening cases of pneumonia. Many empirical observational studies and trials have been conducted to investigate the role of antibiotics in their treatment, with Cochrane reviews providing the best and most accurate summary of the highest quality evidence to date (Sanders *et al*. 2004; Smith *et al*. 2004; Arroll and Kinealy 2009; Spinks *et al*. 2006; Ahovuo-Saloranta *et al*. 2008). In essence, these reviews conclude that the benefit of antibiotics for the average patient is modest or even non-existent. Most of these infections are caused by viruses and therefore would not be expected to respond to antibiotics in any case. Even bacterial infections can be self-limiting and benefit from antibiotic treatment is

often marginal or non-existent. In other words, for most patients these infections will resolve without the need for antibiotics, and the risk of complications is low.

1.5.2 Reducing antibiotic prescribing in the community

Results arising from randomised controlled trials (RCTs), the gold standard of evidence, suggest that RTIs are especially appropriate to consider when aiming to achieve a reduction in antibiotic prescribing since most of these infections can be safely managed without the need of immediate assessment or antibiotic treatment. As a result, several initiatives took place and recommendations were produced to encourage the appropriate prescribing of antibiotics by GPs for RTIs. In September 1998, the UK SMAC report recommended the following actions to influence antibiotic prescribing in RTIs in the community: no prescribing of antibiotics for simple coughs, colds or viral sore throats and limiting prescribing of antibiotics over the telephone to exceptional cases (SMAC 1998). Other sources of prescribing support and guidance are available to aid GPs with antibiotic prescribing in practice (National Institute of Clinical Excellence (NICE) Clinical Guidelines 69 2008, Health Protection Agency, Scottish Intercollegiate Guidelines Network) and on-line guidance (Clinical Knowledge Summaries).

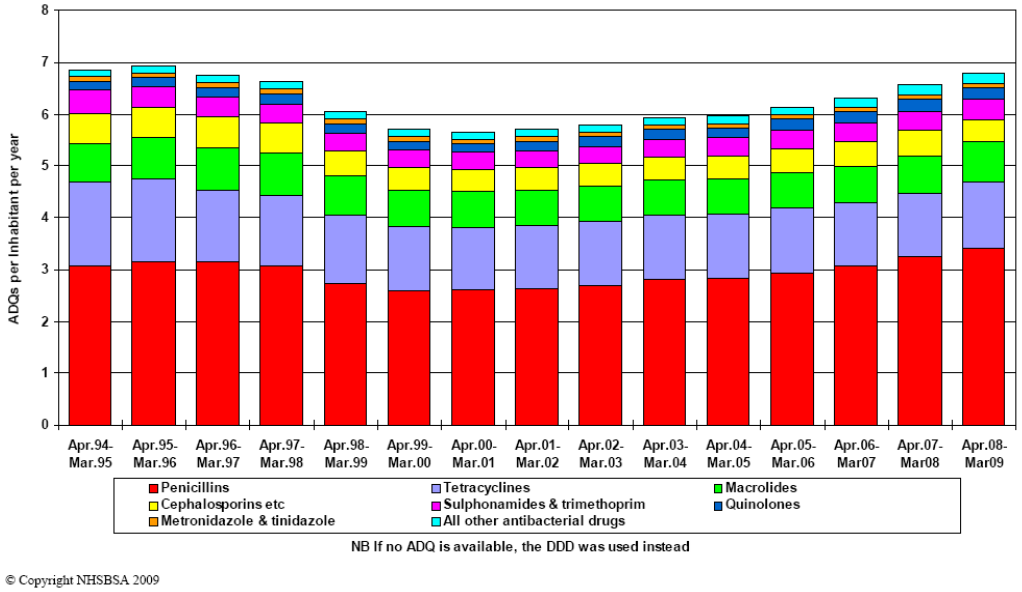
1.5.3 Evidence of a decrease in antibiotic prescribing

Antibiotic prescribing in developed countries rose steadily throughout the 1980s and early 1990s and reached a peak in several countries between 1992 and 1995 (McCaig *et al*. 1995; Metlay *et al*. 1998; Frischer *et al*. 2001; Wrigley *et al*. 2002). Subsequently, and influenced by prescribing guidelines, national reports, and public campaigns by the Department of Health (DOH), antibiotic prescribing in primary care declined in the UK.

Evidence from numerous sources demonstrates a downward trend in antibiotic prescribing up until 2000, with rates levelling out and then increasing slightly again, as shown in Figure 1.2 (Frischer *et al*. 2001; Wrigley *et al*. 2002; Majeed *et al*. 2004; Sharland *et al*. 2005; Fleming *et al*. 2005; Prescribing Review 2006; Schneider-Lidner *et al*. 2011). Data from the DOH's Prescription Cost Analysis for England

showed that the number of antibiotic prescriptions dispensed by GPs decreased by 25% between 1995 and 2000, from 49.4 to 36.9 million prescriptions. A detailed analysis of antibiotic prescribing data from 210 general practices in England and Wales showed that the largest reductions in overall antibiotic prescribing rates were seen between 1995 and 1998 and most marked among children (Frischer *et al*. 2001).

Figure 1.2 Trends in Prescribing of Antibacterial Drugs in General Practice in England (Prescribing Review 2009, NHS Prescription Services)



ADQ=Average daily quantities

This broad pattern was also true for other countries such as the United States (US), Portugal, Spain and Sweden (McCaig *et al*. 2002; Mölstad *et al*. 2002), whereas countries such as France and Greece experienced an increase in the number of antibiotic prescriptions between 1994 and 1997 (Mölstad *et al*. 2002).

A study specifically examining the impact of the SMAC report on prescribing for coughs/colds and sore throats using General Practice Research Database (GPRD) data found that, whilst there were significant annual decreases in antibiotic prescriptions for sore throat prior to its publication (Jan. 1993 to Sept. 1998), no significant annual change occurred thereafter (Smith *et al*. 2004). Conversely, there was a significant annual increase in antibiotic prescriptions for coughs/colds after the publication (Oct 1998 to Dec 2001). Similarly, trends in antibiotic dispensing in

children (using oral liquid formulations of antibacterials as a proxy) showed a decline in prescriptions between 1996 and 2004 although there was evidence of a slight increase after 2000 (reduction of 64% between 1996 and 2000 and 55% between 1996 and 2005) (Sharland 2007).

The SMAC report of 1998 was regarded as an important landmark but evidence hints towards trends in prescribing falling prior to this, with little evidence to suggest a major decrease after the report. This suggested that maybe GPs were already aware of the need to reduce antibiotic prescribing and of the limited effectiveness of antibiotics for many RTIs, and had begun to change their prescribing practice to reflect this.

There are other possible explanations of the decline observed in antibiotic prescriptions in the community. Fleming *et al*. (2003) studied 73 practices in England and Wales and found a reduction of consultations for RTIs and concluded that this was the main contributor or explanation for the widespread decline in antibiotic prescribing. This decline in RTI consultations could have either represented a true decrease in the incidence of infections or changing thresholds for patient consultation behaviour. Indeed, Ashworth *et al*. (2006) reported that patients were not consulting as often for common infections. Reassuringly, even though RTI consultations have decreased, the proportion of antibiotics prescribed for RTIs has also decreased, suggesting a true change in GP prescribing behaviour (Frischer *et al*. 2001; Ashworth *et al*. 2004; Gulliford *et al*. 2009). Ashworth *et al*. (2004) and Gulliford M *et al*. (2009) additionally ascertained that the proportion of antibiotics prescribed for upper RTIs (URTIs) declined between 1994 and 2000 whilst antibiotic prescribing for lower RTIs (LRTIs) remained static. The largest relative reductions of prescribing occurred in patients diagnosed with influenza, upper RTIs, laryngitis and sore throats. These findings were also replicated in a study in children from the US; additionally they found no significant decline in prescribing for acute otitis media (AOM), sinusitis and bronchitis (McCaig *et al*. 2002).

1.6 Advantages of reducing antibiotic prescribing

It has been demonstrated that reducing the use of antibiotics is essential to the

problem of resistance but reducing antibiotic use is important for many other reasons (Butler *et al*. 1998a). Firstly, there are resource implications; receiving antibiotics reinforces patients' perceptions that antibiotics are *needed* for common infections, encouraging them to consult with similar infections in the future, a cycle known as medicalisation. A survey from the US found that previous antibiotic usage had a strong relationship with belief in the effectiveness of antibiotics in the treatment of URTIs (Mainous III *et al*. 1997). Another study in England found that 38% of patients initially prescribed an antibiotic re-consulted with a sore throat in the future, compared with 27% not prescribed an antibiotic (Little *et al*. 1997).

The financial implications of reducing antibiotic prescribing have also been highlighted. In 1994 the Audit Commission estimated that the NHS could save up to £425 million a year if general practitioners changed their prescribing habits by controlling the volume of prescribing, increasing rates of generic prescribing, and using expensive products more appropriately, with £77 million in savings made from rational antibiotic prescribing (Audit Commission 1994). More recently, the Audit Commission developed a national prescribing savings database from which they estimated that in 2002/03, the potential saving for the average primary care trust (PCT) in England was £430,000, of which £59,000 was specifically in antibiotic prescribing (Audit Commission 2003).

Finally, antibiotics may cause as much illness as they reduce. In children with otitis media, antibiotic treatment may cause an increase in adverse effects such as nausea, diarrhoea, and rash (Glasziou *et al*. 2004). In adults with bronchitis, patients reported adverse effects such as nausea, vomiting, headaches, skin rash, and vaginitis (Fahey *et al*. 2004).

1.7 Disadvantages of reducing antibiotic prescribing

Just as there have been positive consequences of the increased use of antibiotics in the community during the past 50 years, there may also have been unintended consequences of reducing antibiotic usage in the community. Firstly, patients who expect or demand antibiotics from their GP, but do not receive them, may be dissatisfied with care, and this could potentially damage the doctor-patient

relationship. One study reported that patients with LRTIs who did not receive an antibiotic that they hoped for were much more likely to express dissatisfaction to their doctor (Macfarlane *et al*. 1997). Doctors are also fully aware of this problem and report preserving the doctor-patient relationship as one of the reasons for prescribing antibiotics, although not the primary reason (Bradley 1992; Butler *et al*. 1998b; Kumar *et al*. 2003).

Perhaps more important is the potential for unintended adverse events such as complications arising from untreated common infections. One possible explanation for the turn-around in antibiotic prescribing is concern amongst GPs that reduced levels of antibiotic prescribing have been associated with increases in complications from common infections. Fear of medico-legal problems if a patient acquires a complication is an important reason why GPs do not reduce antibiotic prescribing beyond a certain threshold (Butler *et al*. 1998b).

This concern is supported by several qualitative interview studies in which clinicians are invited to reflect on individual cases. One GP described how, by changing practice policy to stop all antibiotic prescribing for sore throats, the practice saw "an unprecedented rise in the number of patients with quinsy" (Kumar *et al*. 2003). After returning to prescribing antibiotics for the severest sore throat symptoms, cases of quinsy fell. Another GP recollected that on one occasion when antibiotics were withheld, the patient subsequently developed streptococcal septicemia. More generally, a GP wrote that not using antibiotics in the NHS has *"caused an increase in LRTI and death"* (Searle 2004) and recent NICE guidelines recognised the concern of GPs and patients regarding the danger of complications (NICE Clinical Guidelines 69 2008). There is also concern that GPs may miss serious illness due to early symptoms being identical to those seen in common infections. In a recent editorial, Harnden (2007) raised concern regarding missing meningococcal infections in feverish young children, as their symptoms are the same as those of self-limiting viral infections.

Responsible reductions in antibiotic prescribing should limit inappropriate prescribing without denying benefits to those patients who are likely to derive benefit from antibiotic treatment (Woodhead *et al*. 2004). However, concerns have been raised by some GPs that some prescribers are aiming to achieve a 'blanket'

reduction, rather than one targeted at reducing *inappropriate* prescribing (prescribing that does not benefit patients). This 'blanket' reduction may then lead to patients who need antibiotics, and are likely to gain most benefit from them, not actually receiving them, and, as a result, being put at a higher risk of developing a complication (Wilkinson 2006). In addition, alongside the development of complications comes the accompanying downside of additional costs driven largely by possible hospital admissions and inpatient stays.

1.8 The relationship between antibiotic use and complications

The need for further research into the relationship between complications and antibiotic prescribing has been called for by many leading professionals in the field (Woodhead *et al*. 2004; Price *et al*. 2004a; Goossens *et al*. 2005). These calls have focussed on the merits of using patient-level data to clarify the relations between antibiotic use, resistance and clinical outcomes that could be obscured by group-level data. The potential problem in using group level data has been demonstrated by Donnan and colleagues where, at a practice level, trimethoprim prescribing was not related to trimethoprim resistance, but at an individual level a strong association existed between the two (Donnan *et al*. 2004).

A number of studies have already examined the relationship between complications and antibiotic prescribing at both an ecological and individual level. These studies are described more fully in Chapter 2. In summary, ecological level analyses showed evidence of a negative relationship between antibiotic use and certain complications (diagnosed in either primary or secondary care). Recent evidence from individual patient level studies using data from the UK-based GPRD, examining the protective effect of antibiotics in patients with RTIs against the risk of complications, did not provide conclusive answers. Most of the studies of individual patient data showed there was a higher risk of developing a complication if antibiotics were not prescribed for an acute RTI, but the risk of developing a complication was still low, with large numbers needed to treat, apart from specific patient sub-groups (quinsy in patients with a diagnosis of tonsillitis and pneumonia in the elderly) (Dunn *et al*. 2006; Petersen *et al*. 2007). The research from this thesis hopes to contribute to this important debate of the relationship between antibiotic use and complications.

1.9 Limitations of the evidence base

Whilst the ecological level studies have provided useful results at both national and international levels, they are limited for several reasons.

- They have generally not examined the relationship between prescribing and complications using antibiotic prescribing data for all commonly used antibiotics in primary care over several years.
- Outcomes were restricted to a narrow set of complications in some of the studies.
- There are many challenges and competing factors in deciding whether to prescribe antibiotics or not, and these need to be balanced. For example, as a result of reduced prescribing, does the gain to society of possible reduced resistance outweigh the risk of developing a complication in any one individual? Several studies have shown that GPs see the risk of patients developing serious problems outweighing the risk of developing bacterial resistance (Wood *et al*. 2007; Simpson *et al*. 2007).
- None of the ecological studies so far have adequately examined confounding factors, such as practice and GP characteristics that could alter the relationship between antibiotic prescribing and the occurrence of complications.
- These studies used large units of aggregation and may have suffered from the 'ecological fallacy' in which erroneous inferences regarding individuals within the same area are made from ecological models based on aggregate data. The evidence base of these studies has been questioned for these reasons (Woodhead *et al*. 2005).

Group level studies may be helpful, either by producing convergent data with individually linked studies or by raising questions on the validity of conclusions from such studies. In fact the effect of antibiotic prescribing on rare complications of acute RTIs has already been examined at an individual patient level by several studies (Dunn *et al*. 2006; Petersen *et al*. 2007; Thompson *et al*. 2009a; Winchester *et al*. 2009, Crocker *et al*. 2012). Whilst these studies have been very useful, and have involved a large study population using the GPRD, they may have failed to capture the true incidence of complications in the population. Complications can develop and

be managed by a number of different pathways. Firstly, they can be diagnosed and treated entirely within primary care by the GP (either in practice or during an out of hours (OOH) home visit). Alternatively, they can be diagnosed in general practice but then urgently referred to secondary care for treatment (possibly with no record of a complication recorded within the GP system). Complications can also be solely diagnosed and treated outside of general practice but still within primary care services such as in accident and emergency (A&E) or OOH consultations and possibly admitted to secondary care as in-patients.

Whilst GPs contributing to the GPRD are asked to record OOH consultations and home visits, under-recording is likely. GPs should also be informed of any patient hospitalisations, although again this information may be under-recorded in their electronic clinical records and there may also be an associated time lag in recording the information. More research is therefore needed to identify, more robustly, complications of common infections managed initially in primary care.

Most studies on individual patients have not controlled for important confounders. Patients, who are more ill, with co-morbidities or immunosuppression, are more likely to be given antibiotics for these reasons and are also more likely to have adverse outcomes (Coenen and Goossens 2007). Lastly, whilst these studies are useful in showing the protective effect of antibiotics against complications, there is no evidence to show that this level of protection has changed over time, during the same period when antibiotic prescribing declined.

1.10 The need to monitor trends

The need to monitor the incidence of antibiotic prescribing, resistance and complications has been highlighted (Goossens *et al*. 2006; Cosby *et al*. 2007; Hayward *et al*. 2007; Thompson *et al*. 2009b). This is especially true in countries where national campaigns to reduce antibiotics are undertaken, to ensure that any changes in antibiotic use are not causing harm. There is a continually changing relationship between bacteria, human host and antibiotic as the social determinants of disease change, bacteria change and antibiotic prescribing exerts their influence over time. Several programmes have been undertaken by The Royal College of General

Practitioners, the Prescriptions Pricing Authority's Prescribing Analysis and Cost (PACT) data and the Health Protection Agency (HPA) to examine issues of resistance and prescribing but they are based on less than perfect data and surveillance (Hayward *et al*. 2007; Wise R 2007). For outcomes of infections, hospital episode statistics (HES) are the best source for monitoring trends since they cover the whole population (and therefore incur no bias as would general practice based databases), but this monitoring is not carried out routinely in England and Wales. Additionally, very few studies have examined time trends in complications arising from RTIs at a national level for some of the more rare complications.

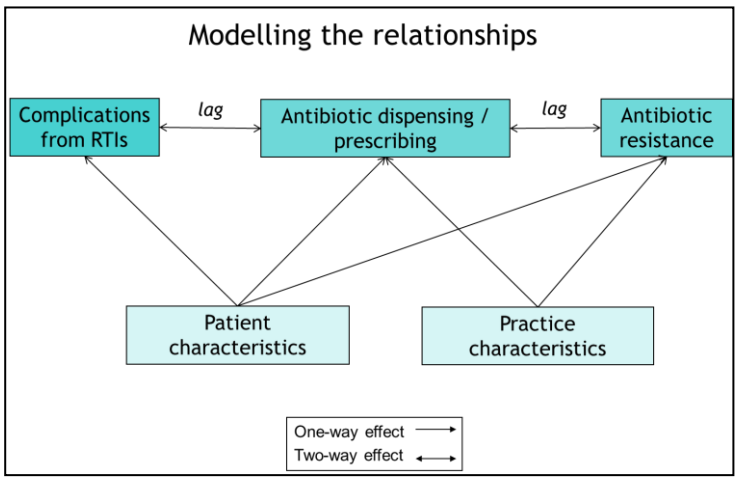
1.11 Aims and objectives

This introduction has identified a possible relationship between antibiotic prescribing and risk of resistance and presented some evidence to suggest that antibiotics have a protective effect against serious complications arising from acute RTIs. As a result the following hypothesis was generated:

> *Reduced levels of community antibiotic prescribing are associated with higher levels of complications arising from common RTIs.*

Figure 1.3 shows the main relationship between antibiotic use and complications and other measureable factors that could also impact on complication rates and their relationships with one another.

Figure 1.3 Modelling the relationship between antibiotic use, complications, resistance and other factors.



Therefore, the main focus of this thesis will be on investigating these relationships whilst taking the field forward by (a) the use of improved statistical methods; (b) controlling for certain confounders that could also affect the relationship, and (c) paying additional attention to possible biases found in data sources (such as the possible undercounting of complications in individual studies based on GP held data alone). This relationship will be investigated by using a number of datasets at both the general practice level (using national routinely collected data from Wales) and individual level (using a general practice database from the UK). The advantage of investigating this relationship at both geographical levels is that a comparison can be made of the results, thus exploring the 'ecological fallacy'.

The objectives of the thesis are as follows:

At a general practice level:

I. To examine national (Wales) trends in antibiotic dispensing and antibiotic resistance data in primary care, and complications of RTIs managed in secondary care;
II. To examine the variation in trends in these data between general practices and Local Health Board areas in Wales and determine possible practice and GP factors associated with any variation;
III. To examine the relationship between antibiotic dispensing and resistance in primary care and investigate whether reductions in dispensed antibiotics are related to changes in antibiotic resistance;
IV. To examine the relationship between antibiotic dispensing in primary care and complications from RTIs in secondary care and investigate whether reductions in dispensed antibiotics are related to changes in complications.

At an individual patient level:

V. To investigate the effect of antibiotics prescribed in primary care on the risk of developing a complication arising from an RTI in both primary and secondary care using up-to-date data;
VI. To identify sub-groups of patients benefiting most from antibiotics.

1.12 Structure of the thesis

Chapter 1 provided an overview of the direct issues to be examined in this thesis; the underlying evidence is presented more comprehensively in Chapter 2. This will examine the role of antibiotics in RTIs and their complications, the relationship between antibiotic dispensing and complications, and between dispensing and resistance and whether resistance modifies this relationship. Chapter 3 describes the datasets that were used in the current general practice and individual level analyses as well as providing an overview of the statistical methods used throughout this thesis.

Chapter 4 allows an initial exploration (at a general practice level) of the hypothesis on the relationship between dispensing and complications for a sample of Welsh practices and the feasibility of carrying out further analysis on larger datasets. Chapters 5 to 8 examine the trends in dispensing, resistance and complications and the relationship between them for the whole of Wales at a practice level. Chapter 9 examines the relationship at an individual patient level using a general practice dataset. Finally Chapter 10 will return to the initial aims and objectives, summarising the achievements in the thesis and highlighting strengths and weaknesses, and discussing the implications of the results in clinical practice and future research. It will also contain the conclusions of the thesis.

Chapter 2 Detailed appraisal of the evidence base supporting the rationale for the current study

2.1 Introduction

The purpose of this chapter is to identify, describe and appraise the evidence that has led to the specific hypotheses and objectives outlined in Chapter 1. Firstly respiratory tract infections (RTIs) and their complications will be defined. Secondly the evidence on the effectiveness of antibiotics in the treatment of RTIs and their complications will be reviewed and summarised. The current evidence surrounding the relationship between antibiotic prescribing and complications arising from RTIs will also be reviewed, as will the relationship between prescribing and resistance.

2.2 Search strategy

To identify relevant literature, MEDLINE, EMBASE and all Evidence-Based Medicine (EBM) Reviews (Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE), and the Cochrane Controlled Trial Register (CCTR)) were searched in February 2006 and updated in June 2009.

Two comprehensive search strategies were developed to identify all papers relating to (a) antibiotic prescribing and resistance and (b) antibiotic prescribing and complications arising from infections using the search strategies in Appendix I. Inclusion and exclusion criteria were developed to assess abstracts for inclusion in the review. Literature that examined prescribing and resistance in hospital settings (e.g. Intensive Care Units) and studies examining the effect of antibiotic consumption in animals were excluded.

Papers included were categorised from level 1 to 4; level 1 literature was directly relevant to the study aims whilst literature falling into levels 2 to 4 contributed to the background of the study (Table 2.1). References of selected studies and relevant reviews were hand-searched to find additional relevant studies and other studies were obtained from expert colleagues. There were no language or publication restrictions.

Additionally, Zetoc alerts were created to identify possible relevant literature using the terms ‘antibiotic’ and ‘antimicrobial’ and updates were received from selected journals known to contain relevant papers (Zetoc, Mimas).

Table 2.1 Categorisation of included studies from the literature search

Level 1 evidence	- Associations between prescribing and resistance in primary care. - Associations between prescribing in primary care and complications in primary or secondary care.
Level 2 evidence	Factors associated with: a. GP prescribing b. Antibiotic resistance levels c. Patients consulting with an RTI d. Patients’ inappropriate use of antibiotics i. use without a prescription e.g. hoarding, borrowing ii. compliance
Level 3 evidence	- Prescribing or resistance levels within/between countries. - Trends in prescribing, complications or serious common infections or resistance
Level 4 evidence	- Cochrane reviews examining effect of antibiotics on RTIs. - Letters or studies indicating a need for further research into the relationship between complications and prescribing. - Methodology (e.g. methods for comparing prescribing between GPs etc)

2.3 Respiratory tract infections

The respiratory tract is the part of the anatomy that is involved in the process of respiration. The passageway through which air travels is traditionally divided into two sections: the upper respiratory tract and the lower respiratory tract. The upper respiratory tract includes the nose, throat, larynx, and trachea and the lower respiratory tract includes bronchi, bronchioles, and alveoli (NHS direct). The respiratory tract is a common site for infections and the spectrum of diseases affecting it ranges from the common cold to life-threatening cases of pneumonia. Infections are also classified according to whether they mainly affect the upper (URTIs) or lower respiratory tract (LRTIs). URTIs are most commonly caused by viruses, especially rhinovirus, influenza virus, and respiratory syncytial virus (Makela *et al*. 1998; Gwaltney 2002; Wat 2004) and are rarely serious in developed countries. Symptoms/diagnoses include the common cold, ear infections (otitis media), sore throat/pharyngitis, tonsillitis, and sinusitis. A study from the Netherlands found that 53% of all acute URTIs (mainly diagnoses of flu-like illness, common cold, acute pharyngitis and tonsillitis) were viral, with rhinovirus as the most frequent pathogen found (25% of all URTIs) (Van Gageldonk-Lafeber *et al*. 2005). Bacterial infections were found in 18% with group A β-hemolytic streptococcus (GABHS) and *Staphylococcus aureus* most frequently found.

LRTIs are also caused by both viruses and bacteria and include diagnoses of acute cough, acute bronchitis and pneumonia. In a study by Holm *et al.* (2007), pathogens were identified in 40% of patients, with bacterial (including *Streptococcus pneumoniae* and *Haemophilus influenzae*) and viral infections (including rhinovirus and influenza A virus) equally common. *Streptococcus pneumoniae* is the primary cause of community-acquired pneumonia (CAP) in the UK (Macfarlane *et al*. 2001; Holm *et al*. 2007).

2.4 Complications arising from RTIs

Complications are defined as those that can either develop from an RTI or as a new presentation of a more serious illness. Complications that can arise from RTIs include mastoiditis (may complicate acute otitis media (AOM)), peritonsillar abscess

(quinsy), epiglottitis, rheumatic fever and acute glomerulonephritis (may complicate a streptococcus infection in the throat), and empyema and pneumonia (complicate a simple lower or upper RTI). Other potential complications of RTIs are brain abscesses, meningitis, and periorbital infections. Some complications, such as septicaemia or pyelonephritis, can originate in other sites such as in skin and urinary tract infections, as well as the respiratory tract.

A complication can arise either from an untreated bacterial infection, a viral infection that goes on to become more serious (e.g. viral pneumonia) or develop from a secondary bacterial infection, or from a failure of treatment due to the antibiotic prescribed (incorrect type, dosage or duration). However, not all bacterial infections need antibiotics, depending on the patient's own ability to fight the infection and the virulence of the organism. Some bacterial infections, although self-limiting, might recovery more quickly if treated with antibiotics (such as in streptococcal pharyngitis).

2.5 The role of antibiotics in RTIs

RTIs such as the common cold, ear infections (AOM), sinusitis, sore throat, acute cough and bronchitis are those most commonly presented to GPs and therefore most commonly treated with antibiotics in primary care. In the following sections the current evidence for the efficacy of antibiotics for specific RTIs is presented, based on recently updated systematic reviews from The Cochrane Library. The results are summarised in Table 2.2 and section 2.5.1 below.

2.5.1 Evidence from Cochrane systematic reviews

In the Cochrane review for common cold and purulent rhinitis (Arroll and Kinealy 2009), there was no benefit for antibiotics although there was an increase in adverse events and therefore routine use was not recommended by the authors. In acute maxillary sinusitis (Ahovuo-Saloranta *et al*. 2008), antibiotics resulted in a lower clinical failure rate, defined as lack of cure or improvement at follow-up, than placebo at 7 to 15 days after the start of treatment in participants with acute sinusitis. However, 80% of patients treated with a placebo also improved within two weeks.

The authors concluded that clinicians needed to weigh the moderate benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level.

For acute sore throats (Spinks *et al*. 2006), antibiotics had a beneficial effect on both non-suppurative complications (acute rheumatic fever within two months) and suppurative complications (acute otitis media within 14 days, and peritonsillar abscess (quinsy) within two months). Antibiotics also had a beneficial effect on symptom reductions such as sore throat and headache at day 3, and also sore throat at one week. The authors concluded that antibiotics give relative benefits (reducing complication rates) in the treatment of sore throat but the absolute benefits in terms of resolution of symptoms were modest; the average duration of symptoms was only reduced by about 16 hours. Protecting against these complications would require treating many with antibiotics for one patient to benefit.

For AOM in children (Sanders *et al*. 2004), antibiotics had no early impact on pain reduction and only a modest overall impact on the clinical course of AOM. Children given antibiotics did however have increased side effects such as vomiting, diarrhoea and rash. Most cases settle spontaneously in a couple of days and again the authors concluded that benefits must be weighed against the possible harms. Antibiotics were most useful in children under two years of age, with bilateral AOM, and with both AOM and discharging ears.

In the Cochrane systematic review for acute bronchitis (Smith *et al*. 2004), patients given antibiotics were less likely to have a cough or a night cough at follow-up, less likely not to improve according to the clinician's global assessment and have an abnormal lung examination. Antibiotic-treated patients also had a reduction in days feeling ill and in days with limited activity. Antibiotics appeared to have a modest beneficial effect in patients and the authors concluded that the magnitude of the benefit needed to be weighed up against problems associated with prescribing antibiotics such as side effects, medicalisation and resistance.

Table 2.2 Summary of Cochrane reviews for the efficacy of antibiotics in RTI (Comparisons are antibiotics vs. placebo; Risk Ratio (RR)<1 or mean difference <0 provide evidence for the efficacy of antibiotics)

Condition (reference)	**Outcomes**	**No. of studies**	**N. of participants**	**Risk Ratio (RR) (95% CI)**
Common cold and acute purulent rhinitis (Arroll and Kinealy 2009)	*Persisting symptoms 1 to 7 days:*	6	1047	0.95 (0.59 to 1.51)
	In adults	4	891	0.92 (0.78 to 1.07)
	In children	2	449	1.36 (0.59 to 3.15)
	Adverse effects:	6	1495	1.80 (1.01 to 3.21)
	In adults	4	1267	2.62 (1.32 to 5.18)
	In children	2	228	0.91 (0.51 to 1.63)
	Persistent rhinitis (clear)	2	227	0.58 (0.23 to 1.48)
	Persistent rhinitis (purulent)	5	772	0.60 (0.37 to 0.98)
Acute maxillary sinusitis (Ahovuo-Saloranta *et al*. 2008)	*Clinical failure defined as lack of cure or improvement:*			
	7 to 15 days	7	631	0.66 (0.44 to 0.98)
	16 to 60 days	1	169	0.85 (0.36 to 1.98)
Acute sore throat (Spinks *et al*. 2006)	*Symptom reduction (at day 3):*			
	Sore throat	15	3621	0.68 (0.59 to 0.79)
	Headache	3	911	0.44 (0.27 to 0.71)
	Fever	7	1334	0.71 (0.45 to 1.10)
	Symptom reduction (at 6-8 days (one week)):			
	Sore throat	13	2974	0.49 (0.32 to 0.76)
	Non-suppurative complications:			
	Acute rheumatic fever (within 2 months)	16	10,101	0.27 (0.12 to 0.60)
	Acute glomerulonephritis (within 1 month)	10	5147	0.22 (0.02 to 2.08)
	Suppurative complications:			
	Acute otitis media (within 14 days)	11	3760	0.30 (0.15 to 0.58)
	Acute sinusitis (within 14 days)	8	2387	0.48 (0.08 to 2.76)
	Peritonsillar abscess (quinsy) (within 2 months)	8	2433	0.15 (0.05 to 0.47)

Table 2.2 Summary of Cochrane reviews for the efficacy of antibiotics in RTI (Comparisons are antibiotics vs. placebo; Risk Ratio (RR)<1 or mean difference <0 provide evidence for the efficacy of antibiotics)

Condition (reference)	**Outcomes**	**No. of studies**	**N. of participants**	**Risk Ratio (RR) (95% CI)**
Acute otitis media in children (Sanders *et al*. 2004)	Pain at 24 hours	5	1229	0.90 (0.78 to 1.04)
	Pain at 2 to 7 days	10	2791	0.72 (0.62 to 0.83)
	Abnormal tympanometry at 1 month	4	927	0.89 (0.75 to 1.07)
	Abnormal tympanometry at 3 months	3	808	0.97 (0.76 to 1.24)
	Perforation	2	381	0.55 (0.24 to 1.27)
	Vomiting, diarrhoea, or rash	5	1401	1.38 (1.09 to 1.76)
	Contralateral otitis (in unilateral cases)	3	579	0.47 (0.17 to 1.36)
	Late recurrences	6	2153	0.93 (0.79 to 1.10)
Acute Bronchitis (Smith *et al*. 2004)	Cough at follow-up (7 to 15 days)	4	275	0.64 (0.49 to 0.85)
	Night cough at follow-up	4	538	0.67 (0.54 to 0.83)
	Not improved by physicians' global assessment at follow-up	6	891	0.61 (0.48 to 0.79)
	Abnormal lung exam at follow-up	5	613	0.54 (0.41 to 0.70)
	Adverse events	10	1509	1.15 (0.92 to 1.44)
	Productive cough at follow up	7	713	0.97 (0.82 to 1.16)
	Proportion with activity limitations at follow up	5	478	0.75 (0.46 to 1.22)
Condition (reference)	**Outcomes**	**No. of studies**	**N. of participants**	**Mean difference (95% Confidence interval)**
Acute Bronchitis (Smith *et al*. 2004)	Days feeling ill	5	809	-0.64 (-1.16 to -0.13)
	Days of impaired activities	6	767	-0.49 (-0.94 to -0.04)
	Days of cough	6	969	-0.44 (-0.95 to 0.07)
	Days of productive cough	6	699	-0.43 (-0.93 to 0.07)

2.5.2 Additional evidence

There is some recent evidence not yet included in Cochrane reviews. A study examining the effectiveness of amoxicillin, compared to no antibiotic treatment, in adults with acute maxillary sinusitis showed that neither management was effective in altering the symptom severity, duration or the natural history of the condition (Williamson *et al*. 2007). Young *et al*. (2008) carried out a meta-analysis of RCTs based on both aggregate and individual patients' data from adults with clinical signs and symptoms of rhinosinusitis. For the aggregate data (based on 11 RCTs), the estimated odds ratio (OR) for the overall treatment effect of antibiotics relative to placebo was 1.35 (95% CI=1.15 to 1.59), based on having no or mild symptoms in the 8-15 days after receiving treatment. Based on the individual data, the OR was increased slightly to 1.37 but with wider confidence intervals (95% CI=1.13 to 1.66). Fifteen patients would have to be given antibiotics before an additional patient would benefit (with no or mild symptoms). The authors concluded that antibiotics were not justified for adult patients with rhinosinusitis-like complaints, even if the patient reported symptoms for longer than 7–10 days.

Rovers *et al*. (2006) carried out a meta-analysis of individual data from trials examining the effect of antibiotics in preventing an extended course of AOM (defined as pain, fever or both at 3-7 days) in children. They found that antibiotics were protective in children aged less than two years with bilateral acute otitis media, and in those with both acute otitis media and otorrhoea (ear discharge). In these groups the NNT was three to four children to prevent an extended course of the disease in one child. The authors recommended observation rather than immediate antibiotic treatment for most other children with acute otitis media. The meta-analysis was not adequately powered to determine the protective effect of antibiotics for otitis media against the risk of mastoiditis.

2.6 Relationship between antibiotic use and complications

2.6.1 Evidence from Cochrane systematic reviews

The effect of antibiotics on complications was assessed only in the reviews for sore throat and AOM (Table 2.2). In the sore throat systematic review by Spinks *et al*. (2006), several studies found a protective effect of antibiotics against acute rheumatic fever (within two months of diagnosis) which reduced the risk of this complication to about one quarter of that in the placebo group (risk ratio (RR)=0.27, 95% CI=0.12 to 0.60). The incidence of quinsy was also reduced in relation to the placebo group (RR=0.15, 95% CI=0.05 to 0.47). There is some doubt regarding the relevance of these results since the studies that reported incidence of acute rheumatic fever were set in the 1950s-60s, a period where the background incidences of rheumatic fever and quinsy were much higher in Western society than they are now. Studies from the late 20th century had virtually no occurrences of acute rheumatic fever in either the antibiotic or placebo group. However, more recent clinical trials provided some evidence that targeting penicillin to a subset of patients with higher clinical likelihood of group A β-hemolytic streptococcus (GABHS) showed a lower development of quinsy when compared to the placebo group but these studies were not powered on this outcome (Dagnelie *et al*. 1996; Zwart *et al*. 2000). For acute glomerulonephritis, out of ten studies reporting acute glomerulonephritis as an outcome, only two studies reported any cases, amounting to a total of two individuals (both in the placebo group) (Chamovitz *et al*. 1954; Siegel *et al*. 1961). The estimate of the effect thus has very low precision (RR= 0.22, 95% CI=0.02 to 2.08) and concluding that antibiotics are protective from acute glomerulonephritis is not possible.

For AOM, only one case of mastoiditis occurred (in the penicillin group when compared to the untreated group) in over 2,000 children included in the studies summarised in the Cochrane review (Sanders *et al*. 2004). However one study, excluded from the review, found a higher rate of mastoiditis in the untreated group (17%, 1.5% and 0% in the placebo, sulphonamide and penicillin groups respectively) (Rudberg RD 1954). The overall evidence for the protective effect of antibiotics against mastoiditis is limited.

2.6.2 Ecological level evidence

An ecological study is one in which the unit of observation is at an aggregate level (population-level), such as a group of people living within a geographically-defined area (for example a general practice population), rather than at an individual level. One of the main reasons for using ecological models is the relative ease of obtaining data at aggregate level.

To date ecological studies have been performed at the general practice (GP), primary care trust (PCT), health authority (HA) and country level for a variety of complications (Table 2.3). Findings from some of these analyses of routine health care databases suggest that the reductions in GP prescribing of antibiotics may be associated with increases in rare complications of bacterial infection. For example, Little and colleagues examined primary care prescribing of penicillin and hospital admissions for complications and acute RTIs at the HA level, for a cross-sectional population in England (Little *et al*. 2002). After adjusting for age, gender, deprivation and standardised mortality ratio they found higher levels of primary care prescribing of penicillin significantly associated with lower rates of admissions (per 10,000 HA residents) for both quinsy and mastoiditis. A comparative study across several European countries, Canada, Australia and the US was performed to examine the incidence rate of acute mastoiditis in children discharged from hospital and compare it with antibiotic prescribing rates for AOM, between 1991 and 1998 (Van Zuijlen *et al*. 2001). This study demonstrated that countries practising a restrictive use of antibiotics, such as in the Netherlands, had a comparable rate of acute mastoiditis to Norway and Denmark, who are higher prescribers. In all other countries where prescribing rates were high, incidence rates were low. Lastly a study examined aggregate data (at a PCT level) for pneumonia mortality, incidence of primary care visit for influenza or influenza-like illness, and their relationship with antibiotic prescribing for LRTIs in 12-week winter periods between 1993/4 and 1999/2000 in England and Wales (Price *et al*. 2004b). The results from a negative binomial regression model show that antibiotic prescribing (per 1,000 population) for LRTI had a significant association with excess winter pneumonia mortality even after adjusting for influenza incidence.

Not all studies demonstrated an association. In the USA, a longitudinal study compared the percentage of patients with episodes of acute bronchitis and cough that were prescribed an antibiotic and hospitalisations for RTIs (including pneumonia and empyema) (Mainous III *et al*. 2006). Antibiotic prescribing declined up until 2001 and then increased, and appeared to have a weak negative correlation with hospitalizations for all RTIs (Spearman's correlation coefficient r_s=-0.22). More recently a study conducted in Spain at the GP level examined the relationship between antibiotic prescribing indicators (e.g. total prescribing defined daily doses) and hospital admissions for complications of pneumonia and chronic obstructive pulmonary disease (Fernández Urrusuno *et al*. 2008). A linear regression model showed a *positive* association between hospital admissions and prescription of antibiotics.

However, one of the problems with ecological level data is that association at this population level may not hold at local levels. For example, Majeed and colleagues found that while antibiotic prescribing reducing in England coincided with an increase in hospital admissions for RTIs at a national level, at a PCT level a moderate *positive* association held (r_s=0.51) (Majeed *et al*. 2004). They suggested that the finding at the national level would benefit from further investigation.

Table 2.3 Summary of evidence from studies examining the association between antibiotic prescribing in general practice and complications arising from of RTIs – ecological level

Reference	Study population and period	Study design	Antibiotics data	Clinical outcomes	Findings
Van Zuijlen *et al.* 2001	UK, Netherlands, Denmark, Norway, Canada, US and Australia, 1991-1998. Children aged≤14 years	Cross-sectional comparative analysis	Antibiotic prescription rates for acute otitis media, by country	Incidence rates of hospitalisations with acute mastoiditis	Incidence of acute mastoiditis was lower (1.2-2.0 per 100,000 person-years) in countries with high (>96%) antibiotic prescribing rates and higher (3.5-4.2) in countries with lower (31-76%) antibiotic prescribing rates.
Little *et al.*2002	82 Health Authorities (HAs) in England, 1997-1998 All ages	Cross-sectional comparative	Dispensed penicillins, by HA	Hospital admissions for acute RTI, complications (quinsy, rheumatic fever, mastoiditis, pneumonia, septicaemia, anaphylaxis) and operations related to RTIs.	Higher penicillin use was associated with lower rates of quinsy (p=0.0035), mastoiditis (0.009) and tonsillectomy (0.028) but not pneumonia.
Majeed *et al.* 2004	Primary care trust (PCT) level in England, 1996-2002 All ages	Longitudinal	Antibiotics prescribed within PCTs, weighted by age and sex	Hospital admissions for RTIs	In England, prescriptions decreased over the time period whilst hospital admissions increased between 1996 and 1998 before declining thereafter. However, at a PCT level prescribing was *positively correlated* with hospital admissions (r_s=0.51,p<0.01).

Table 2.3 Summary of evidence from studies examining the association between antibiotic prescribing in general practice and complications arising from of RTIs – ecological level

Reference	Study population and period	Study design	Antibiotics data	Clinical outcomes	Findings
Price *et al.* 2004	England and Wales, 1993 -2000 All ages 1993-2000	Longitudinal	Antibiotics prescribed for LRTI during winter	Winter pneumonia mortality	Antibiotic prescribing had a significant association with pneumonia mortality after controlling for incidence of influenza ($p<0.001$).
Sharland *et al.* 2005	England, 1993-2003 Children aged≤15 years	Longitudinal	Antibiotic prescribing and dispensing from around 130 practices	Hospital admissions for quinsy, rheumatic fever and mastoiditis. General practice episodes of mastoiditis.	A 37% decline in antibiotic prescribing (and similar in dispensing) corresponded with a 19% rise in mastoiditis and simple mastoidectomy. No increase in quinsy or rheumatic fever.
Mainous III *et al.*2006	USA, 1996-2003 Adults 18-64years old	Longitudinal	Ambulatory antibiotic prescribing for bronchitis and cough for a representative sample of the population.	Hospital admissions for lower respiratory tract infections from approximately 500 hospitals.	A weak negative association between antibiotic prescribing for acute bronchitis and cough and LRTI hospitalizations (r_s=-0.22).
Fernández Urrusuno *et al*. 2008	162 GPs in a Primary Health Care Area, Spain, 2004 All Ages	Cross-sectional comparative	Antibiotic prescribing indicators	Hospital admissions due to RTIs in 3 hospitals of the study area	Higher prescribing of antibiotics was associated with a higher number of hospital admissions due complications arising from RTIs ($p<0.001$).

2.6.3 Individual level evidence

At the start of this study, the only published studies examining the effect of antibiotics on complications in the area of RTIs at the individual level were those included in the aforementioned Cochrane reviews (Sanders *et al.* (2004), Spinks *et al*. (2006)). Most of the studies included in the Cochrane reviews were not adequately powered to determine the protective effect of antibiotics against the risk of complications. Since then several studies have been conducted, based on larger retrospective cohorts of patients obtained from the UK General Practice Research Database (GPRD) (Table 2.4). The GPRD is a large computerised database of anonymised longitudinal medical records from primary care with around 3.4 million active patients (around 5% of the UK population) from around 450 general practices in the United Kingdom (UK) (http://www.gprd.com).

Dunn *et al*. (2006) investigated the factors associated with cases of quinsy diagnosed in primary care; these factors included exposure to antibiotics (on the same day as the sore throat diagnosis or within 30 days). In 198,316 episodes of sore throat, they found only 192 cases of quinsy; antibiotic exposure had no significant effect on the occurrence of quinsy. However, there was some evidence to suggest that antibiotics may reduce the risk of quinsy in patients with a diagnosis of tonsillitis (as opposed to sore throat) although this was not statistically significant.

Petersen *et al*. (2007) identified cohorts of patients diagnosed with otitis media, sore throat and chest infection/URTI between 1991 and 2001. The aim of the study was to compare the risk of complications (mastoiditis, quinsy and pneumonia) in the month following otitis media, sore throat and chest infection respectively between patients exposed to antibiotics and those not on the day of the consultation, after adjusting for age, gender and social deprivation. Whilst the absolute risks of complications were low, antibiotics did significantly reduce the risk of complications in all RTI groups. However, the numbers needed to treat (NNT) with antibiotics to prevent one complication were high (over 4,000 patients). For episodes of chest infection, antibiotics reduced the risk of pneumonia across all ages, particularly in the 65 plus age group. The numbers of cases of acute rheumatic fever and glomerulonephritis following sore throat diagnoses were too low to allow investigation of the protective

effect of antibiotics. The authors concluded that, for diagnoses of URTIs, sore throat and otitis media, research should focus on interventions to reduce antibiotic prescribing even further, whilst for chest infections, clinical algorithms and diagnostic technology should be developed to identify those at a higher risk of developing pneumonia.

Thompson *et al*. (2009a) specifically examined the risk of mastoiditis in children (aged 3 months to 15 years) within 3 months of otitis media (OM) diagnosis, in those who were prescribed an antibiotic and those who were not, between 1996 and 2006. In total, from 1,182,272 cases of OM, 288 children developed mastoiditis. The prescription of antibiotics for otitis media halved the risk of mastoiditis but the low absolute risk of mastoiditis meant the number of OM episodes needing antibiotic treatment to prevent one case of mastoiditis (NNT) was very high. When restricted to children with mastoiditis requiring surgery, antibiotics were found to have a more protective effect. Winchester *et al*. (2009) conducted a similar study, but examined patients with a first diagnosis of an acute LRTI in general practice to identify predictors of hospital admissions and death from pneumonia or another LRTI in the 3 months following the LRTI diagnosis. Those who received an antibiotic prescription on the same day as the LRTI diagnosis were less likely to be admitted to hospital with pneumonia or other LRTI after adjusting for age, age squared, sex, NHS region and practice deprivation. The NNT to prevent one hospital admission was 1,002. In age-stratified analyses, same day antibiotic prescribing was associated with a significantly reduced risk of admission in patients aged 18-64 years but not in those aged 1-17 years or ≥65 years. The association between same day prescribing of antibiotics and mortality held for all ages, in the 18-65 and ≥65 age group.

Adding to this pool of evidence, a recent case-control study examined children (aged 6 months to 16 years) presenting to secondary care with radiographic evidence of pneumonia or empyema (cases) from seven hospitals in South Wales (Crocker *et al*. 2012). The study found that the 89 cases were less likely than the 166 matched controls to have been prescribed an antibiotic at the first GP consultation although they were not less likely to have taken antibiotics at any time during the illness prior to the date of hospitalisation.

Table 2.4 Summary of evidence from studies examining the association between antibiotic prescribing in general practice and complications arising from of RTIs – individual level

Author	Study population and period	Study design	Clinical outcomes	Findings
Dunn *et al.* (2006)	Consultations for sore throats identified in the GPRD, 1995-1997 All ages	Retrospective case-control	Case: Quinsy within 30 days of sore throat diagnosis Control: no quinsy within 30 days of sore throat	A total of 606 cases of quinsy but only 192 following a diagnosis of sore throat. The study found that 169/192 (88%) cases and 167,811/198,124 (84%) controls were prescribed antibiotic at the index illness and antibiotic exposure had no significant effect on the occurrence of quinsy (adjusted OR=1.2, 95% CI=0.7 to 2.2). Quinsy presenting without warning had identical risk factors to those presenting in GPs (Male smokers aged 20-39 years).
Petersen *et al.* (2007)	Consultations for chest infection, URTI, sore throats and acute otitis media identified in the GPRD, 1991-2000 All ages	Retrospective cohort	Risk of pneumonia, quinsy and mastoiditis in the month following a diagnosis of URTI and chest infection, sore throat and otitis media respectively.	Same day antibiotic prescribing significantly reduced the risk of complications in all RTI groups. URTI→Pneumonia, adjusted OR=0.68 (95% CI=0.58 to 0.79) Otitis media→Mastoiditis, 0.56 (0.37 to 0.86) Sore throat→Quinsy, 0.84 (0.73 to 0.97) However, the NNT with antibiotics to prevent one complication were high (over 4,000 patients). For episodes of chest infection, antibiotics reduced the risk of pneumonia across all ages, particularly in the 65 plus age group (OR=0.35 (95% CI=0.33 to 0.38) and NNT=39.

Table 2.4 Summary of evidence from studies examining the association between antibiotic prescribing in general practice and complications arising from of RTIs – individual level

Author	Study population and period	Study design	Clinical outcomes	Findings
Thompson *et al*. (2009a)	Consultations for acute otitis media, identified in the GPRD, 1990-2006 Children aged 3 months to 15 years	Retrospective cohort	Risk of mastoiditis within 3 month following a diagnosis of otitis media	An antibiotic prescribed in the same consultation as the OM diagnosis significantly reduced the risk of developing mastoiditis within the following 3 months (adjusted OR=0.56, 95% CI=0.44 to 0.71). A total of 4,831 episodes of otitis media would need to be treated with antibiotics to prevent one child from developing mastoiditis. In sensitivity analyses restricted to children with mastoiditis requiring surgery, the adjusted OR was 0.39 (95% CI=0.28 to 0.55).
Winchester *et al*. (2009)	Consultations for first diagnosis of LRTI identified in the GPRD, 2004 All ages	Retrospective cohort	Hospital admission and death from pneumonia or another LRTI in the 3 months following a diagnosis of LRTI	Patients receiving an antibiotic prescription on the same day as the LRTI diagnosis were less likely to be admitted to hospital (adjusted hazard ratio (HR) =0.73, 95% CI=0.58 to 0.92, NNT=1,002) or die (0.31, 0.26 to 0.37, 7,247). Same day antibiotics also reduced the risk of hospital admissions (HR=0.61, 95% CI=0.44 to 0.84, NNT= 1,222) and death in the 18-64 year olds (0.21, 0.13 to 0.35, 6,329). The risk of death was reduced in the ≥65 years of age (0.31, 0.26 to 0.37, 14,439).

Table 2.4 Summary of evidence from studies examining the association between antibiotic prescribing in general practice and complications arising from of RTIs – individual level

Author	Study population and period	Study design	Clinical outcomes	Findings
Crocker *et al*. 2012	Cases and control with a GP diagnosis of URTI, LRTI or cough. Children aged 6 month to 16 years	Case-control	Cases: diagnosed with pneumonia or empyema and previously seen by a GP for an index illness (URTI, LRTI, cough) Controls: matched on age, GP and had been seen by a GP for a URTI, LRTI or cough	The study found that 31/89 (35%) cases and 83/166 (50%) controls were prescribed antibiotic at the index illness (unadjusted OR=0.53, 95% CI=0.31 to 0.90). No confounders were identified with cases. For prescribing between the index date and the hospitalisation date, cases were still less likely to have received antibiotics than controls (40/89 (45%) vs. 96/166 (58%), adjusted OR=0.62, 0.37 to 1.04).

2.6.4 Summary

The majority of RTIs are self-limiting illnesses for most patients. While antibiotics reduce intensity and duration of some symptoms or pain, they generally provide only marginal benefit for the otherwise healthy patient with an RTI. Antibiotics are of some benefit in protection from complications (with a higher risk of developing a complication if antibiotics were not prescribed) for acute RTIs, but as the risk of developing a complication is exceedingly low in resource-rich countries, the number of patients required to be treated with antibiotics to protect one from a complication are large, apart from for specific high-risk patient sub-groups. Therefore, based on current evidence, recommendations are that further gains are to be made in reducing inappropriate antibiotic prescribing in the community as antibiotics are of little benefit for the majority of patients. This reduction of antibiotic prescribing would be of benefit as widespread antibiotic prescribing is known to encourage clinic visits for subsequent episodes (medicalisation of RTIs), intensify pressure on clinicians to prescribe, increase risk of exposure to antibiotics and antibiotic use, and increase antibiotic resistance.

2.7 Relationship between antibiotic use and resistance

Evidence examining the relationship between antibiotic usage and resistance rates is mostly derived from urine coliform infections (such as *Escherichia coli* (*E.coli*)), although recently respiratory pathogens (such as *Streptococcus pneumoniae* (*S. pneumoniae*) and *Haemophilus* species*)* have been examined too. Most studies have demonstrated associations between antibiotic usage and resistance though proving causality is difficult.

2.7.1 Ecological level evidence

Until recently the association between antibiotic use and resistance had only been examined at a country or general practice level. At country level, studies have mainly used data from the European Surveillance of Antimicrobial Consumption (ESAC) project that maps out national antibiotic prescribing and resistance rates longitudinally across numerous European countries. These studies showed significant correlations between antibiotic use and resistance generally, but especially in *S.*

pneumoniae (Goossens *et al*. 2005; Van de Sande-Bruinsma *et al*. 2008). Whilst significant correlations existed at a country level, there was wide variation in the association between different European countries. For example, Sweden and Denmark had higher rates of penicillin use than the UK but had lower resistance, whilst Finland had lower rates of penicillin use but higher resistance. The authors suggest that the variation between countries can be explained by differential selection pressure for resistance within countries. Subclasses and different classes of antibiotics may select for resistance to both that antibiotic class and sub class and also to other antibiotics.

At a general practice level, studies have shown low correlation coefficients and hence weak associations, mostly in urine coliforms, whilst others found a strong correlation between the use of trimethoprim and amoxicillin and resistance to ampicillin and trimethoprim (Steinke *et al*. 1999; Magee *et al*. 1999; Howard *et al*. 2001; Priest *et al*. 2001, Hay *et al*. 2005). A recent study in coliform isolates from urine samples has shown that general practices with the greatest reduction in overall dispensed antibiotics showed a significant reduction in antibiotic resistance to ampicillin and trimethoprim when compared with practices that reduced their antibiotic dispensing the least (Butler *et al*. 2007).

As previously discussed, interpretation of these ecological level analyses should be made with caution as conclusions arising from these aggregate data may not necessarily apply to individuals within that area. This problem can be overcome by use of individual patient data.

2.7.2 Individual level evidence

In UTIs, Donnan and colleagues demonstrated how results from group level analyses could disguise individual level effects by performing a multilevel model analysis at both the practice and individual level (Donnan *et al*. 2004). They compared trimethoprim prescribing with resistance to trimethoprim in gram negative bacilli in urine samples routinely submitted from GPs and found that when analysed at a practice level, using practice rates of resistance and usage, trimethoprim prescribing was not related to trimethoprim resistance, but when using individual level data a

strong association existed between the two. A key issue in ecological studies is that prescribing at a practice level is related to resistance in urine submitted for patients within the practice and many of these patients may not themselves have been prescribed antibiotics in the recent past. Indeed, many will not have had antibiotics recently, and it is the consumption of recent antibiotics by individuals that is the greatest risk factor for infection with a resistance compared to a sensitive uropathogen. This stresses the problem that can be created by ecological level studies and evidence arising from them is much weaker**.** A similar study, again involving urine samples, showed no evidence of a dose-response relationship between exposure to any antibiotic prescribed over a 12 month period and resistance to amoxicillin and/or trimethoprim (Hay *et al*. 2005). However, greater levels of resistance were found in patients recently (within 2 months of the sample submission) exposed to any antibiotic and there was a dose–response relationship to increasing exposure to trimethoprim.

Several recent studies have shown that using antibiotics is associated with resistance in respiratory pathogens in individuals. A cohort study in children with acute RTIs found that the community prescribing of beta-lactam antibiotics at presentation of RTI doubled the prevalence of antibiotic resistant *Haemophilus* isolates in individual children compared to no prescription (Chung *et al*. 2007). Malhotra-Kumar *et al*. (2007) found that macrolide use was the single most important driver of the emergence of macrolide resistance in oral streptococci flora in individual adults. Another study by Nasrin *et al*. (2002) showed an association between beta lactam use and the carriage rates of penicillin resistant pneumococci in children aged less than 4 years. However, in a recent study by Sundqvist *et al*. (2010), the potential of reversing antibiotic resistance by decreasing use of trimethoprim was examined in *E. coli* samples. Whilst trimethoprim prescribing use was greatly reduced (by 85% over 2 years), resistance rates in *E. coli* samples were practically unaffected and did not follow that trend. The model did show a halt in the rise of trimethoprim resistance but only a slow reversibility in resistance rates. This is contradictory to what Butler *et al*. (2007) found at general practice level. This was highlighted in an article by Enne (2010) where some studies showed a reduction in resistance in response to prescribing reduction, while others did not. The reason for these differences could be due to factors not measured, such as the clonality of resistant isolates, co-selection or

the fitness cost of resistance. A more prudent approach is therefore required to obtain as much information on the resistance problem as possible.

2.8 Summary of Chapter 2

This chapter has reviewed the current evidence on the effectiveness of antibiotics in the treatment of RTIs and their complications and also the relationship between antibiotics and resistance. The evidence so far indicates that for most patients, RTIs are self-limiting and last roughly the same duration regardless of whether or not antibiotics are prescribed. Therefore antibiotics are not indicated for most of these infections. For resistance, the results do show an association between dispensing and resistance between certain organisms and antibiotics. The next chapter will describe the ecological and individual datasets that were used in this thesis to examine the relationship between antibiotic prescribing in primary care and complications arising from RTIs, and the general statistical methods used.

Chapter 3 Overview of methods and datasets

3.1 Introduction

To examine the relationship between antibiotic prescribing, complications arising from respiratory tract infections (RTIs), and antibiotic resistance, a number of datasets at both the general practice level (using national routinely collected data) and individual level (using general practice databases) will be utilised. An overview of these datasets is given in this chapter; further details will be given in later chapters when relevant.

3.2 Ecological studies

An ecological study is one in which the unit of observation is at an aggregate level rather than at an individual level. Data collection at this level is relatively easier than at an individual level, where data is either not readily available, too costly to obtain or raises issues of confidentiality. A major disadvantage, however, is that inferences made from ecological models regarding the relationship between risk factors and outcome may not apply to individuals within those areas. This is sometimes referred to as the "*ecological fallacy"*. Ecological studies however can be useful, especially in the generation of hypotheses and to determine whether it is necessary, or useful, to proceed to an individual-level analysis. For this reason, the following five chapters (4 to 8) concentrate on trends in antibiotic dispensing, complications and antibiotic resistance, and the relationships between them, at the level of general practice. In this thesis, this relationship was firstly examined for a sample of Welsh practices and then for all practices in Wales. The datasets and methods used in the individual-level analysis are covered later in this chapter.

3.2.1 Study population – Wales

Data required for this section of the study was obtained from all-Wales data sources providing data on all general practices and their populations (people resident in Wales) in the study period (1996 to 2006). The exception was data used from the General Practice Morbidity Database (GPMD), which was based on a representative sample of practices across Wales. The research sample is therefore representative of

the Welsh population, which at the 2001 UK Census was 2,903,085 (National Statistics). Wales is an ideal country for data analysis; it has a good mix of rural-urban areas (36%-64%) and of deprived-affluent areas (Rural and Urban Classification 2004), and has a relatively stable population (useful when looking at trends). It is also advantageous since data flows from different administrative areas, such as health trusts and local health boards, to a central repository, ensuring high quality and comparable data.

3.2.2 Geographical areas

Wales was previously subdivided into 22 unitary authority (UAs) areas which were responsible for the provision of all local government services, including education and social work services. UAs are divided into electoral divisions (n=884 as of April 2009), and are the base unit of Welsh administrative geography used to elect local government councillors to County Councils (local authorities). The 2001 Census Output Areas were specifically created for statistical purposes which delivered areas with populations of 125 households. Super Output Areas (SOAs) are geographical units designed for the collection and publication of small area statistics and were introduced at the 2001 Census. There are currently two layers of SOA (middle and lower level), with areas intermediate in size between 2001 Census Output Areas (OAs) and local authorities, and with each layer nesting inside the layer above. SOAs were designed to have similar population sizes and be as socially homogenous as possible and will not be subjected to regular boundary change. This makes them ideal for analyses as they are comparable across countries and allow trends to be monitored. In Wales, there are 413 Middle Layer SOAs (built from groups of Lower Layer SOAs) which have a minimum population of 5,000 and 1,896 Lower Layer SOAs (built from groups of OAs), which have a minimum population of 1,000.

Local Health Boards (LHBs) are the health administrative areas in Wales and manage all primary care services and work with local authorities and other agencies to provide health and social care locally. They are comparable to Primary Care Trusts (PCTs) in England, Local Health Care Co-operatives (LHCCs) in Scotland and Local Health and Social Care Groups (LHSCGs) in Northern Ireland.

3.2.3 Identifying general practices

The Welsh Demographic Service (WDS) is a database of every person registered to a general practitioner in the country, and is maintained for NHS purposes by NHS Wales Informatics Service (NWIS). The WDS was therefore used to identify the number of general practices existing in Wales over the 11-year period of this study (January 1996 to December 2006) and also to obtain a monthly practice population (list size) by age group and gender for each of these practices.

Each general practice in the UK is allocated a unique identification code. The conventional codes are those allocated by the Prescription Pricing Authority (PPA); a 6-digit code where character 1 is W for Wales (W-codes), S for Scotland and Y for England. To ensure complete practice anonymity, NWIS provided unique encrypted practice codes to replace the original W-codes. For datasets that were obtained with W-codes attached, such as the resistance data and some dispensing data, these were linked and replaced with encrypted codes by NWIS, hence preserving the anonymity of practices.

3.2.4 Practice populations and characteristics

The WDS database provides a historical record of person movements within Wales and therefore there can be many records for a single individual, showing where a person has lived (and de/re-registered) over time. The WDS is also used to produce alternative local area population estimates, especially at smaller areas such as electoral divisions and LSOAs. While these population estimates are widely acknowledged as being slightly inflated due to time lags involved in updating birth and death registrations, and also due to double registrations of its university age population, its strength is that it can be analysed at a low geographic level, i.e. electoral division and postcode (Local Government Data Unit - Wales 2005). The main purpose for it in this study, however, is to obtain practice populations and it was possible to obtain the number of individuals registered to a general practice at any given time period and by age group and gender.

The WDS additionally holds certain practice information and the following practice

characteristics were obtained for each practice: the local health board (LHB) in which the practice lies, the number of GPs within each practice, the average age and gender of these GPs, single-handed status, and deprivation score and quintile of the practice population (Townsend scores based on 2001 census) (Townsend *et al*. 1988). All information was taken from practices as they were in June 2007.

3.2.5 Deprivation Measures

Two measures of deprivation were used in this thesis: the Townsend Material Deprivation Score (Townsend *et al.* 1988) and the Index of Multiple Deprivation (Office for National Statistics).

3.2.5.1 *The Townsend Material Deprivation Score*

The Townsend Material Deprivation Score uses four Census variables to assess the following: general lack of material resources and insecurity (unemployment), material living conditions (overcrowding), wealth (owner occupation is used as a proxy indicator), and income (car ownership is used as a proxy indicator). These four measures can be combined to construct a single measure of deprivation. For the purposes of this study, Townsend deprivation scores were derived from 2001 census data by linking the postcode of each person currently registered (as of June 2007) in the practice to a Townsend score via the LSOA code. For each practice, the Townsend scores were summed and divided by the number of persons registered. Scores tend to range from -12 (least deprived) to +12 (most deprived) although in certain circumstances they can lie outside this range. Quintiles were constructed by ordering the practices by their scores and dividing them into five equal population groups, so that each quintile had the same total population (around 650,000). Quintile 1 indicates the least deprived practices and quintile 5 the most deprived practices.

3.2.5.2 *The Index of Multiple Deprivation (IMD)*

The Index of Multiple Deprivation (IMD) is the official measure of deprivation for small areas in the UK. The IMD is made up of eight separate domains of deprivation, including health and income, and can be combined to create an overall deprivation (using specific weights for each domain depending on importance). Deprivation

scores have been calculated for each LSOA, with a higher score indicating more deprivation. IMDs are constructed separately (and sometimes using different measures) for each country in the UK. Therefore, one limitation of the IMD is that the deprivation scores cannot be compared with those from the deprivation indexes of other UK Countries.

3.3 Ecological level datasets

3.3.1 Antibiotic dispensing data

Prescribing Analyses and Cost (PACT) data is the main source of information on general practitioners' (GPs) dispensing in Wales. The Prescribing Services Unit (PSU) in NWIS collects information on all prescriptions issued by general practitioners (GPs) in Wales that are dispensed by community pharmacists in England and Wales, dispensing GPs or personally administered by GPs in Wales, or appliance contractors. It is also responsible for the provision of prescribing information and information systems to enable drug expenditure to be monitored. Data is captured to enable the payment of dispensing contractors in Wales and to allow a unique database of dispensing information to be created.

The database contains information on each drug and is classified into 4 levels from the British National Formulary (chapter, section, sub-section and chemical) (Joint Formulary Committee 2007). For example, information is available for individual drugs or chemicals (for example erythromycin), the antibiotic class or sub-section (such as macrolides), the section it falls under (such as antibacterial drugs) and the chapter (such as infections). The information collected includes the name of the drug, the basic cost attributed to the dispensed antibiotic, the number of items dispensed and the quantity of the drug dispensed (an item is defined as each preparation on the prescription). This information is available from April 1996 onwards and at individual practice level, local health board level, and national level, allowing for different analyses.

3.3.1.1 *Dispensing measures*

Items of antibiotics are used as a measure of the quantity of antibiotic dispensing. They do not always give a good indication of total use unless total amounts of drugs per item are also being considered. However, as well as being easy to measure, items are of great value in measuring the frequency of prescribing where treatments are given largely or entirely as courses, such as in antibiotics or immunisations (Prescription Pricing Division, 2007). The World Health Organisation (WHO) recommends using the number of defined daily doses (DDD) as a measurement unit for inter-country comparisons of antibiotic usage. The definition of DDD is the assumed average maintenance dose (per day) for a drug used for its main indication in adults (Jones *et al*. 2004). The number of DDDs can be calculated by multiplying the quantity of each dosage prescribed by the strength of each dosage, then dividing by the DDD. In an outpatient setting, a very strong correlation has been shown to exist between antibiotic items and DDD, both for total usage and for specific classes of antimicrobials (Monnet *et al*. 2004). Additionally Davey *et al*. (2008) concluded that DIDs (DDD per inhabitant per day) were inadequate as a single measure of antibiotic use and that using prescriptions per inhabitant per day (PIDs) provided important additional insight.

Dispensing data is an imperfect proxy for antibiotic consumption as there may be a very small proportion of patients who receive the antibiotics but do not actually take them. This would therefore lead to a very small bias in dispensing data.

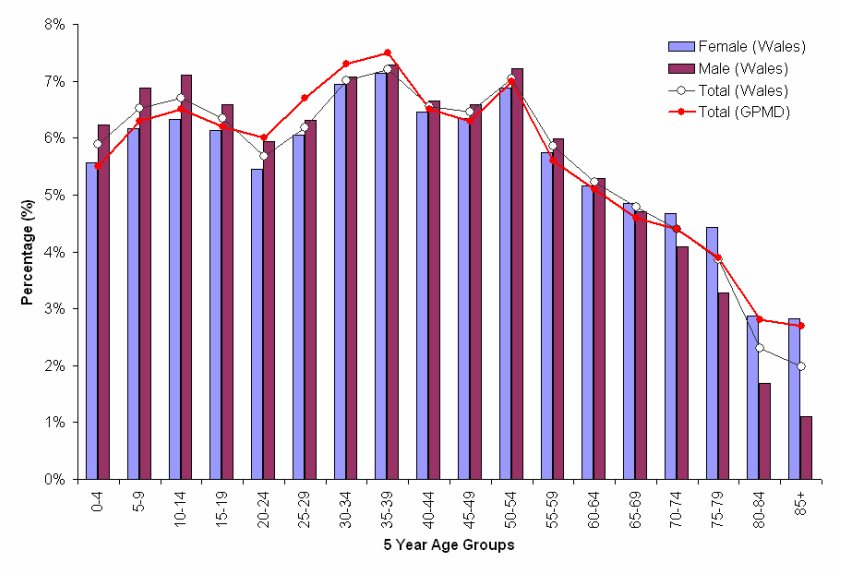
3.4 Individual level datasets

3.4.1 General Practice Morbidity Database

The General Practice Morbidity Database (GPMD) was a primary care database held and maintained by Heath Solutions Wales (Evans *et al*. 1997). The GPMD recorded clinical data (using 5-byte version of Read Codes) held at the level of individual consultations from 1996 up to 2000, and included detailed information on consultations, risk factor data and prescriptions. It was derived from 45 general practices in Wales covering a population of nearly 400,000 patients, thus providing approximately a 13% sample of the Welsh population. The age and gender

distribution of the GPMD closely mirrored that of the Welsh population for all ages (Stats Wales, Wales Assembly Government) (Figure 3.1). Although now old, these data are useful as they provide trends during a time of rapid reduction in antibiotic prescribing in primary care.

Figure 3.1 Age/sex distribution of the Welsh population and patients included in the GPMD in 1999/2000



3.4.2 Hospital Episodes Statistics

The Patient Episode Database for Wales (PEDW) is held by NWIS and contains records of all inpatient and day case activity undertaken in NHS Wales (including community hospitals), together with data for Welsh residents treated in English Trusts. Individuals can be traced across different spells of inpatient or day case care using personal identifiers, such as NHS number or case record number. PEDW contains other personal information such as age, gender and postcode as well as registered GP and practice details. The database also holds details relating to the spell of care such as date and method of admission/discharge along with diagnosis and procedure codes using the World Health Organization (WHO) International Statistical Classification of Diseases (ICD). Information is available from 1991 to present.

3.4.3 Antibiotic resistance data

Resistance data is available from the Microbiology system called DataStore. DataStore is a relational database management system developed by the National Public Health Service (NPHS) for Wales. DataStore provides a robust automated transfer of bacteriology and virology reports (negative and positive) from 18 Welsh and Welsh border laboratories serving Welsh practices. Laboratory results are entered into the laboratory information management systems (LIMS), which automatically generates an electronic copy of the report and outputs the report in a standard format. The formatted reports are input into various databases of which DataStore is one.

Data from DataStore is available from 1st January 1998 onwards at an individual level. The database contains information on all samples (taken from a patient) or isolates (a sample with an identified organism) sent for testing from GPs, including the following bacteria: *Escherichia coli* or lactose-fermenting coliform (referred to collectively as coliforms), Methicillin sensitive and resistant *Staphylococcus aureus* (MSSA/MRSA), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Haemophilus Influenza*. For each isolate reported the following information is available: date of isolation, surgery address, specimen type, hospital number, age and gender of the patient, specimen number, organism isolated, duplicate isolate (defined as isolates occurring within 91 days of a prior organism from the same patient with the same resistance pattern) and resistance results (resistant, sensitive or intermediate) for up to 13 antibiotics (where tested). Each isolate record included a practice identifier to enable linkage to dispensing data available only at a practice level.

Also available was sampling data, again from 1st January 1998 and from each of the 18 laboratories. This data consisted of the total number of samples sent to a laboratory by a practice and included the number of samples sent by the practice per month, the site the sample was taken from, and to which laboratory it was sent for testing.

3.4.4 General Practice Research Database

The General Practice Research Database (GPRD) is the world's largest computerised database of anonymised longitudinal medical records from primary care with around 3.4 million active patients (around 5% of the UK population) from around 450 general practices in the United Kingdom (UK) (http://www.gprd.com). It is managed by the GPRD Group within the Medicines and Healthcare products Regulatory Agency (MHRA). Individual patient level data can be obtained for a fee, or free to UK academics through a Medical Research Council (MRC) licence. Although no patient or practice identifiable data are collected, each patient has an encrypted unique number, which allows their records to be linked over time. For each patient GPRD collects and makes available information such as demographic details (gender, year of birth and practice location), all clinical information (diagnoses, symptoms, procedures, and medical history using the Read/OXMIS coding system), all prescriptions issued, referrals to secondary care, test results, and lifestyle information (such as smoking and drinking status). GPRD data is available from 1990 although the number of practices contributing data and up-to-standard (fulfill the routine quality assurance checks) will vary over the years.

3.5 Statistical methods

Some of the analyses in this thesis use multilevel regression models to account and correct for variation at the level of LHBs and Welsh general practices. Analysing data at the all-Wales level is of importance as it gives a general picture of dispensing over time. However, it does not take into account variations in dispensing data at a LHB and/or general practice level. Using a single-level linear regression model of dispensing rates on time assumes that observations are independent. However, data with a hierarchical or multilevel structure violate this assumption, since correlations usually exist between observations within a level (for example, annual dispensing rates within a practice or practices within an LHB). If the hierarchical structure is ignored, and the observations are regarded as independent, then standard errors are generally under-estimated. This can lead to spurious precision of estimates and relationships can be interpreted as statistically significant where in fact they are not. Multilevel modelling overcomes this by incorporating the hierarchical structure of

the data into the model, by allowing for the dependencies that exist between rates within a practice.

A single-level linear regression model can be expressed as:

$$y_i = \beta_0 + \beta_1 x_i + e_i$$

where y_i is the outcome, β_0 is the intercept, β_1 is the slope, x_i is the explanatory variable and e_i is the Normally distributed error term. For example, y_i might be a rate of antibiotic dispensing in year *i* and x_i the year, where *i*=1996 to 2006. The parameter β_0 is the intercept (or the overall mean) and β_1 is the estimate for trend.

For a multilevel linear regression model the outcome y_i (e.g. antibiotic dispensing) can vary at different levels (e.g. 2-levels: *i* (time) and *j* (general practice)) and the model can be written as:

$$y_{ij} = \beta_{0ij} x_0 + \beta_{1ij} x_{1ij}$$

where

$$\beta_{0ij} = \beta_0 + u_{0j} + e_{0ij}$$

and

$$\beta_{1ij} = \beta_1 + u_{1j} + e_{1ij}$$

The parameter β_{0ij} is an intercept which is allowed to vary randomly about the overall mean β_0 by a random variable u_{0j} (level 2 residuals) representing each general practice's difference from the mean intercept. The parameter β_{1ij} similarly is a slope which is allowed to vary from the mean slope β_1 by a random variable u_{1j} representing each general practice's difference from the mean slope. The terms u_{0j} and u_{1j} follow a multivariate Normal distribution with mean vector 0 and covariance matrix Ω_u. The elements of Ω_u are:

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{bmatrix}$$

where variance of u_{0j} (σ^2_{u0}) is the variation in the intercepts between practices and

σ^2_{u1} is the variation in the slopes between practices. The covariance of u_{0j} and σ^2_{u1} (σ_{u01}) is the covariance between the slopes and intercepts.

The terms e_{oij} and e_{1ij} are the individual or level 1 residual terms (between time within practice variation) and are independently distributed variables representing the parts of dispensing not explained by the other factors.

$$\begin{bmatrix} e_{0ij} \\ e_{1ij} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} \sigma^2_{e0} & \\ \sigma_{e01} & \sigma^2_{e1} \end{bmatrix}$$

As with any regression analysis, different models are used depending on the type or distribution of the outcome. For example for data available at a level of general practice, such as antibiotic dispensing data, a 3-level linear regression model was used (local health board (LHB) (level *k*), practice (*j*) and time (*i*)). The numbers of dispensed antibiotic items per practice per time period are generally large and were approximately normally distributed. For hospital episodes of complications the counts are smaller and could not be assumed to be normally distributed; therefore a 3-level Poisson regression model was used. Details of the models used will be described in each chapter.

For data available at an individual patient level, such as the antibiotic resistance data, and the data arising from the GPRD, a 3-level (LHB, practice and individual) logistic regression model was used with a binary outcome (resistant to antibiotics or not, and complication diagnosed or not, respectively). Models were fitted using MLwiN software (Rasbash *et al*. Centre for Multilevel Modelling, University of Bristol). Models were fitted using a maximum likelihood (ML) method, known as iterative generalized least squares (IGLS) which is an iterative procedure based on estimating the random and fixed parts of the multilevel model alternately, assuming the estimates for the other part are correct. This involves iterating between two generalized least squares (GLS) model fitting steps until the estimates converge to ML point estimates. Initial estimates were obtained by using the restricted iterative generalized least squares (RIGLS) estimation procedure. Final parameters were estimated using Markov Chain Monte Carlo (MCMC) methods to give less biased

estimates and also to derive confidence intervals for non-symmetrical distributions.

Although Chapter 4 uses multilevel modelling, since it is a preliminary examination of the relationship between antibiotic dispensing and complications using a smaller sample, the full details of the process of model fitting and interpretation such as examining the variation in intercepts and slopes at different levels and the use of different estimation techniques are not covered until Chapter 5 (in antibiotic dispensing).

Additional statistical analyses were undertaken using SPSS for Windows (SPSS for Windows).

3.6 Ethical approval

Ethical approval for the all-Wales analysis was gained through the South East Wales board and, for the General Practice Research Database, approval was granted by the Independent Scientific Advisory Committee (ISAC).

Chapter 4 Antibiotic dispensing and complications arising from RTIs: a study of a sample of Welsh practices

4.1 Introduction

The aim of this chapter was to test the hypothesis that there is an association between antibiotic dispensing and the rate of complications arising from respiratory tract infections (RTIs) diagnosed in primary care, using data from the Welsh General Practice Morbidity Database (GPMD). Due to the small number of practices involved and the aggregated nature of the data, these results do not allow us to draw robust conclusions regarding the relationship between antibiotic dispensing and complications at an individual level. Instead they allow an exploration into the relationship, and assess how feasible it is to carry out further analyses on larger datasets.

4.2 Methods

4.2.1 Complications arising from respiratory tract infections

The GPMD provided annual numbers (1996 to 2000) of diagnoses for certain complications diagnosed in primary care with sufficiently large incidence to enable analysis at the general practice level. These are complications arising from common RTIs and the Read codes are listed in Table 4.1 (NHS Connecting for Heath). For the purpose of this analysis, data were obtained for practices that contributed continuously to the GPMD over the five-year period.

4.2.2 Antibiotic dispensing data

Dispensing data is based on information obtained from prescriptions sent by pharmacies to the Prescribing Management System at the Prescribing Services Unit, NHS Wales Informatics Service for payment (as described in section 3.3.1). Dispensing data therefore covers all routine prescriptions dispensed in the community including prescriptions written by General Practitioners (GPs) in Wales, community pharmacists, dentists and hospital doctors. Dispensed antibiotics (rather

than prescriptions for antibiotics) are a better proxy for antibiotic consumption, especially given the rising use of delayed prescribing strategies in primary care.

Table 4.1 Read codes for selected complications arising from RTIs

Read Code	Complications
A38..	Septicaemia
F00..	Bacterial Meningitis
F040.	Intracranial abscess
F53..	Mastoiditis and related conditions
G0…	Acute rheumatic fever
H043.	Epiglottitis
H15..	Peritonsillar Abscess (Quinsy)
H2...	Pneumonia *excluding Influenza (H27..), Other specified or Not otherwise specified pneumonia or influenza (H2y.. and H2z..)*
H50..	Pleural empyema
K00..	Acute glomerulonephritis

Quarterly dispensing data were obtained for the same continuously contributing practices from April 1996 until December 2000. For simplicity, the items dispensed for the following eight antibiotic groups (based on definitions from Joint Formulary Committee, British National Formulary (BNF) section 5.1 (with the exception of anti-tuberculosis and antilepromatous drugs) were summed to produce a measure of total dispensing for antibiotics most commonly used to treat RTIs:

- Benzylpenicillins and phenoxymethylpenicillin (Penicillin)
- Penicillinase-resistant penicillins (Flucloxacillin)
- Broad-spectrum penicillins (BSPs)
- Trimethoprim
- Macrolides
- Cephalosporins and other beta-lactams (Cephalosporins)
- Quinolones
- Tetracyclines
- Total antibiotics

4.2.3 General practice populations

Quarterly and annual permanent patient registrations were obtained from the GPMD for each general practice.

4.3 Statistical analysis

Annual rates of diagnoses for complications of acute RTIs (per 100,000 practice population (pp)) and quarterly and annual rates of antibiotic dispensing (per 1,000 pp) were calculated. For complications, a two-level repeated measures Poisson regression model was used to account and correct for variation at the level of general practice and time (five study years from 1996 to 2000). Expected counts of complications per practice per annum were calculated based on the practice's list size (calculated by multiplying the complication rate over all practices by the practice's list size). An offset variable was created as the $\log_e$ expected counts.

The Poisson model is as follows:

$$\log_e(obs\ counts) = \log_e(\exp\ counts) + \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots$$

$$log_e\left(\frac{obs}{exp}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots$$

$$\text{Standardised Incidence Ratio (SIR)} = \left(\frac{obs}{exp}\right) = exp^{(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots)}$$

For a one-unit change in the predictor variable x, the log of the ratio of observed to expected counts would change by β (the regression coefficient), given the other predictor variables in the model were held constant. The Standardised Incidence Ratio (SIR) (that is the ratio of observed to expected counts) is therefore given by exp(β). For example, the SIR, based on the coefficient of time in years, compares the ratio of the incidence rates in successive years. Therefore an SIR >1 indicates an increase in complication rates between successive years while an SIR <1 indicates a decrease in the rates. Results from all Poisson models were reported as SIRs, with 95% confidence intervals (95% CIs).

Although antibiotic dispensing items were count data, the large numbers of items at practice level meant the rates were approximately normally distributed. Therefore trends for total and individual antibiotic dispensing were examined using a two-level repeated measures linear regression with seasonality adjustment using categorical variables to indicate the quarter of the year. Initial estimates were obtained by using

the restricted iterative generalized least squares (RIGLS) estimation procedure. Final parameters were estimated using Markov Chain Monte Carlo (MCMC) methods to give less biased estimates and also to derive confidence intervals for non-symmetrical distributions (Rasbash *et al*. Centre for Multilevel Modelling, University of Bristol).

4.3.1 Patterns of dispensing and complications

Pragmatic comparisons were used to examine the association between rates of complications (outcome) and rates of antibiotic dispensing (explanatory variable) using a two-level repeated measures Poisson regression model after adjusting for time (year). Since the first-line antibiotics of choice for acute RTIs are penicillins, associations between complications and both penicillin and BSPs were explored. Macrolides, tetracyclines and cephalosporins are generally considered as second line treatment and were also examined.

Parameters were again estimated using MCMC methods with initial estimates obtained by using RIGLS; confidence intervals were derived from the MCMC results. In this analysis, the dispensing variables were scaled so that the SIR compares the ratio of the incidence rates at the 75^{th} percentile to the 25^{th} percentile of dispensing rates for each antibiotic. For example, the 25^{th} and 75^{th} percentiles for penicillin dispensing are 48 and 86 items per 1,000 pp (interquartile range is 38 items per 1,000 pp). The SIR therefore compares the complication rate in a practice which dispenses 86 items per 1,000 pp with one which dispenses 48 items per 1,000 pp; a value >1 indicates that the rate of complications is higher at the higher level of dispensing.

4.3.2 Changes over time

To examine whether practice changes in complications during the study period were related to changes in dispensing of total antibiotics, practices were divided into two equal groups based on their change in total antibiotic dispensing rates between 1996 and 2000 (the rate in 2000 minus that in 1996). This change was divided into two groups; one with the smallest reduction in dispensing rates over time, and the other

with the largest reductions. Due to the small number of episodes for some complications, only changes in pneumonia were examined. Differences between the two groups in the change of complication rates were analysed using a Mann-Whitney test since the changes in pneumonia rates had skewed distributions.

All multilevel modelling was performed using MLwiN version 2.10 and all other analyses using SPSS version 14.0.

4.4 Results

A total of 26 practices contributed data for all five years between 1996 and 2000, with a total registered population of 232,500 per annum. Practice list sizes ranged from 2,660 to 19,523 patients.

4.4.1 Trends in dispensed antibiotics

BSPs were the most commonly dispensed antibiotic in primary care and accounted for around 40% of total dispensed antibiotics. For total antibiotics, and for the majority of the antibiotics studied, trends in dispensing decreased during the study period (Figure 4.1). A two-level multilevel model identified that over the five year period, dispensing for total antibiotics fell by 2.89 per 1,000 pp per quarter ($p<0.001$) equating to 11.55 per 1,000 pp per annum (Table 4.2).

Figure 4.1 Quarterly trends in dispensing rates of total antibiotics and flucloxacillin from 1996 to 2000 for 26 practices contributing data to the GPMD

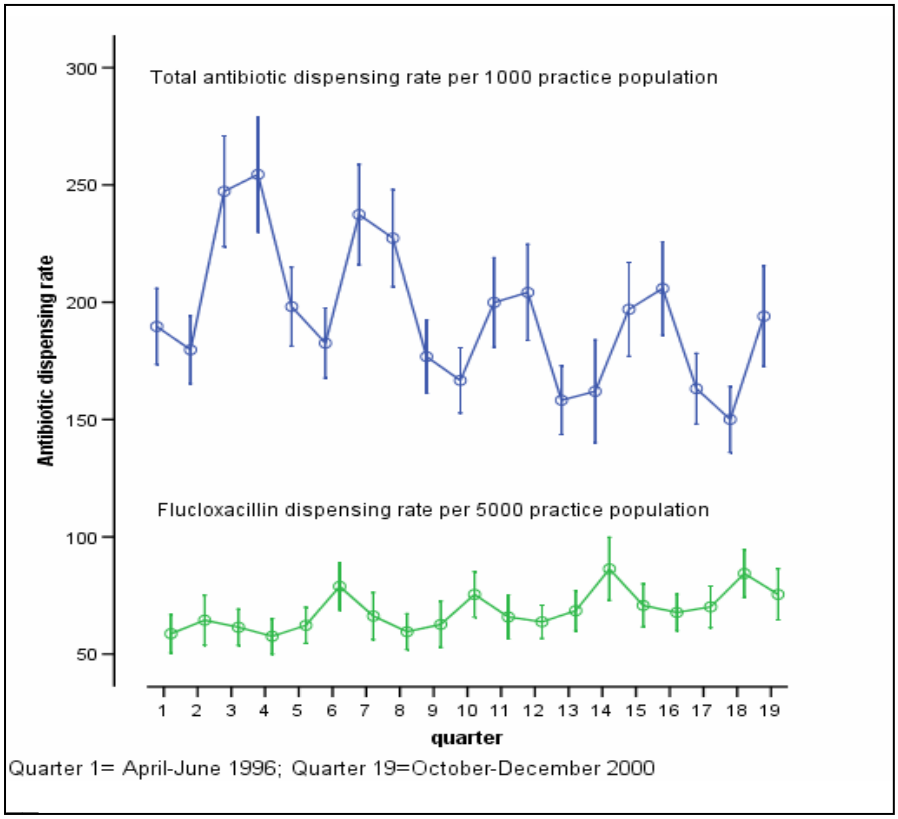


Table 4.2 Linear regression models to estimate trends in antibiotic dispensing in general practice per 1,000 practice population from 1996 to 2000

Antibiotic	Median (25th to 75th percentiles) dispensing rates 1996	2000	Annual rate of change	95% CI for change	p-value	Annual % change[i]
Penicillin	68 (50 to 105)	67 (41 to 81)	-1.20	-1.63 to -0.81	<0.001	-1.9
BSPs	348 (304 to 413)	269 (224 to 343)	-7.20	-9.20 to -5.29	<0.001	-2.5
Flucloxacillin	48 (38 to 60)	61 (48 to 69)	0.72	0.42 to 1.02	<0.001	1.1
Cephalosporins	67 (49 to 81)	63 (51 to 87)	-0.90	-2.14 to 0.30	0.145	-1.3
Tetracyclines	50 (38 to 62)	50 (40 to 59)	-0.23	-0.58 to 0.11	0.197	-0.4
Macrolides	112 (69 to 142)	82 (59 to 110)	-2.44	-3.10 to -1.84	<0.001	-2.7
Trimethoprim	53 (46 to 62)	53 (42 to 64)	-0.16	-0.60 to 0.27	0.486	-0.3
Quinolones	30 (21 to 37)	29 (18 to 38)	-0.02	-0.39 to 0.36	0.917	-0.1
Total antibiotics	822 (723 to 918)	705 (606 to 842)	-11.55	-13.96 to -9.18	<0.001	-1.6

[i] *As a % of current annual rates (up to end of June 2003)*

This quarterly fall equated to a reduction of 11.55 per 1,000 pp per annum, approximately 1.6% of current annual total dispensing rates. Similarly, dispensing for BSP, penicillin and macrolides all decreased significantly over the study period ($p<0.001$). The exception to this trend was flucloxacillin, which increased over the study period by 0.72 dispensed prescriptions per 1,000 pp per annum ($p<0.001$), approximately 1.1% of current annual flucloxacillin dispensing rates. There were no discernible trends in the dispensing of cephalosporins, tetracyclines, trimethoprim and quinolones.

4.4.2 Trends in complications arising from RTIs

The most common complications of RTIs diagnosed in general practice were pneumonia and quinsy, with on average 145 and 26 cases per 100,000 pp per annum respectively (Table 4.3). Episodes of intracranial abscesses, rheumatic fever and epiglottitis were rare, with on average less than 1.1 per 100,000 pp per annum. Poisson regression analysis showed considerable variation, both between practices and also within practices from year to year, with some evidence to suggest an increase in mastoiditis over the five-year period ($\beta=0.327$, 95% confidence interval (CI)= 0.114 to 0.543). There was also evidence for a decrease in certain complications arising from chest infections, such as pneumonia ($\beta=-0.215$, 95% CI=-0.314 to -0.100) and empyema ($\beta=-1.564$, 95% CI=-2.469 to -0.948).

Table 4.3 Primary care diagnoses of complications arising from RTIs in 26 general practices between 1996 and 2000

Read code	Complications	Total diagnoses	Mean rate per annum[i]	Coefficient for trend (SE)	p-value
H2...	Pneumonia (exc. influenza)	1690	145.36	-0.215 (0.057)	<0.001
H15..	Quinsy	306	26.32	-0.084 (0.051)	0.100
A38..	Septicaemia	176	15.14	-0.241 (0.175)	0.168
F53..	Mastoiditis	71	6.11	0.327 (0.110)	0.003
K00..	Acute glomerulonephritis	33	2.84	-0.050 (0.164)	0.760
H50..	Empyema	27	2.32	-1.564 (0.408)	<0.001
F00..	Bacterial Meningitis	23	1.98	-0.061 (0.207)	0.768
H043.	Epiglottitis	12	1.03	*NA*	*NA*
G0…	Acute rheumatic fever	12	1.03	*NA*	*NA*
F040.	Intracranial abscess	2	0.17	*NA*	*NA*

[i] *Rate per 100,000 practice population*
NA = not analysed

4.4.3 Associations between complications and dispensed antibiotics

Analyses were only performed for pneumonia, septicaemia, quinsy and mastoiditis; episodes for the remaining complications were too rare to model. Multilevel Poisson regression showed several negative associations indicating that lower antibiotic dispensing rates were significantly associated with higher episodes of complications in general practice (Table 4.4). Specifically, a lower incidence rate of pneumonia and mastoiditis was found in practices with a higher dispensing rate of penicillin. The SIR for pneumonia was 0.80 (95% CI=0.68 to 0.93, p=0.005), suggesting the incidence rate of pneumonia in a practice dispensing penicillin at the 75th percentile of 86 items per 1,000 pp per annum would be 80% of that at the 25th percentile of 48 items per 1,000 pp per annum. Similarly, the incidence rate of mastoiditis in a practice dispensing penicillin at the 75th percentile would be 48% (95% CI=23 to 87%, p=0.024) of that in one at the 25th percentile.

A lower incidence rate of pneumonia, quinsy and septicaemia was found in practices with a higher dispensing rate of BSP. This indicates lower rates of these complications in practices whose dispensing rate of BSP was at the 75th percentile (379 items per 1,000 pp per annum) compared to the 25th percentile (257 items per 1,000 pp). The model also showed positive relationships between tetracyclines and episodes of quinsy, and cephalosporins and episodes of both pneumonia and quinsy. The SIR for quinsy and tetracyclines was 1.59 (95% CI=1.14 to 1.89, p<0.001), suggesting the incidence rate of quinsy is 59% higher in practices whose tetracyclines dispensing rate was at the 75th percentile (61 items per 1,000 pp per annum) compared to those at the 25th percentile (40 items per 1,000 pp per annum). Similarly, the SIRs for cephalosporins and pneumonia and quinsy are 1.29 (95% CI=1.07 to 1.54, p=0.006) and 1.30 (95% CI 1.17 to 1.44, p<0.001) respectively. This indicates higher rates of complications in practices whose dispensing rate of cephalosporins was at the 75th percentile (97 items per 1,000 pp per annum) compared to the 25th percentile (51 items per 1,000 pp per annum).

Table 4.4 Multilevel Poisson regression models examining the relationship between primary care diagnosed complications and antibiotic dispensing

	Log_e Parameter estimate	Standard error	Dispensing rate IQR[i]	SIR (IQR)[ii]	95% CI Lower limit	Upper limit	p-value
Pneumonia (exc. influenza)							
Total antibiotics	-0.0007	0.0004	234.61	0.85	0.74	1.05	0.080
Penicillin	-0.0059	0.0021	37.76	0.80	0.68	0.93	0.005
BSPs	-0.0046	0.0007	121.97	0.57	0.46	0.67	<0.001
Cephalosporins	0.0057	0.0012	45.81	1.30	1.17	1.44	<0.001
Macrolides	-0.0012	0.0010	65.65	0.92	0.84	1.10	0.230
Tetracyclines	0.0043	0.0038	20.52	1.09	0.93	1.24	0.258
Quinsy							
Total antibiotics	-0.0003	0.0006	234.61	0.93	0.74	1.26	0.617
Penicillin	0.0062	0.0047	37.76	1.26	0.88	1.80	0.187
BSPs	-0.0038	0.0013	121.97	0.63	0.46	0.85	0.004
Cephalosporins	0.0055	0.0020	45.81	1.29	1.07	1.54	0.006
Macrolides	-0.0023	0.0027	65.65	0.86	0.66	1.36	0.394
Tetracyclines	0.0227	0.0062	20.52	1.59	1.14	1.89	<0.001
Septicaemia							
Total antibiotics	-0.0011	0.0012	234.61	0.77	0.38	1.24	0.359

Table 4.4 Multilevel Poisson regression models examining the relationship between primary care diagnosed complications and antibiotic dispensing

	Log_e Parameter estimate	Standard error	Dispensing rate IQR[i]	SIR (IQR)[ii]	95% CI Lower limit	Upper limit	p-value
Septicaemia							
Penicillin	0.0013	0.0064	37.76	1.05	0.72	1.94	0.839
BSPs	-0.0064	0.0027	121.97	0.46	0.17	0.67	0.018
Cephalosporins	0.0040	0.0041	45.81	1.20	0.84	1.79	0.329
Macrolides	-0.0005	0.0040	65.65	0.97	0.00	1.58	0.901
Tetracyclines	0.0081	0.0111	20.52	1.18	0.64	1.64	0.466
Mastoiditis							
Total antibiotics	-0.0020	0.0016	234.61	0.63	0.39	1.68	0.211
Penicillin	-0.0196	0.0087	37.76	0.48	0.23	0.87	0.024
BSPs	-0.0010	0.0030	121.97	0.89	0.48	1.91	0.739
Cephalosporins	-0.0025	0.0049	45.81	0.89	0.60	1.45	0.610
Macrolides	-0.0075	0.0058	65.65	0.50	0.29	1.30	0.070
Tetracyclines	-0.0218	0.0157	20.52	0.64	0.39	1.39	0.165

[i] *Inter quartile range (IQR) = difference between the 75th and 25th percentile of the dispensing rate distribution;*
[ii] *Standardised Incidence Ratio (SIR) =SIR of complications at 75th percentile of dispensing distribution compared to the 25th percentile*

These results show an association between practice dispensing rates and episodes of certain complications but they do not imply a causal relationship as other factors could account for both high antibiotic dispensing rates and many complications in a practice, such as a large elderly population. To further explore the impact of reducing antibiotic dispensing on rates of complications, the association between change in dispensing and change in complications was examined.

4.4.4 Changes in dispensing of total antibiotics and complications

Practices did not all change their dispensing of total antibiotics in the same way or observe the same changes in the number of complications between 1996 and 2000. For total antibiotics, the vast majority of practices decreased their total antibiotic dispensing rates but three practices increased. The average change in total antibiotic dispensing rates over all 26 practices was -109.03 items per 1,000 pp (SD = 96.65, range -284.18 to 155.03 per 1,000 pp). The median rate of change in pneumonia diagnoses was 5.41 (25^{th} to 75^{th} percentiles= -71.98 to 45.95 per 100,000 pp).

The 26 practices were divided into two equal groups based on change in total antibiotic dispensing rates between 1996 and 2000; one group contained practices with the smallest reduction and the other those with the largest reductions. Initial rates (1996) for practices that reduced their dispensing the most were higher than for practices that reduced their dispensing the least (mean=882.69 and 761.86 items per 1,000 pp per annum respectively, t=1.88, p=0.072). Mean total antibiotic dispensing rates were similar for both groups in 2000.

Practices with the largest reductions in total antibiotic dispensing rates had lower rates of pneumonia in 1996 (median=37.23 per 100,000 pp) than practices with the smallest reductions in total antibiotic dispensing rates (median=199.40 per 100,000 pp) (Figure 4.2). They also experienced an increase in the rate of pneumonia, with a median increase of 41.7 (range -459.92 to 235.84) per 100,000 pp from 1996 to 2000. In contrast, practices with the smallest reductions in total antibiotic dispensing rates experienced a reduction in the rate of pneumonia over the study period, with a median reduction of -18.94 (range -365.45 to 45.33) per 100,000 pp. The difference in change between the two groups was statistically significant (Mann-Whitney test =

36.0, p = 0.012) (Figure 4.3).

Figure 4.2 Box-whisker plot of pneumonia rates per 100,000 pp in 1996 and 2000 by practices' change in dispensing rates of total antibiotics

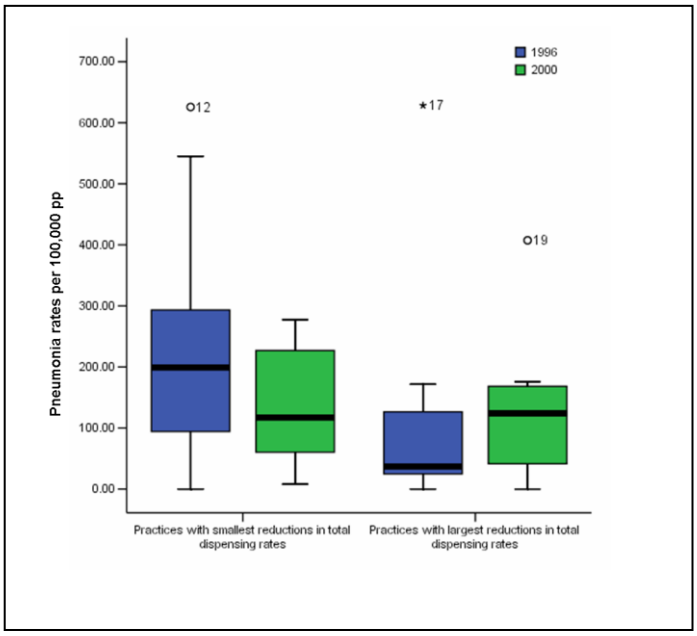
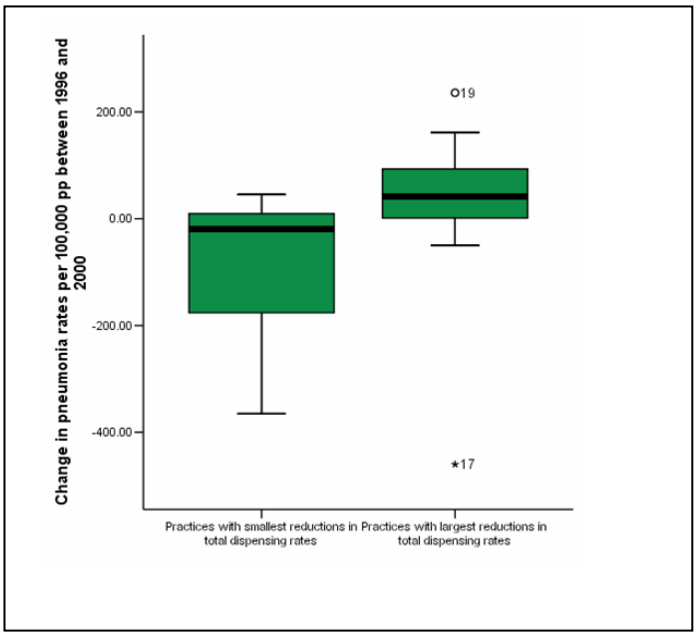


Figure 4.3 Box-whisker plot of change (2000-1996) in pneumonia rates per 100,000 pp by practices' change in dispensing rates of total antibiotics



4.5 Discussion

4.5.1 Main findings

This population based study based on a sample of Welsh practices showed that during a period when overall dispensing of antibiotics in primary care reduced sharply, primary care diagnoses of mastoiditis significantly increased whilst rates in both pneumonia and empyema significantly decreased. Only dispensing of flucloxacillin saw a significant increase during these 5 years.

Initial results suggest an apparent negative relationship between antibiotic dispensing and certain primary care diagnosed complications. For example, practices with lower rates of penicillin and broad spectrum penicillin (BSP) dispensing had a higher rate of pneumonia, BSP dispensing and quinsy, penicillin dispensing and septicaemia and mastoiditis. However a positive relationship was observed between dispensing of cephalosporins and primary care diagnosed quinsy and pneumonia, and also between tetracycline dispensing and quinsy.

Practices with the largest reductions in total antibiotic dispensing rates over the five-year period also saw a small increase in pneumonia rates over the time period whilst practices with the smallest reductions in total antibiotic dispensing rates saw a sizeable decrease in pneumonia rates. The difference in change of pneumonia rates between these two groups was statistically significant.

4.5.2 Strengths and weaknesses of the study

While many studies have examined the relationship between antibiotic prescribing and complications at an aggregate level, none have examined the impact of general practice level change in antibiotic dispensing on change in complication rates over time. While there was some evidence to suggest that a reduction in antibiotic dispensing may be related to change in the incidence of pneumonia over time, it cannot be concluded that there is a causal link, as other factors not adjusted for could also affect changes in complications. Although this study was ecological, the unit of aggregation was smaller than levels used in previous studies. Outcomes at the general practice level are important since strategies for enhanced antibiotic

prescribing are often targeted at practices.

The GPMD practices were broadly representative of all general practices in Wales and the age-sex distribution is comparable to that of the Welsh population (Delahunty *et al*. 2001). At present, one major disadvantage of using the GPMD is that data collection stopped in 2000 and hence later trends using this data source cannot be presented. With only five years of data to analyse, it is also difficult to gain an understanding of a trend, as there is considerable variation between both practices and years.

Studies have highlighted the possible problem of GPs changing the way they use diagnostic codes in order to justify antibiotic prescribing, known as *'diagnostic drift'*. It could be argued that a GP may record a diagnosis consistent with their decision on whether or not to prescribe an antibiotic. If this had occurred to a substantial extent, a shift in classification would have been expected, with a reduction of RTI diagnoses not requiring antibiotics and a rise in more severe RTIs or certain complications. This might be a factor in the significant increase in mastoiditis diagnoses over time and the higher number of quinsy cases in our sample. In this study, trends in acute RTIs were not examined; however, other studies examining trends in RTIs have considered this unlikely since possible consultations codes for RTIs showed no concomitant increases (Ashworth *et al*. 2005).

Whilst the majority of RTIs present in primary care, complications arising from them can appear in either primary or secondary care. There are different pathways by which complications are diagnosed; for example a patient could present to, and be treated by, their GP, or they may present to their GP and be referred to secondary care. They could even be admitted to, and diagnosed in, secondary care via an accident and emergency department without ever contacting primary care. This analysis has only considered complications recorded in primary care. Our figures may not, therefore, reflect the true incidence of complications in the practice population, since diagnoses made in hospital or out-of-hours (and not previously seen by GPs) may not have been captured in the GPs notes. This may account for the small number of cases of certain complications.

One weakness of the dispensing data is that patient details such as age and gender are not recorded, or information relating to the indication for which the antibiotic was prescribed. Only overall dispensing of antibiotics for all indications could be examined (approximately 50% of all community used antibiotics are prescribed for RTIs) (Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance 2003), and not dispensing specifically for RTIs. Thus the proportion of patients with an actual RTI could not be ascertained. Currently, this information is only obtainable through examination of observational datasets such as the General Practice Research Database (GPRD) where individual GP consultations can be examined. There is also a risk that there is an underestimation in the dispensing of antibiotics, as dispensing by out of hours service providers may not be recorded.

Another weakness of dispensing data (and any data examining antibiotic prescribing or dispensing) is that dispensing of antibiotics is an imperfect proxy for antibiotic consumption. There may be a very small proportion of patients who receive the antibiotics but do not actually take them. However, evidence suggests that the majority of adults in the UK (90%) claim to finish their course of antibiotics (Pecherer 2001). This would therefore lead to a very small bias in dispensing data although this bias may vary by the type of acute RTI (the more serious the infection, the higher the likelihood of dispensing the prescription and adhering to the antibiotic). Dispensing will however more closely approximate consumption than prescribing and it is consumption that is the key issue in relation to complications.

4.5.3 Comparisons with existing literature

As already discussed in earlier chapters, the reduction in overall antibiotic dispensing identified in these 26 practices was consistent with the pattern of antibiotic dispensing for the whole of Wales and that found in other studies (Majeed *et al*. 2004; Sharland *et al*. 2005; Ashworth *et al*. 2004). Comparable data on incidence rates and trends in complications arising from respiratory tract infections presenting in primary care are limited. The rate of quinsy in our study is nearly four times higher than that from a study using data from the General Practice Research Database around the same period (Dunn *et al*. 2007). This discrepancy could be due to higher ascertainment of cases in our sample or because GPs may have recorded a

severe pharyngeal infection as quinsy to justify use of an antibiotic. The rate of mastoiditis in our study is comparable with that found by Sharland and colleagues (Sharland *et al*. 2005).

Several studies have found an association between antibiotic dispensing and complications. Little and colleagues used data at the level of health authority, combining hospital admissions data and PACT data for the years 1997-1998, and found a significant but weak association, with higher penicillin dispensing being associated with lower hospital admissions for quinsy and mastoiditis (Little *et al*. 2002). Van Zuijlen and colleagues compared the total incidence of acute mastoiditis in patients aged 14 years and younger in ten first world countries for a period of 3-5 consecutive years between 1991 and 1998, and found a lower incidence of acute mastoiditis in countries with higher rates of antibiotic prescribing (Van Zuijlen *et al*. 2001). The results from these studies, however, are not comparable to ours, as they performed cross-sectional analyses and did not compare trends during their study periods. It is therefore difficult to infer from such studies that changes in prescribing or dispensing are associated with changes in complications rates.

4.5.4 Implications of findings for clinical practice and future research

Due to both the small number of practices involved and the aggregated nature of the data, these results do not allow us to draw conclusions regarding the relationship between antibiotic dispensing and complications at an individual level. Nevertheless, there is some evidence to support the argument that reduced prescribing could be harmful (possibly resulting in higher rates of pneumonia) and that those patients who may benefit the most from antibiotics may not have received them. The decline in dispensed antibiotics, which may have a bearing on cases of complications arising from acute RTIs, can be attributed to either a decline in patient consulting behaviour for acute infections and/or the prescribing behaviour of general practitioners and nurses (Ashworth *et al*. 2003; Fleming *et al*. 2003).

Conclusions arising from this chapter should therefore be treated as hypothesis generating as it has highlighted the areas where further work is required to examine trends in, and associations between, antibiotic dispensing, resistance and

complications over a longer period of time and for a larger population. The following four chapters will deal with these enhancements using other datasets to attempt to overcome some of the limitations found here in the dispensing data (such as lack of patient demographics and indications) and in the complications data (such as determining the true incidence of complications in the population by ensuring complete capture of all primary and secondary care data).

4.6 Introduction to All-Wales general practice level analysis

The following four chapters will be based on general practice level data for the entire population of Wales. Longitudinal analyses of three administrative datasets covering antibiotic dispensing, antibiotic resistance and hospital admissions (of complications arising from RTIs) will be carried out, covering the period between 1996 and 2006. In Chapters 5-7 each of the individual datasets will be interrogated and analysed fully; the relationship between the three datasets will be analysed and discussed in Chapter 8.

These chapters will improve on the model tested in this chapter in three ways. Firstly, an extended model of the relationship between antibiotic dispensing in primary care and complications arising from RTIs will be considered examining not only the direct relationship between the latter but also the relationship between antibiotic dispensing, complications *and* resistance whilst taking certain other influencing factors into account, such as practice characteristics. Secondly, the sample size will be increased greatly using data from every general practice with reliable data in Wales, thus covering the entire Welsh population. Thirdly, the period will be extended and updated, covering the years 1996 to 2006.

Chapter 5 Antibiotic dispensing in Wales

5.1 Introduction to antibiotic dispensing data

This chapter examines the patterns and trends in community antibiotic dispensing in Wales. Quarterly and monthly trends in antibiotic dispensing were examined retrospectively over the period 1996 to 2006 for all ages and also specifically for paediatric dispensing. The variation in trends of antibiotic dispensing by general practices and Local Health Boards (LHBs) were examined, and possible practice demographic factors were determined that may be associated with variation in dispensing. Broad and narrow spectrum dispensing patterns were also examined over the period.

5.2 Methods

5.2.1 Antibiotic dispensing data

Two datasets on antibiotics dispensed by general practitioners in Wales were obtained from the Prescribing Services Unit (PSU) at NHS Wales Informatics Service (NWIS) as previously described in section 3.3. The first contained quarterly data from April 1996 to June 2003 (inclusive), and the second contained monthly data from April 2000 to March 2006 (inclusive). These datasets were then linked to create a file of quarterly dispensing data from April 1996 to March 2006. Each dataset contained the total number of items of dispensed antibiotics by month or/and quarter and year, and subdivided into antibiotic sub-section and chemical (based on British National Formulary (BNF) classifications), for each general practice in Wales (Joint Formulary Committee. 2007). An item was defined as one preparation on a prescription. As already mentioned in Chapter 4, the amount of dispensed antibiotics may be different from that prescribed, as fewer antibiotics will be dispensed than prescribed due to delayed prescribing and patients not filing their prescriptions filled for a variety of reasons. Dispensing will more closely approximate consumption than prescribing and it is consumption that is the key issue regarding complications and resistance.

5.2.2 Type of antibiotics

Chapter 5.1 of the BNF covers antibacterial drugs for infection, classified by group (sub-section) and type of antibacterial (chemical). Total antibiotic dispensing was examined to give an indication of overall use in primary care and the antibiotic groups most commonly used in the treatment of respiratory tract infections (RTIs) were examined individually. Antibiotics used in the treatment of RTIs, and their inclusion in the two datasets, are shown in Appendix II. Since the dataset covering the earlier time period (April 1996 to June 2003) mostly included only broad antibiotic groups rather than type of antibiotics, only these groups will be examined in the 1996 to 2006 dataset. The following antibiotics were not included as these medications were uncommonly used in the treatment of typical RTIs:

- BNF 5.1.1.4 Antipseudomonal penicillins
- BNF 5.1.1.5 Mecillinams
- BNF 5.1.4 Aminoglycosides
- BNF 5.1.6 Clindamycin
- BNF 5.1.7 Some other antibacterials (inc. fusidic acid, chloramphenicol)
- BNF 5.1.9 Antituberculosis drugs
- BNF 5.1.10 Antileprotic drugs
- BNF 5.1.11 Metronidazole and tinidazole
- BNF 5.1.13 Urinary-tract infections (inc. nitrofurantoin).

Trimethoprim, a drug associated with treatment of urinary tract infections in the UK, can also be used for RTIs. This drug was examined on its own, with sulphonamides and co-trimoxazole excluded. The items dispensed for the following eight antibiotic groups were summed to produce a measure of total antibiotic dispensing for RTIs:

- Benzylpenicillins and phenoxymethylpenicillin (Penicillin)
- Penicillinase-resistant penicillins (Flucloxacillin)
- Broad-spectrum penicillins (BSPs)
- Trimethoprim
- Macrolides
- Cephalosporins and other beta-lactams (Cephalosporins)
- Quinolones
- Tetracyclines.

5.2.3 Practice characteristics

It was essential that the variation in antibiotic dispensing was modelled at the level of general practice in order to identify factors associated with high dispensing. Monthly practice population data, that is the number of individuals registered to a general practice (list size), was provided for each practice, month and year by NWIS from the Welsh Demographic Service (WDS). To evaluate the importance of practice characteristics on antibiotic dispensing, the following factors were obtained from the WDS for each practice: LHB, single-handed status, number of GPs, age of GPs, proportion of male GPs and practice deprivation based on Townsend 2001 scores. All practice characteristics information was taken from the practice's status when the data was requested in June 2007.

5.2.4 Data quality and exclusions

5.2.4.1 *Monthly dispensing data: April 2000 to March 2006*

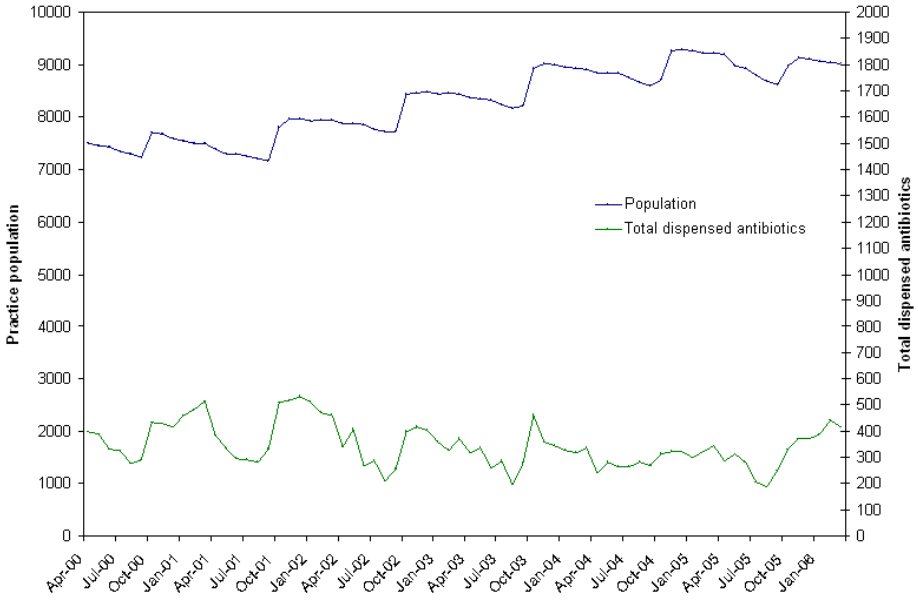
For the dataset covering the period of April 2000 to March 2006, monthly antibiotic dispensing data was provided for 533 general practices with a total population (list size) of 3,136,002 (taken on March 2006), which exceeded the total Welsh population. The official estimated Welsh population (people resident in Wales) was 2,965,900 (taken on June 2006) (Welsh Assembly Government Aug 2007). Practices with relatively stable populations over time were included in the analyses. To assess stability, a coefficient of variation (CV) was calculated for the monthly series of list sizes for each practice to examine the variation in monthly populations. Any practice with a CV less than 5%, indicating very little monthly variation, was automatically included for all analyses. Practices with a CV greater than or equal to 5% (n=147), were investigated further by examining the general pattern of the monthly populations in conjunction with the monthly dispensing of all antibiotics.

From these 147 practices, 25 were excluded due to small monthly populations ($\leq$100) which are not credible values. A further 49 practices were excluded due to sudden increases or decreases in monthly populations which were not reflected in the number of items dispensed that month, resulting in unstable rates. A partner leaving a practice and apparently taking patients with them, or the merging of more than one

practice, could explain a sudden change in population. In such changes, dispensing and practice population would be expected to change simultaneously, resulting in relatively unchanged rates. For five practices, antibiotic dispensing items (based on overall dispensing) were missing for the entire period or a large part of the period. For practices with data missing for a part of the period, the assumption that no antibiotics were dispensed was implausible as this was not consistent with adjacent months.

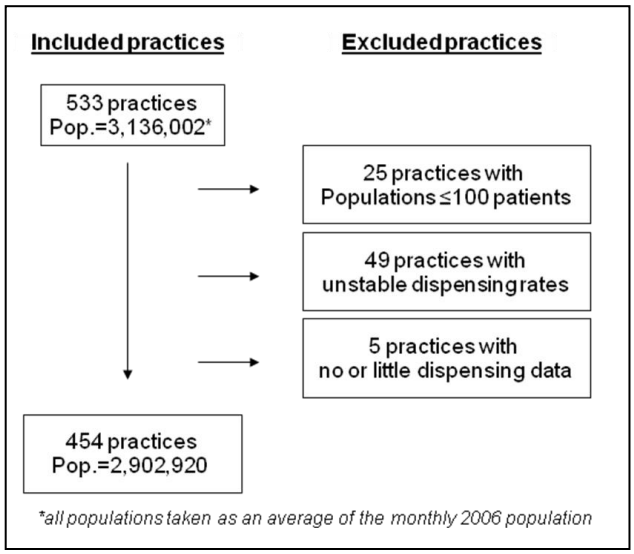
A total of 79 practices were excluded in total, with a population of 233,082 (7.4%). The remaining 68 practices were included in spite of their populations having CVs greater than 5% (range=5.0% to 27.2%). Although their populations had an unexpected pattern (sudden increase, decrease or cyclical), the pattern was also reflected in the monthly items dispensed. For example, many practices were areas where a large proportion of the population consisted of university students and population changes were cyclical with increases in the autumn as term commenced and decreases until the next intake (Figure 5.1).

Figure 5.1 Monthly populations and dispensing from a practice based in a university area



Therefore, a total of 454 practices, with a population of 2,902,920, were included in the analyses. Of these, 292 had 72 months of data for each of the 8 antibiotic groups; the remaining practices had varying degrees of empty monthly cells per antibiotic. Empty data cells indicated that a practice had not dispensed a particular antibiotic for that month, not that data was missing. This was because dispensing for adjacent months was low and the assumption that no antibiotics were dispensed per month was plausible. A flow chart of the process of excluding practices is shown in Figure 5.2.

Figure 5.2 Flow chart of the process of excluding practices dispensing data from April 2000 to March 2006



5.2.4.2 *Quarterly dispensing data: April 1996 to June 2003*

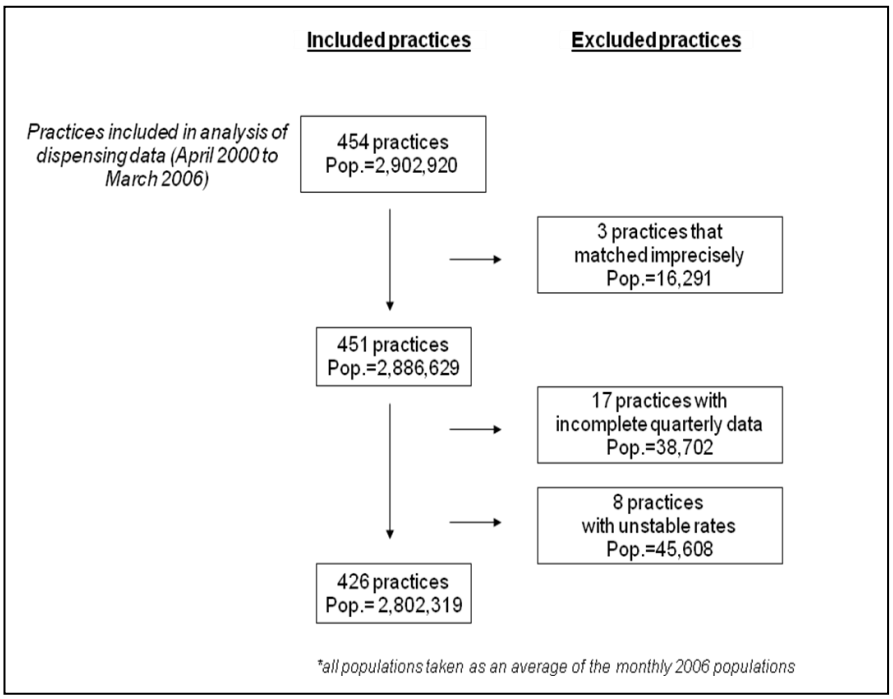
In total, 540 Welsh unique practices had dispensing data recorded between April 1996 and June 2003, with quarterly antibiotic dispensing data ranging from five quarters to the maximum 29 quarters. These data had previously been cleaned ready for analysis as part of a previous study (Welsh Antibiotic Study Group 2005) but nevertheless additional checks were made after linking the two datasets.

5.2.4.3 *Linking the antibiotic datasets*

Since the two antibiotic datasets were provided with differing practice codes (W-codes and the new encrypted codes) to preserve the anonymity of the practices, NWIS carried out the linkage to create one dataset containing dispensing data between 1996 and 2006. Three practices were excluded due to imprecise matching (one W-code to two encrypted-codes) and a further 17 practices had incomplete quarterly dispensing data for the period, with data ranging from 26 to 39 quarters (out of a possible 40 quarters). Since there was an overlap of 13 quarters in the two datasets, each practice's dispensing items were compared for this period between the two datasets for two reasons: firstly to verify that the antibiotics had been grouped in the same way and secondly to verify that practices had been linked correctly. From this exercise it was established that the dispensing data from 1996 to 2003 contained the BNF chemical phenoxymethyl-penicillin (Penicillin V) and not the BNF sub-section benzylpenicillin and phenoxymethyl-penicillin as included in the 2000 to 2006 data. The former was retained.

For each practice and for each quarter, there was perfect agreement between the data, apart from one practice that had a lack of agreement for the second quarter (April-June) of 2000 for seven of the eight antibiotic groups. For this practice, the figures from the 2000 to 2006 dataset were higher than the figures from 1996 to 2003 dataset. After examination of the dispensing data in the adjacent time periods and examining the trends using both sets of figures, the figures from the 1996 to 2003 dataset seemed more plausible and these were used. Additionally, the stability of each practice's antibiotic dispensing rates (dispensed items divided by the practice's population) were checked (by calculating the CV) and eight practices were excluded as they were deemed to have a sudden increase or decrease in practice population not reflected in the total dispensing items or a sudden increase in the total items dispensed not accounted for by an increase in practice population between April 1996 and March 2000. Therefore, out of a possible 454 practices, 426 (94.5% of the official Welsh population) had stable and complete data (40 quarters between April 1996 and March 2006). Figure 5.3 shows a flow chart of the practices included in the analysis of quarterly antibiotic dispensing data from April 1996 to the end of March 2006.

Figure 5.3 Flow chart of the linkage of practices from the April 2000 to March 2006 dataset and practices from the April 1996 to March 2000 dataset



5.2.5 External validity of the practices

Only practices with complete and stable population and dispensing data were included in these analyses (dubbed as Up-To-Standard practices (UTS)). Therefore, all analyses using the *quarterly* antibiotic dispensing data for the 10 year period (April 1996 to March 2006) were based on the 426 practices identified in section 5.2.4.3. When using the *monthly* dispensing data or analysing by antibiotic type by using the data from April 2000 to March 2006, data from 454 practices were used (identified in section 5.2.4.1). However, by excluding practices that were deemed as having less reliable data, some bias might have been incurred.

Comparing the characteristics of the 426 included practices against the 107 that were excluded, some bias was present, with excluded practices more likely to be run single-handedly ($p<0.001$) and from more deprived areas ($p=0.003$) (Table 5.1). These biases will be considered when the results are interpreted.

Table 5.1 Characteristics of included and excluded practices from April 1996 to March 2006

	Included (UTS) N=426	**Excluded N=107**	**Test statistic, p-value**
Practices with no characteristics data	6	31	-
Single-handed N (%)	67 (15.9)	29 (35.4)	χ^2=16.91, p<0.001
Practice deprivation[i] mean (SD)	0.13 (1.91)	0.99 (2.02)	t=3.60, p=0.001
Age of GPs (years) mean (SD)	50.48 (6.64)	52.04 (8.43)	t=1.86, p=0.115
Male GPs (%) median (25^{th} to 75^{th} percentiles)	66.7 (50 to 100)	70.8 (50 to 100)	MW, p=0.267

[i] *Practice deprivation based on Townsend 2001 scores*
MW=Mann Whitney

5.2.6 Sub-group analyses

5.2.6.1 *Antibiotic dispensing in children*

Antibiotic dispensing data are currently recorded without any patient or clinical information attached and it is therefore impossible to examine antibiotic dispensing rates by age, gender or diagnosis. However, a recent study on behalf of the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) Paediatric Subgroup demonstrated how dispensing data could be used to approximate the amount of dispensing for children by using liquid formulations of antibiotics as a proxy measure (Sharland *et al*. 2007). To be able to use this proxy, detailed dispensing data was obtained from PSU to identify all oral liquid antibiotics. Oral liquid antibiotics were classed as preparations recorded as powders, dispersible tablets, solutions, liquids, syrups, granules for syrups, elixirs, powders for elixirs, sachets, powder sachets, suspensions, powders for suspensions, granule straws and infusions (classed as mg/ml). Capsules, tablets, non-dispersible tablets, injections (IV), powders for IV, nebuliser solutions and preparations that were specifically recorded as adult suspensions (such as Laratrim and Septrim) were all excluded. A

complete list of oral liquid antibiotic preparations is given in Appendix III.
The SACAR Paediatric Subgroup validated the assumption that virtually all oral liquid formulations of antibiotics were prescribed for children, especially younger children under the age of 12 years old, although a minority could be dispensed for older patients (personal communication with Dr Sharland). The group speculated that older children were more likely to receive solid oral antibiotics. Therefore by looking at liquid oral antibiotics, dispensing in children would be underestimated. They also noted that amoxicillin liquid formulations are also given to children out-of-hours and without prescription. These biases will be considered when the results are interpreted.

5.2.6.2 *Broad- vs. narrow-spectrum antibiotic dispensing*

Antimicrobial agents are classified as being either narrow-spectrum or broad-spectrum, depending upon their activity against a range of organisms. For example, the term broad-spectrum antibiotic refers to an antibiotic with activity against a wide range of disease-causing bacteria whilst narrow-spectrum antibiotics are only effective against specific families of bacteria.

Although some evidence exists of a decline in antibiotic prescribing, there are still concerns that broad-spectrum antibiotics are commonly used in treatment of community acquired infections (Steinman *et al*. 2003a). Broad-spectrum antibiotics are properly used empirically, prior to identifying the causative bacteria, when there is a wide differential diagnosis and delay may cause deterioration in the patient. Most GPs are faced with having to decide upon treatment without identification of the bacterium and antibiotic resistance (Wood *et al*. 2007). Ideally, the narrowest spectrum antibiotic most appropriate to the identified bacterium should be used as this is believed to limit the development of antibiotic resistance as well as side-effects and cost (Ball *et al*. 2002).

The distinction between broad versus narrow is not always clear and classifying antibiotics into these categories is not straightforward. For this reason, no such generally agreed categorisation of antibiotics exists at present. For example,

tetracycline and chloramphenicol were both traditionally classified as broad-spectrum agents, but the development of resistance to these drugs has changed their classification. Imipenem is classed as a broad-spectrum antibiotic whilst erythromycin is classified as narrow-spectrum. However, there are at least as many organisms that are sensitive to erythromycin but not imipenem (e.g. mycoplasma, Chlamydia) as there are that are sensitive to imipenem but not erythromycin (e.g. coliforms).

A study published in 2003 categorised the following antibiotics used specifically in the treatment of acute RTIs (Steinman *et al*. 2003b) as broad-spectrum with all other antibiotics classed as narrow-spectrum: quinolones, amoxicillin/clavulanate (co-amoxiclav), the second- and third- generation cephalosporins, azithromycin and clarithromycin. However, some of the more obvious broad-spectrum antibiotics were omitted from this list such as amoxicillin, the cephalosporins and tetracyclines. The categorisation of broad- and narrow-spectrums used in this analysis is listed in Appendix IV.

5.3 Statistical analysis

5.3.1 Population and rates

Different analyses used different time units (months, quarters and study years) and practice populations were aggregated to the relevant level to calculate rates per 1,000 population. For annual data, study years were used; for example, 1996 denotes the study year from April 1996 to March 1997. Rates for antibiotic dispensing in children (using dispensed liquid oral formulations as a proxy) were calculated using practice populations for age 15 years and under. Rates of antibiotic dispensing for children were likely to be under-estimated as the age cut-off point for liquid oral formulations was likely to be less than 15 years old but could not be determined precisely at this point.

To aid comparison between the data for 1996 to 2006 (quarterly) and 2000 to 2006 (monthly), monthly rates per 1,000 practice population were converted to quarterly rates per 1,000 pp.

5.3.2 Multilevel modelling

Since each practice had counts of dispensed antibiotic items at regular time intervals (either monthly or quarterly), a multilevel repeated measures model was used to examine trends in longitudinal data. The model had three levels of data: local health board (level 3), general practice (level 2) and time (level 1) and intercepts and slopes were allowed to vary randomly. Dispensing rates were based on large numbers of items and were approximately normally distributed. Trends for antibiotic dispensing were therefore modelled using linear regression, with seasonality adjustment using categorical variables to indicate the quarter of the year. For all antibiotics, adjusting for seasonality in the model reduced the within practice random variation and improved the fit of the model, significantly reducing the -2log-likelihood (deviance). There was some evidence of non-linearity in the pattern of dispensing rates over time and quadratic models were fitted to improve the fit. The goodness of fit of the models was assessed by analysis of the residuals and from the change in deviance. Significance of the trend was assessed initially using the standardised regression coefficients, z=slope/standard error (SE), which are approximately normally distributed.

Initial estimates were obtained by using the restricted iterative generalized least squares (RIGLS) estimation procedure. Final parameters were estimated using Markov Chain Monte Carlo (MCMC) methods to give less biased estimates and also to derive confidence intervals for non-symmetrical distributions. The Raftery-Lewis diagnostic *Nhat* was used to estimate the length of Markov chain required to estimate the 2.5% and 97.5% quantiles to a given accuracy (Raftery & Lewis 1992).

All multilevel modelling was performed using MLwiN version 2.10 and all other analyses using SPSS version 16.0.

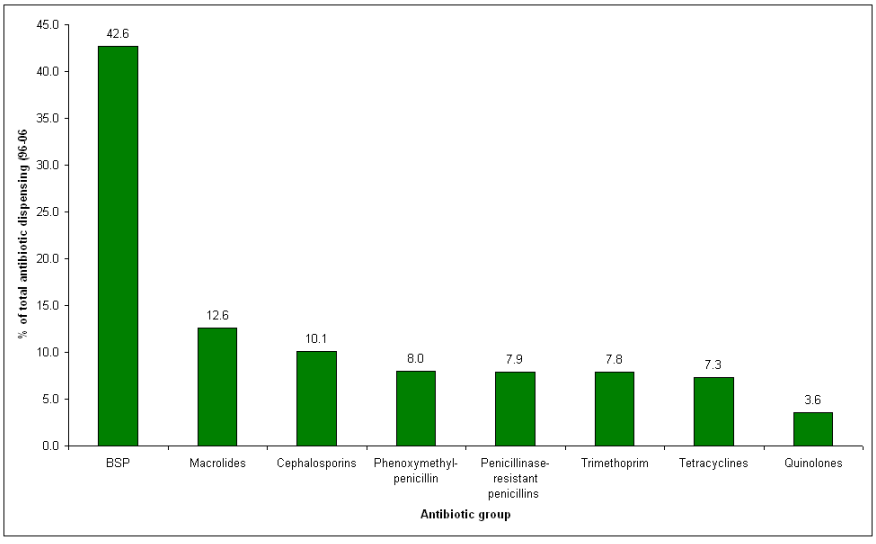
5.4 Results

For the analyses, the total number of dispensed items of antibiotics was defined as the sum of the items of the following antibiotics most commonly used for the treatment of RTIs: phenoxymethylpenicillin (penicillin), broad-spectrum penicillins (BSPs), penicillinase-resistant penicillins (flucloxacillin), cephalosporins, tetracyclines, macrolides, trimethoprim and quinolones.

5.4.1 Antibiotic dispensing in Wales: 1996 to 2006 (quarterly data)

Antibiotic dispensing data from 426 UTS practices were available for analysis with complete data for 40 quarters. These practices covered 2,802,319 (94.5%) of the Welsh population (2,965,900 in 2006). A total of 20,813,964 antibiotic items were dispensed over this ten year period (April 1996-March 2006). Of the antibiotics analysed, BSPs were most commonly dispensed and accounted for 43% of total dispensed antibiotics, followed by macrolides and cephalosporins, which accounted for 13% and 10% respectively (Figure 5.4).

Figure 5.4 Dispensing by antibiotic group as a proportion of total antibiotics



5.4.1.1 *Annual trends in Wales*

There was a marked decline in the dispensing of total antibiotic items over the period. Dispensing was at its highest in Wales in 1996 (April 1996 to March 1997),

with a dispensing rate of 958 items per 1,000 practice population (pp) per annum (Figure 5.5). A marked decline was observed between 1997 and 1998, with a 12% decrease in dispensing rates (from 925 to 812 pp per annum). Thereafter, antibiotic dispensing declined until 2004, reaching a low of 676 items per 1,000 pp (a decrease of 29% from 1996). In 2005, rates increased slightly to 680 items per 1,000 pp. Figure 5.6 shows the breakdown of total antibiotics by antibiotic group (sub-section).

Figure 5.5 Dispensed antibiotic items rates in primary care in Wales per 1,000 practice population, by study year 1996 to 2005

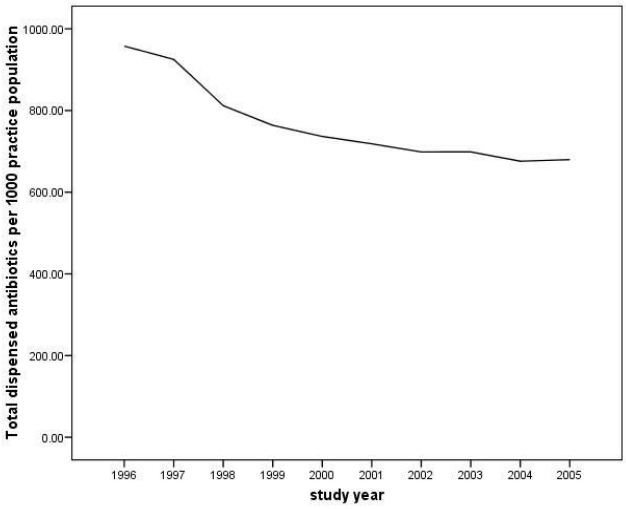


Figure 5.6 Stacked bar-chart of dispensing rates in primary care in Wales per 1,000 practice population, by antibiotic group and study year 1996 to 2005

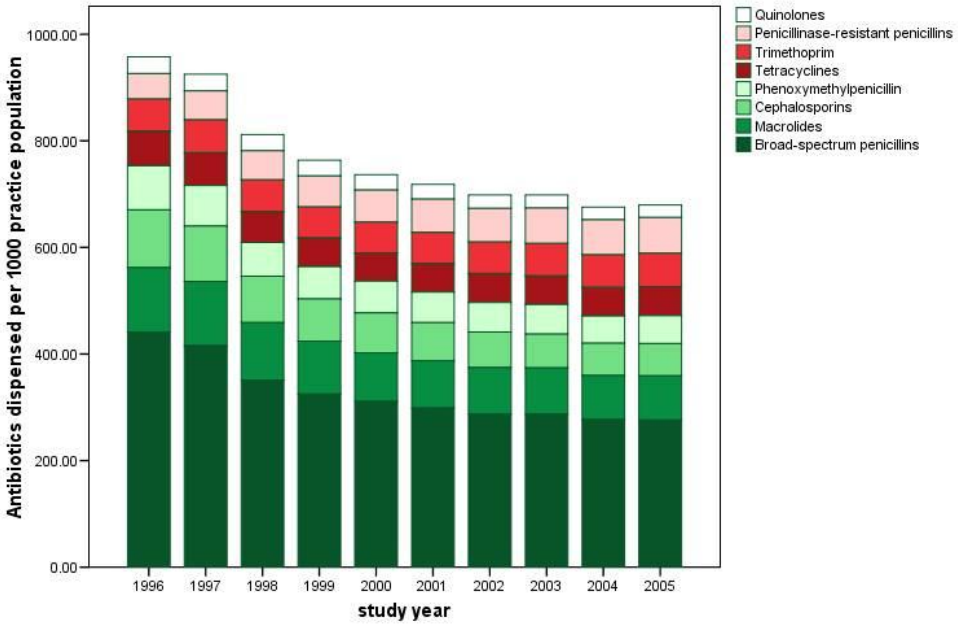
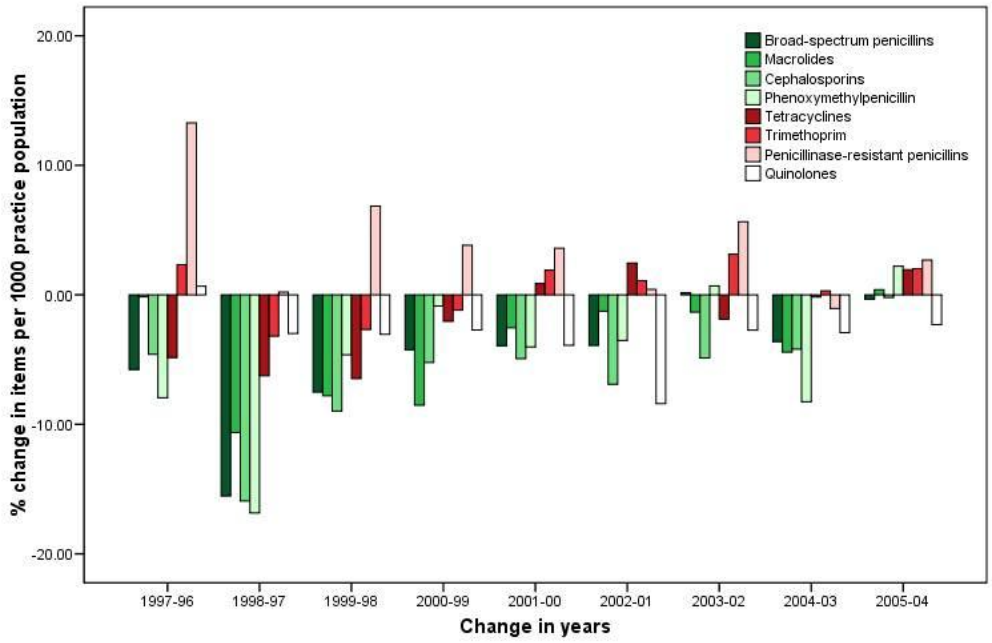


Figure 5.7 shows the year upon year percentage rates of change. For example, a negative rate of change, such as -5.28% for BSPs in 1997-96, indicates a decrease in dispensing between the study years 1996 (April 1996 to March 1997) and 1997 (April 1997 to March 1998). Dispensing for most antibiotics decreased over time, with the largest reductions seen between 1997 and 1998. The exception to this was the dispensing of penicillinase-resistant penicillin (flucloxacillin) which increased annually, though the rate of increase reduced over time. Of interest is phenoxymethylpenicillin (penicillin) which increased between 2004 (April 2004 to March 2005) and 2005 (April 2005 to March 2006) after a continuous decrease in dispensing for most of the previous years.

Figure 5.7 Annual percentage change in antibiotic items dispensed in primary care in Wales per 1,000 practice population by antibiotic group 1996 to 2005



Negative change indicates a decrease in rates between years
Positive change indicates an increase in rates between years

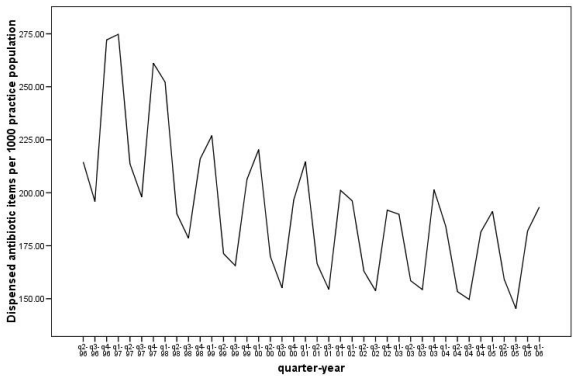
5.4.1.2 *Quarterly trends in Wales*

Figure 5.8a to f show the quarterly trends by antibiotic groups as well as total antibiotic dispensing in Wales (the vertical scales differ by antibiotic group so comparing patterns is meaningful). The decrease in total antibiotic dispensing over the 10 year time period can be seen with the greatest decline in primary care dispensing of antibiotics taking place in the earlier period (between 1996 and 2000). Although the overall rate was significantly decreasing over time with a slope β=-7.60 per annum (95% confidence interval (CI) =-9.04 to -6.20, $p<0.001$) and the variation explained by a single-level linear regression model after adjusting for seasonality was high (87%), the trend in total antibiotic dispensing appeared to be non-linear. For most antibiotic groups, the rate of dispensed antibiotics decreased over time; the exception was flucloxacillin, which increased (Figure 5.8d). After an initial decrease, trimethoprim increased from 2001 onwards. Most trends were non-linear, with a greater decline in dispensing at the beginning of the period; there was little overall change for tetracyclines and quinolones.

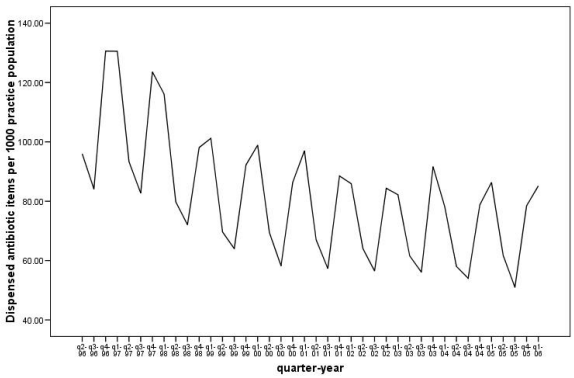
Seasonality is evident in total antibiotic dispensing and in most groups. Generally dispensing rates peaked during the winter quarters (quarters 4 and 1: October to December and January to March respectively) and were lower in quarters 2 and 3 (April to June and July to September). There was also some indication that seasonality became less pronounced through the study period. Again the exception to this was flucloxacillin where the reverse was true, with dispensing rates peaking in quarter 3 (July to September).

Figure 5.8 Number of antibiotic items dispensed per quarter in primary care in Wales per 1,000 practice population, by antibiotic group, 1996 to 2005

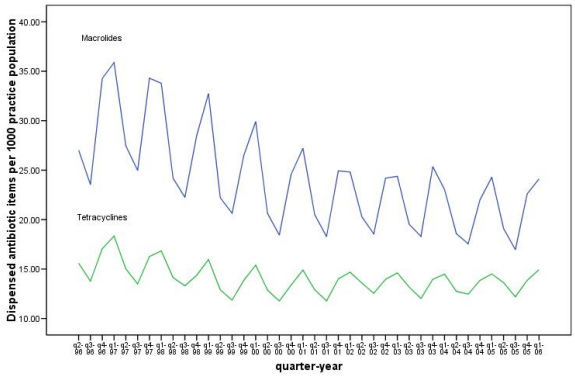
a. Total antibiotics



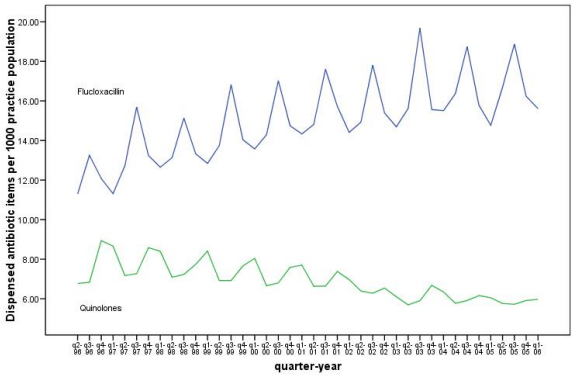
b. BSPs



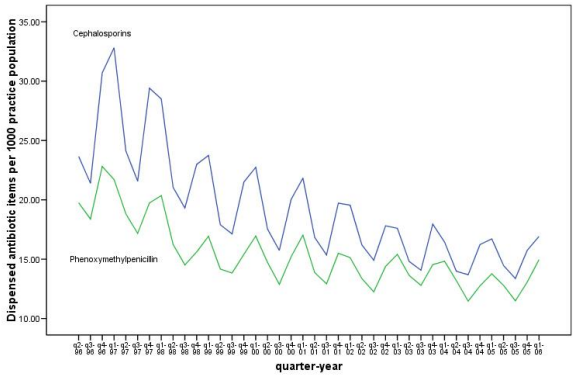
c. Macrolides and Tetracyclines



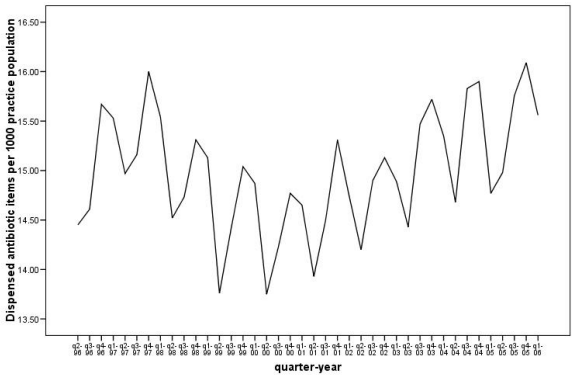
d. Flucloxacillin and Quinolones



e. Penicillin and Cephalosporins



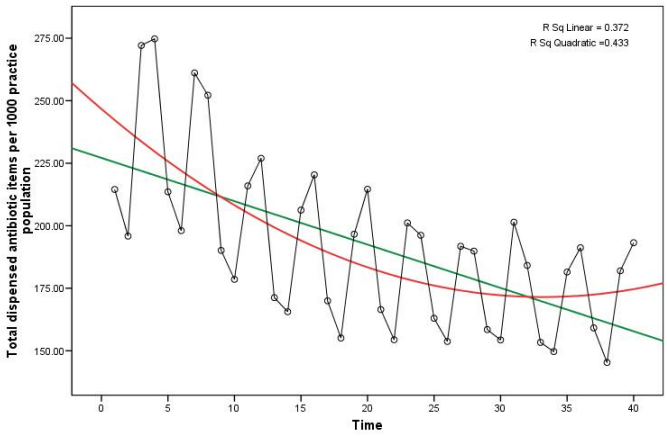
f. Trimethoprim



NB: Vertical scales differ by antibiotic group

There was indication of curvature in total antibiotic dispensing over time with a steep decline and a plateau thereafter, with a hint of an upward rise at the winter months of 2005-06 even after adjusting for seasonality. This trend may therefore be better described using a quadratic model (Figure 5.9).

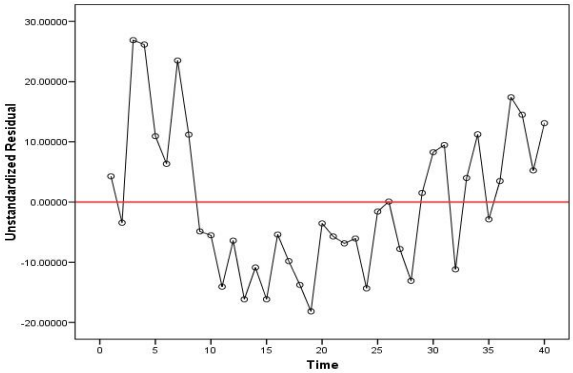
Figure 5.9 Total antibiotic dispensing per quarter per 1,000 pp, with fitted linear and quadratic models



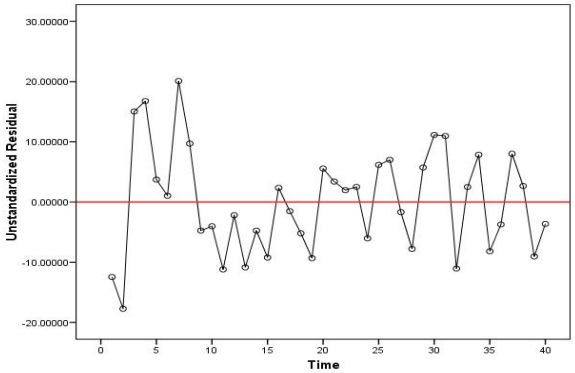
The fitted quadratic model, after adjusting for seasonality, explained approximately 93% of the variation in antibiotic dispensing rate and the estimate of the quadratic term was positive (β=0.07, 95% CI=0.04 to 0.09) indicating a positive curvature. A plot of the residuals against time for both the linear and quadratic model suggests a poorer fit to the data in the earlier period (Figure 5.10). However, the residuals in the linear case showed a clearer pattern than in the quadratic case.

Figure 5.10 Residual plots (actual antibiotic dispensing rates – predicted rates from fitted model) for linear and quadratic models

a. Linear model



b. Quadratic model



NB. The closer the residuals are to zero, the better the fit of the model

5.4.1.3 *General Practice variation: the two-level model*

Analysing antibiotic dispensing rates at the all-Wales level is of importance as it gives a general picture of dispensing over time. However, it does not take into account variations in dispensing data at a general practice level; multilevel modelling overcomes this. Full details of the modelling used are shown for total antibiotic dispensing only; results for the each of the antibiotic groups are summarised later in this chapter. A two-level repeated measures linear regression model with random intercept and slopes, for total antibiotic dispensing rates, adjusting for seasonality, gave a mean slope (β_1) of -2.09 (SE=0.08) (per 1,000 pp per quarter), indicating a general decrease in rates over time (Figure 5.11). However, the standard deviation (SD) of the practices' slopes (σ_{u1}) of 1.57 ($=\sqrt{2.476}$) implies substantial variation, since assuming normality, 5% of the practices have slopes more than two SDs from the overall mean.

Figure 5.11 MLwiN output for two-level repeated measures linear model for total antibiotic dispensing rates (estimated by RIGLS method)

$$\text{TOTALr}_{ij} \sim \text{N}(XB, \Omega)$$

$$\text{TOTALr}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{time}_{ij} + \text{-46.210(0.523)quarter\_2}_{ij} + \text{-55.534(0.522)quarter\_3}_{ij} + \text{-5.349(0.522)quarter\_4}_{ij}$$

$$\beta_{0ij} = 266.965(3.326) + u_{0j} + e_{0ij}$$

$$\beta_{1j} = \text{-2.090(0.078)} + u_{1j}$$

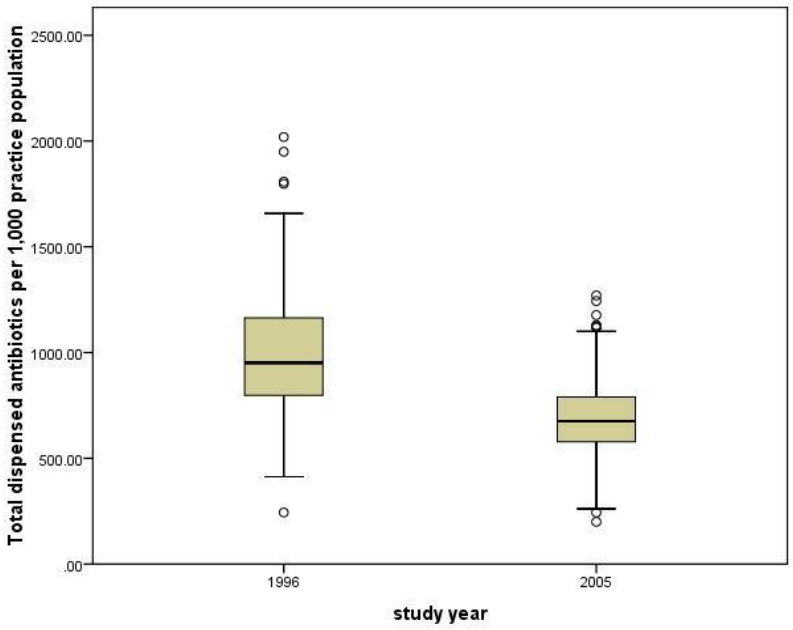
$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0, \Omega_u) : \Omega_u = \begin{bmatrix} 4601.421(318.635) & \\ \text{-85.261(6.784)} & 2.476(0.177) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0, \Omega_e) : \Omega_e = \begin{bmatrix} 578.745(6.432) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 160122.000(17040 of 17040 cases in use)

Between-practice variation reduced over time with those with the highest dispensing in 1996 reducing the most. For total antibiotic dispensing, the interquartile rate fell from 366.15 per 1,000 pp in 1996 to 211.41 per 1,000 pp in 2005 (Figure 5.12).

Figure 5.12 Box-whisker plot of total antibiotic dispensing rates in 1996 and 2005



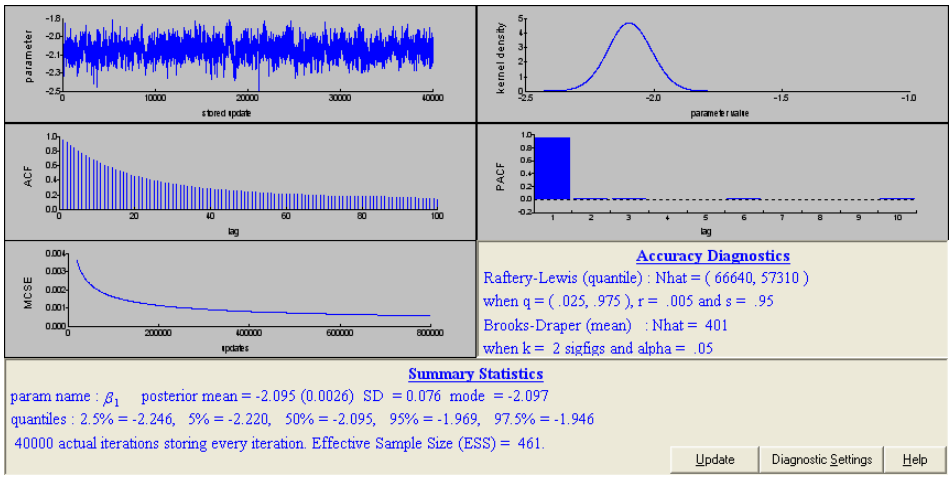
There was also more variation due to inter-practice differences (σ_{u0}=67.83) than intra-practice differences (σ_{e0}=24.06), with 89% of the total variation due to inter-practice differences (otherwise known as the intra-class correlation). The model also shows that quarters 2 and 3 have lower dispensing rates than quarter 1 (the reference category). Comparing the results from the 2-level model (with random slopes) to those from a single-level model (fixed slope model), the mean of the random slopes was very similar to the slope in the fixed slope model (Table 5.2). However, the results showed that in the single-level model the standard errors are underestimated, leading to an overstatement of significance.

After deriving initial estimates from the RIGLS method, MCMC methods were used to fit the model. After running the default of 5,000 iterations, the run length required to accurately estimate β_1 was between 25,350 and 38,358, based on the Raftery-Lewis statistic. However, after re-running the Markov chain for 40,000 iterations, the Raftery-Lewis statistic increased to 57,000 although estimates seemed stable and the run was not extended (Figure 5.13).

Table 5.2 Comparison of parameter estimates (SE) from the single- and two-level repeated measures linear model for total antibiotic dispensing rates (estimated by RIGLS method)

Parameter	**Parameter estimate (SE)**	
	Single-level model	**Two-level model**
Intercept (β_0)	266.97 (1.17)	267.14 (3.28)
Slope (β_1)	-2.09 (0.04)	-2.10 (0.08)
Quarter 2	-46.21 (1.20)	-46.21 (0.52)
Quarter 3	-55.53 (1.20)	-55.53 (0.52)
Quarter 4	-5.35 (1.20)	-5.35 (0.52)
Between practice slope variance (σ_{u02})	Not applicable	2.50 (0.18)
Between practice intercept variance (σ_{u12})	Not applicable	4636.75 (318.64)
Within practice variance (σ_{e02})	3049.67 (33.03)	578.81 (6.40)

Figure 5.13 Diagnostics for the slope parameter β_1 for total antibiotic dispensing rates (after 40,000 iterations)



The 95% confidence interval (CI) for the slope β_1 was -2.25 to -1.95, which was highly significant. This slope equated to an annual decrease of about 8.4 items per 1,000 practice population per annum, around 0.9% of the annual total.

Figure 5.14 MLwiN output for two-level repeated measures linear model for total antibiotic dispensing rates (estimated by MCMC methods)

$$\text{TOTALr}_{ij} \sim \text{N}(XB, \Omega)$$

$$\text{TOTALr}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{time}_{ij} + \text{-46.211(0.523)quarter\_2}_{ij} + \text{-55.535(0.524)quarter\_3}_{ij} + \text{-5.351(0.521)quarter\_4}_{ij}$$

$$\beta_{0ij} = 267.144(3.281) + u_{0j} + e_{0ij}$$

$$\beta_{1j} = \text{-2.095(0.076)} + u_{1j}$$

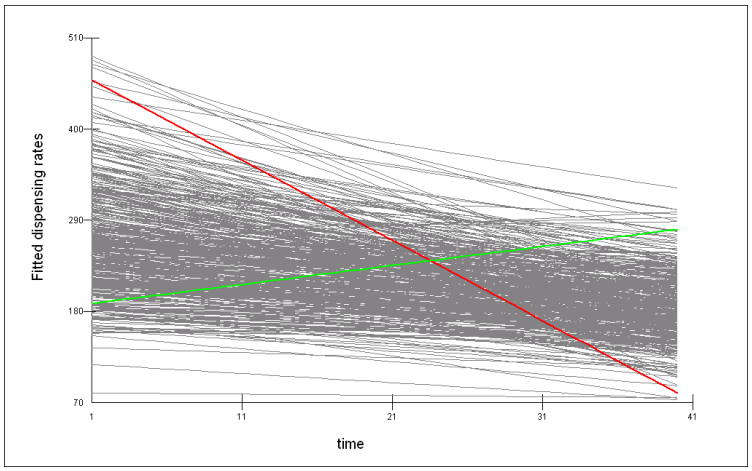
$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} 4636.750(322.940) & \\ \text{-85.941(6.921)} & 2.496(0.181) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e) \ :\ \Omega_e = \begin{bmatrix} 578.813(6.398) \end{bmatrix}$$

Deviance(MCMC) = 156747.700(17040 of 17040 cases in use)

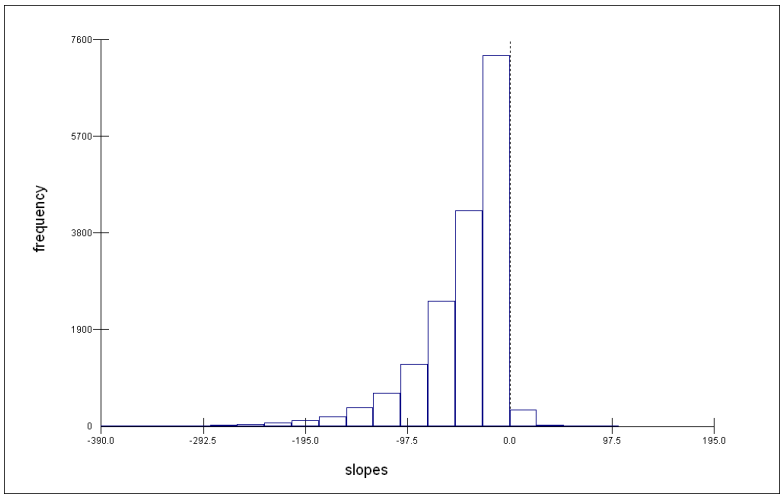
Figure 5.15 shows the predicted values from the fitted model for each of the 426 UTS general practices. Almost all of the practices decreased their dispensing rates over time. Although the dispensing trends of individual practices are hard to see, anomalies can be identified. For example, one practice (highlighted in red) had a high intercept and a steep negative slope, and another practice (highlighted in green) had a lower intercept and a positive slope. Therefore, conclusions based on the whole dataset did not necessarily hold at individual practice level.

Figure 5.15 Fitted total antibiotic dispensing rates from the fitted two-level model by general practices



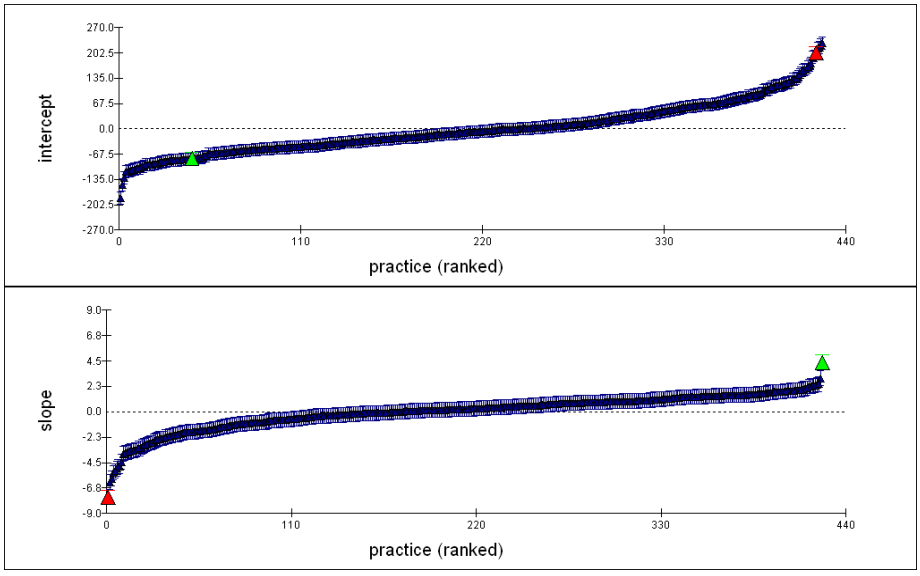
A histogram of the individual practices' slopes shows that most have decreased their dispensing over time but a few had also increased (Figure 5.16).

Figure 5.16 Histogram of the practices slopes from the fitted two-level model for total antibiotic dispensing rates



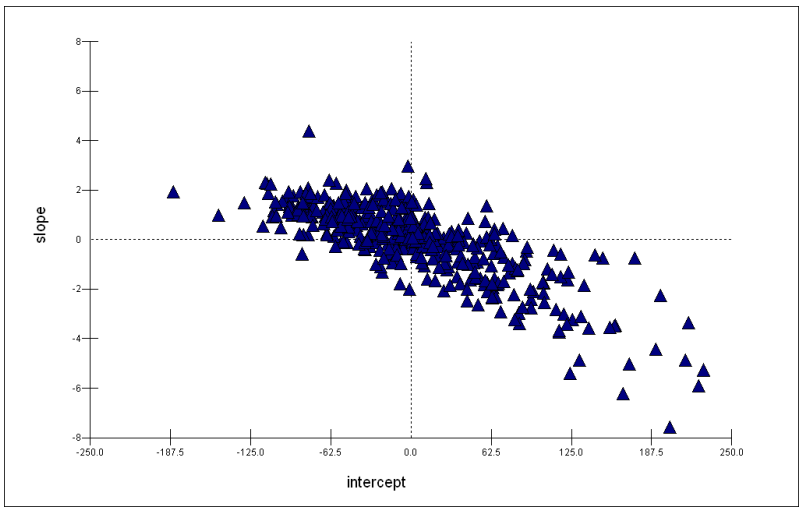
The two highlighted practices in Figure 5.15 are also highlighted in the caterpillar plots in Figure 5.17. These plots display the ranks of the 426 practices against their raw residuals (± 1.96SD); the top plot is for the intercept and the lower plot for the slope or trend. The top plot shows the variation in practices' intercepts which corresponded to the dispensing rate in quarter 1 of 1996, the period immediately before the study period.

Figure 5.17 Caterpillar plots: practice-level residuals for total antibiotic dispensing rates (± 1.96SD) vs. rank



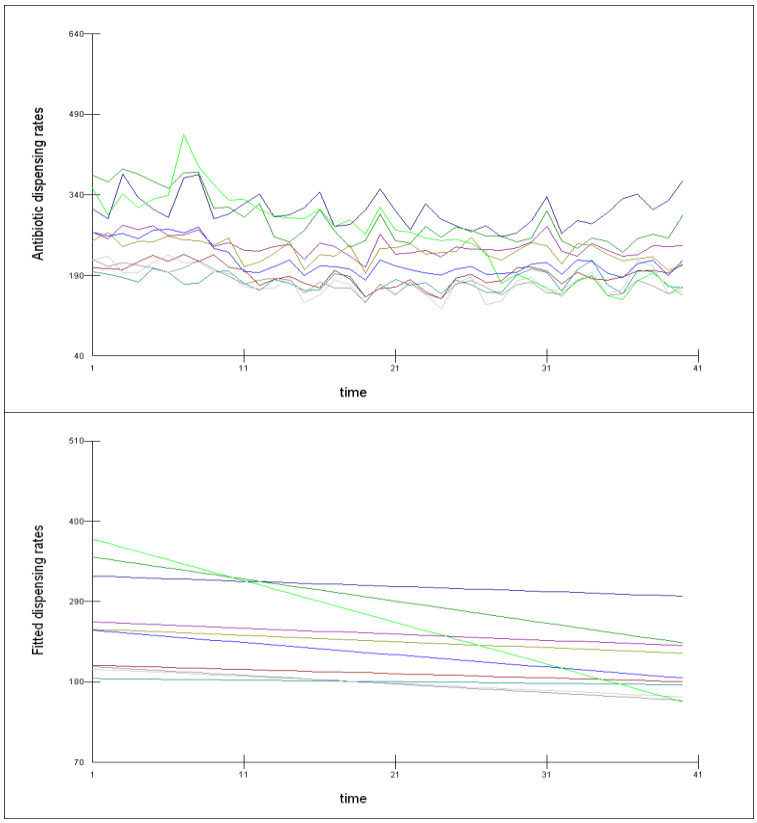
Practices with an intercept residual greater than zero had a larger intercept than the average intercept of 267.92 items per 1,000 pp while those with a residual less than zero had an intercept lower than average. The lower plot essentially shows departures, at practice-level, from the average slope, that is the rate of change of dispensing. The overall average trend was -2.095; practices with a residual greater than 2.095 had an overall upward trend. The practice highlighted in red displayed a higher than average intercept, although it is not the practice with the highest, and the steepest decreasing slope. Alternatively, the practice highlighted in green had a slope residual greater than 2.095 and so had an increasing slope (as was seen in Figure 5.15), but had a lower than average intercept. A scatter plot of these residuals show that practices with the highest intercepts tended to decrease their dispensing the most (Figure 5.18). This negative correlation between the slopes and intercept (shown by the covariance term of -85.94 in Figure 5.14) might reflect the fact that practices with the highest dispensing initially have more scope for reduction.

Figure 5.18 Practice-level standardised residuals for total antibiotic dispensing rates: slope vs. intercept

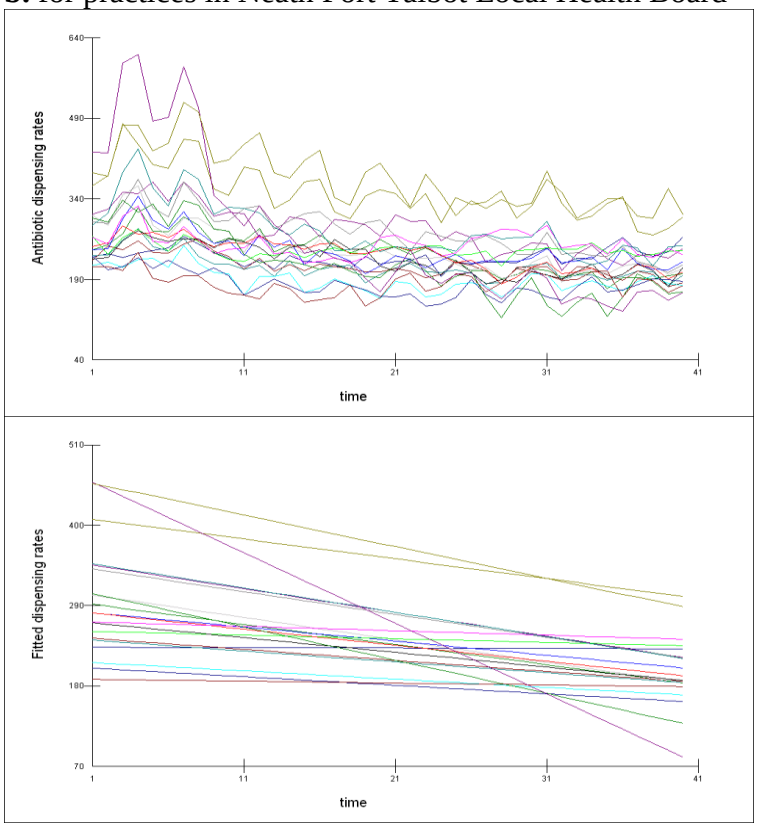


As previously seen, it was difficult to graphically show the variation in trends for each of the 426 individual general practices. Therefore, for illustration, the ten practices within Anglesey Local Health Board (LHB) in North Wales and the 21 practices within Neath Port Talbot LHB in South Wales were examined in depth (Figure 5.19a and b). In the latter figure, one practice can be seen to reduce their dispensing a great amount over time, with a high intercept and a steep slope.

Figure 5.19 Actual and fitted total antibiotic dispensing rates over time:
a. for practices in Anglesey Local Health Board



b. for practices in Neath Port Talbot Local Health Board



5.4.1.4 *Local Health Board variation: the three-level model*

As trends in dispensing rates varied substantially between practices, variation may also have been present at the LHB level, of which 22 existed in Wales until 2009. A three-level model, incorporating variation between LHBs, between practices and within practices, showed that whilst variation due to inter-practice differences had reduced, there was still nearly eight times as much variability due to inter-practice differences (within LHBs) (SD=σ_{u0}=64.05) as there was between LHBs (SD=σ_{v0}=26.31) (Figure 5.20). However, a total of 13% of variation was explained by inter-LHB differences which should not be disregarded and will therefore be taken into account in further models.

Figure 5.20 MLwiN output for three-level repeated measures linear regression model for total antibiotic dispensing rates (estimated by MCMC methods)

$$\text{TOTALr}_{ijk} \sim \text{N}(XB,\ \Omega)$$

$$\text{TOTALr}_{ijk} = \beta_{0ijk}\text{cons} + \beta_{1jk}\text{time}_{ijk} + \text{-46.207(0.524)quarter\_2}_{ijk} + \text{-55.537(0.522)quarter\_3}_{ijk} + \text{-5.348(0.523)quarter\_4}_{ijk}$$

$$\beta_{0ijk} = 267.268(6.650) + v_{0k} + u_{0jk} + e_{0ijk}$$

$$\beta_{1jk} = \text{-2.074(0.168)} + v_{1k} + u_{1jk}$$

$$\begin{bmatrix} v_{0k} \\ v_{1k} \end{bmatrix} \sim \text{N}(0,\ \Omega_v) \ :\ \Omega_v = \begin{bmatrix} 692.041(294.094) & \\ \text{-16.663(7.142)} & 0.464(0.193) \end{bmatrix}$$ LHB

$$\begin{bmatrix} u_{0jk} \\ u_{1jk} \end{bmatrix} \sim \text{N}(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} 4102.563(292.242) & \\ \text{-73.366(6.110)} & 2.145(0.159) \end{bmatrix}$$ Practice

$$\begin{bmatrix} e_{0ijk} \end{bmatrix} \sim \text{N}(0,\ \Omega_e) \ :\ \Omega_e = \begin{bmatrix} 578.782(6.415) \end{bmatrix}$$

Deviance(MCMC) = 156747.543(17040 of 17040 cases in use)

A plot of the fitted model (Figure 5.21) by LHB showed that whilst there was wide variation in total antibiotic dispensing rates at the beginning of the time period in 1996, they converged over the eleven year period. As with practices, the LHB level residuals (slope and intercept) were negatively correlated indicating that the LHBs with the highest initial dispensing reduced their dispensing the most (Figure 5.22).

Figure 5.21 Fitted total antibiotic dispensing rates from the fitted three-level model by Local Health Board

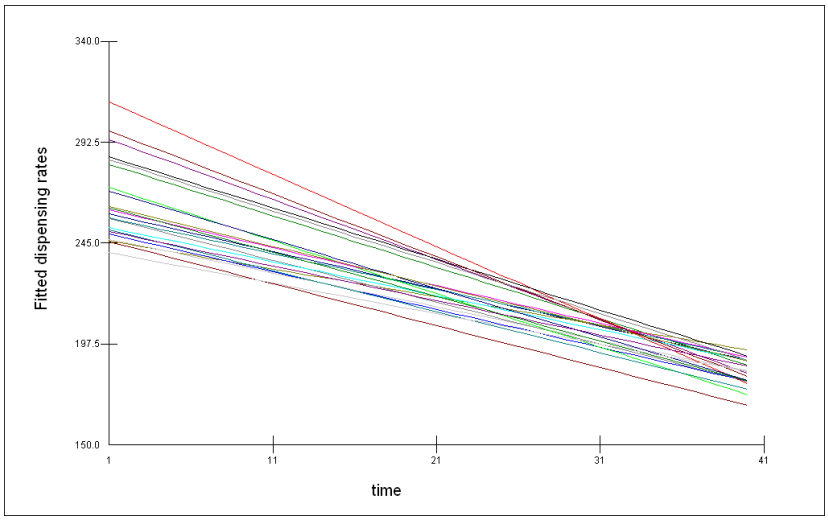


Figure 5.22 Local Health Board-level standardised residual plot for total antibiotic dispensing rates: slope vs. intercept

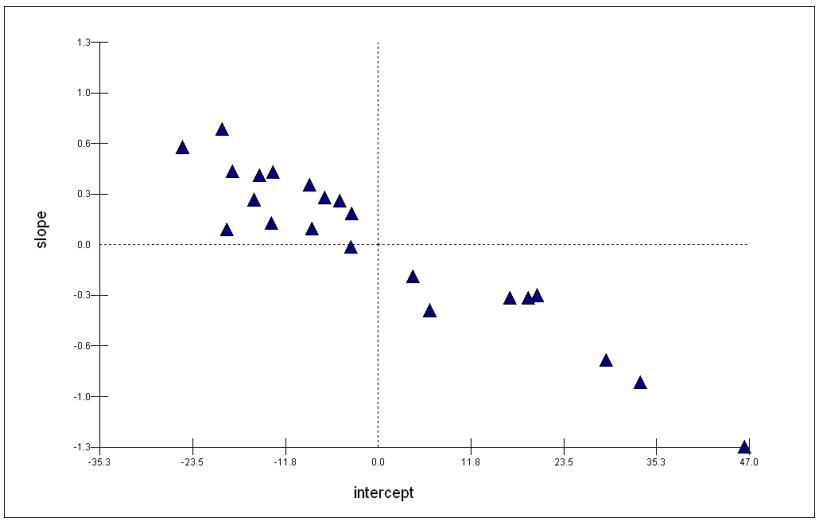
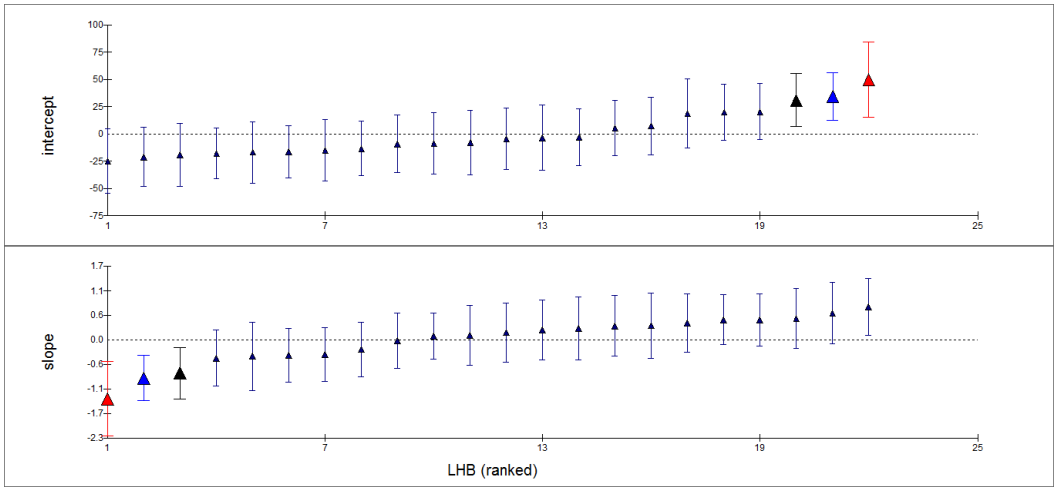


Figure 5.23 shows caterpillar plots at the LHB level; the top plot shows each LHB's residual (± 1.96SD), that is the LHB's departure from the average intercept (β_0), and the bottom plot shows each LHB's departure from the overall slope (β_1). Three LHBs (Merthyr in red/Rhondda in blue/ Caerphilly in black) all had significantly higher (at the 5% level) total antibiotic dispensing rates than the intercept (β_0 =267.27 items dispensed per 1,000 pp). These three LHBs also had the steepest decline in rates over time with negative slopes significantly different from the average slope (β_1=-2.07).

Figure 5.23 Caterpillar plots: Local Health Board-level residuals for total antibiotic dispensing rates (± 1.96SD) vs. rank



5.4.1.5 *The quadratic model*

As was seen in Figure 5.10, including a quadratic term increased the goodness of fit of the model. The results from a three-level model incorporating a quadratic term for time (centred on zero to prevent correlation with the time variable), and random effects at both the LHB and practice level are shown in Figure 5.24. The likelihood statistic (-2LL) decreased by 3366.7, demonstrating that a quadratic time term improved the model. The model showed a positive average quadratic term (β_5=0.07) which indicated either a flattening of the downward trend or an upward curvature. Whilst there was considerable variation in this term between practices (SD=σ_{u5}=0.063), there was a small amount of between LHB variation (SD=σ_{v5}=0.014).

Figure 5.24 MLwiN output for three-level repeated measures quadratic model for total antibiotic dispensing rates (estimated by MCMC methods)

$$\text{TOTALr}_{ijk} \sim \text{N}(XB,\ \Omega)$$

$$\text{TOTALr}_{ijk} = \beta_{0ijk}\text{cons} + \beta_{1jk}\text{time}_{ijk} + \beta_{2jk}\text{time0sq}_{ijk} + \text{-46.209(0.461)quarter\_2}_{ijk} + \text{-55.399(0.456)quarter\_3}_{ijk} + \text{-5.208(0.455)quarter\_4}_{ijk}$$

$$\beta_{0ijk} = 257.701(6.132) + v_{0k} + u_{0jk} + e_{0ijk}$$

$$\beta_{1jk} = \text{-2.100(0.169)} + v_{1k} + u_{1jk}$$

$$\beta_{2jk} = 0.069(0.004) + v_{2k} + u_{2jk}$$

$$\begin{bmatrix} v_{0k} \\ v_{1k} \\ v_{2k} \end{bmatrix} \sim \text{N}(0,\ \Omega_v) \ :\ \Omega_v = \begin{bmatrix} 762.736(330.872) & & \\ \text{-17.931(8.053)} & 0.488(0.212) & \\ \text{-0.012(0.128)} & \text{-0.000(0.003)} & 0.000(0.000) \end{bmatrix}$$

LHB

$$\begin{bmatrix} u_{0jk} \\ u_{1jk} \\ u_{2jk} \end{bmatrix} \sim \text{N}(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} 4022.896(287.163) & & \\ \text{-71.264(6.065)} & 2.222(0.163) & \\ 0.148(0.213) & \text{-0.027(0.005)} & 0.004(0.000) \end{bmatrix}$$

Practice

$$\begin{bmatrix} e_{0ijk} \end{bmatrix} \sim \text{N}(0,\ \Omega_e) \ :\ \Omega_e = \begin{bmatrix} 449.582(5.076) \end{bmatrix}$$

Deviance(MCMC) = 152438.452(17040 of 17040 cases in use)

The fitted model in Figure 5.25 shows the variation in intercepts, slopes and curvature for each of the LHBs. It shows the initial large variation in antibiotic dispensing, the early rapid decrease and also the flattening out and converging of rates. These differences are highlighted even more in the caterpillar plot (Figure 5.26). The LHB highlighted in red can be seen to have the highest initial dispensing rates and the steepest decline. From the third plot, it can be seen that none of the LHBs differ significantly from the overall quadratic term (β_5 =0.07).

Figure 5.25 Fitted total antibiotic dispensing rates from the fitted three-level model by Local Health Board

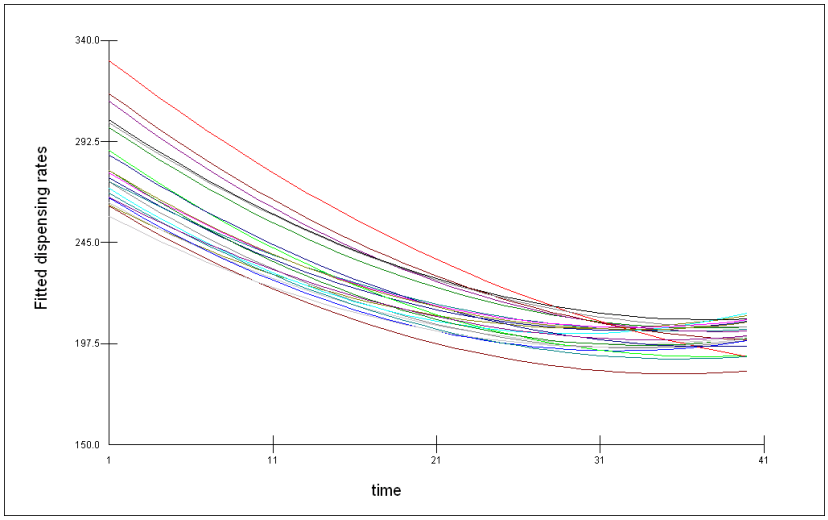
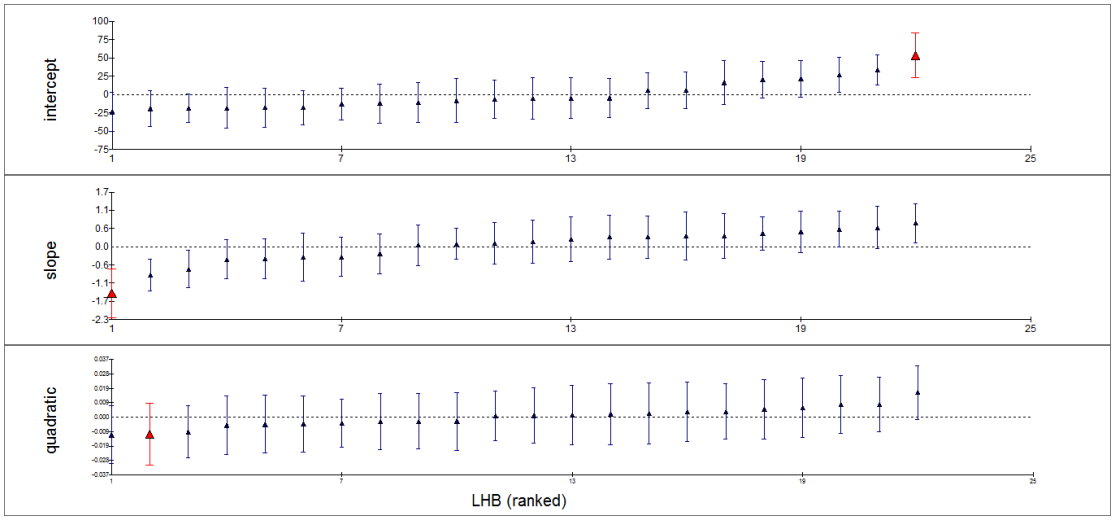


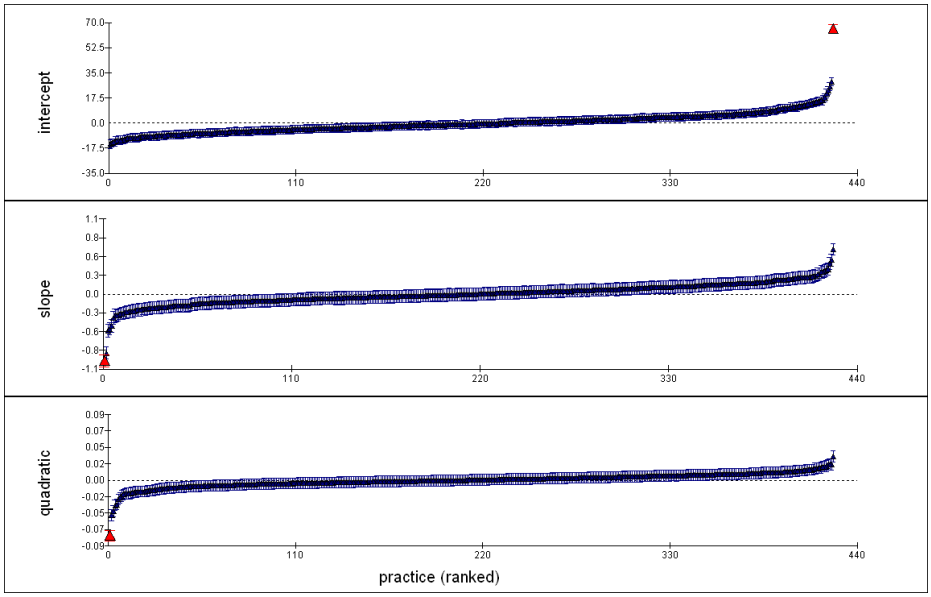
Figure 5.26 Caterpillar plot: Local Health Board-level residuals for total antibiotic dispensing rates (± 1.9SD) vs. rank



5.4.1.6 *Dispensing trends by antibiotic group*

Three-level quadratic models were run for each of the antibiotic groups (Table 5.3). For some of the antibiotics, the variations in the quadratic term (β_5) at the LHB were small and including it as a random term improved the goodness of fit of the model by an insignificant amount. In these cases, the quadratic time coefficients were fixed at the LHB level. As already noted, BSPs had the highest dispensing rate of all the antibiotic groups (β_0=121.88), and quinolones the least (β_0=9.18). For the majority of antibiotics, the average slope (β_1) was negative indicating a decrease in rates over time; flucloxacillin however, significantly increased over the study period (β_1=0.50 per 1,000 pp, p<0.001). Dispensing of trimethoprim did not change significantly over time (β_1=-0.01, p=0.317). Again, for the majority of antibiotics the models showed a significant positive average quadratic term (β_5); the exception was flucloxacillin for which β_5 was negative (β_5=-0.003, p<0.001) indicating a flattening out or a downward curve. Although on average flucloxacillin dispensing increased over time, many practices actually decreased their dispensing (Figure 5.27). In particular, one practice had a very high intercept (highlighted in red), with around 65 items per 1,000 pp (compared to the average of 11.83 per 1,000 pp) and had the steepest decline and a greater downwards curvature to the trend.

Figure 5.27 Caterpillar plots: practice-level residuals of flucloxacillin dispensing rates (± 1.96SD) vs. rank



The percentage of variation in antibiotic dispensing attributable to practice differences was greater than those due to LHB differences and within-practice differences (differences in dispensing over time) for all antibiotic groups, with ICCs of over 72% (Table 5.4). The variation due to LHB differences ranged from 3% in tetracycline dispensing to 19% in BSP dispensing. The highest between practice variation was seen in dispensing of cephalosporins (85%) and the smallest seen in BSPs (72%).

Table 5.3 Parameter estimates for quarterly antibiotic dispensing rates per 1,000 pp, by antibiotic group (estimated by MCMC methods)

Antibiotic	Parameter estimates			p-value		Median (25th to 75th quartile) dispensing rates per 1,000 pp per annum	
	Intercept (SE[i]) β_0	Time (slope) (SE) β_1	Time^2 (SE) β_5	β_1	β_5	1996	2005
Penicillin	19.55 (0.88)	-0.20 (0.02)	0.007 (0.001)	<0.001	<0.001	76.78 (50.96 to 102.32)	49.52 (35.29 to 63.86)
Flucloxacillin	11.83 (0.54)	0.12 (0.01)	-0.003 (0.001)	<0.001	<0.001	45.84 (30.22 to 62.20)	66.55 (53.06 to 82.50)
BSPs	121.88 (4.22)	-1.21 (0.09)	0.040 (0.002)	<0.001	<0.001	429.72 (344.49 to 565.91)	271.76 (233.64 to 342.56)
Trimethoprim	15.32 (0.64)	-0.01 (0.02)	0.002 (0.001)	0.617	0.046	57.97 (45.46 to 72.10)	61.88 (51.72 to 71.04)
Macrolides	34.46 (0.13)	-0.31 (0.03)	0.008 (0.001)	<0.001	<0.001	112.48 (80.39 to 150.97)	77.19 (61.28 to 98.80)
Cephalosporins	29.92 (1.52)	-0.39 (0.03)	0.009 (0.001)	<0.001	<0.001	89.30 (57.63 to 143.28)	48.96 (28.97 to 75.62)
Quinolones	9.18 (0.46)	-0.07 (0.01)	-0.0001 (0.001)	<0.001	0.920	27.70 (16.66 to 41.86)	21.64 (13.83 to 29.96)
Tetracyclines	16.27 (0.49)	-0.07 (0.01)	0.005 (0.001)	<0.001	<0.001	56.34 (42.78 to 79.24)	50.80 (39.49 to 64.62)
Total antibiotics	259.46 (6.70)	-2.15 (0.17)	0.07 (0.004)	<0.001	<0.001	951.12 (797.47 to 1163.62)	675.91 (578.50 to 789.91)

[i] *SE= Standard error*

Table 5.4 Local Health Board and practice variation for dispensing rates by antibiotic group (estimated by MCMC methods)

Antibiotic	Between LHB variation			Between practice variation			Within practice variation	ICC[i] (LHB/ Practice)
	Intercept σ^2_{v0}	Time σ^2_{v1}	Time^2 σ^2_{v5}	Intercept σ^2_{u0}	Time σ^2_{u1}	Time^2 σ^2_{v5}	σ^2_{e0}	
Penicillin	9.55	0.004	NA	130.99	0.10	<0.001	17.55	6%/ 83%
Flucloxacillin	3.29	0.002	<0.001	54.00	0.03	<0.001	8.93	5%/ 82%
BSPs	405.07	0.15	NA	1523.49	0.84	0.002	182.82	19%/ 72%
Trimethoprim	6.18	0.003	NA	50.75	0.04	<0.001	8.18	9%/ 78%
Macrolides	25.05	0.02	<0.001	215.12	0.14	<0.001	30.22	9%/ 80%
Cephalosporins	28.37	NA	NA	383.78	0.27	<0.001	38.49	6%/ 85%
Quinolones	2.34	<0.001	<0.001	34.75	0.02	<0.001	6.33	5%/ 80%
Tetracyclines	2.08	0.001	NA	52.71	0.05	<0.001	9.77	3%/ 82%
Total antibiotics	693.52	0.47	0.0002	4046.73	2.23	0.004	449.42	13%/ 78%

[i] *ICC = Intra-class correlation*

NA = Not applicable. Linear and/or quadratic terms were fixed at LHB level since variation between LHBs did not significantly improve the model.

5.4.1.7 *Factors associated with antibiotic dispensing*

It has been ascertained that general practices' antibiotic dispensing rates vary over time, in both their intercepts and their slopes, but are there any practice level factors that can explain any further variation? Table 5.5 shows the raw mean and standard deviations for total antibiotic dispensing by practice characteristics. Three-level linear repeated measures models (allowing for random slopes and intercepts) were fitted to examine the univariate associations between total antibiotic dispensing and these characteristics, after adjusting for time, time squared, seasonality and the interaction between time and practice characteristics.

Practices that were run multi-handed had lower total antibiotic dispensing rates than practices run single-handed (β=38.89, SE=8.47), although over time the difference between the two categories decreased (β=0.713, SE=0.194) when an interaction term between time and status was fitted (Figure 5.28). Multi-handed practices had an average of 4.41 GPs (SD=1.89). Practices from more deprived areas were also more likely to have higher initial dispensing rates and again the dispensing rates between the groups converged over time (Figure 5.29). Practices with older GPs and a higher proportion of male GPs were more likely to dispense more.

Table 5.5 Univariate associations between total antibiotic dispensing rate per 1,000 and practice characteristics (estimated by RIGLS methods)

Practice characteristics	**Mean dispensing rate (sd) (2000-2006)**	**Parameter estimates (SE)**[i]	**p-value**
Deprivation quintile			
Least deprived =1	179.21 (47.55)	Ref	
2	187.10 (55.06)	10.19 (9.90)	0.303
3	204.90 (63.48)	30.25 (10.07)	0.003
4	206.71 (65.65)	39.84 (10.23)	<0.001
Most deprived =5	209.07 (79.45)	51.28 (10.28)	<0.001
Single-handed status			
Single-handed	219.12 (78.71)	Ref	
Multi-handed	193.17 (60.26)	-38.89 (8.47)	<0.001
GP gender % Male	-	0.48 (0.13)	<0.001
Average GP age (year)	-	2.84 (0.48)	<0.001

[i] *adjusted for time, quadratic time term, seasonality and the interaction between time and practice characteristics*

Figure 5.28 Fitted total antibiotic dispensing rates from the fitted three-level model by single/multi-handed status of the practice

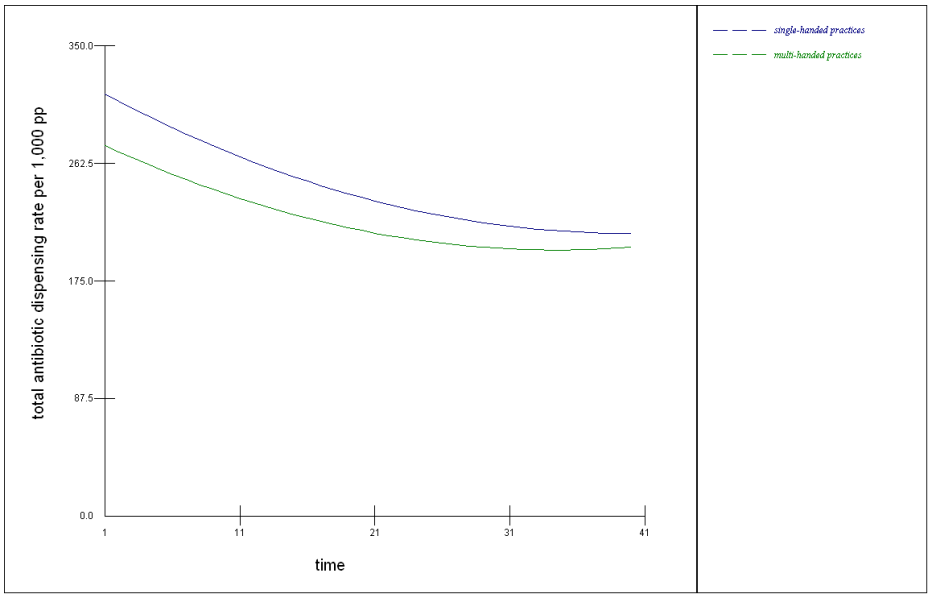
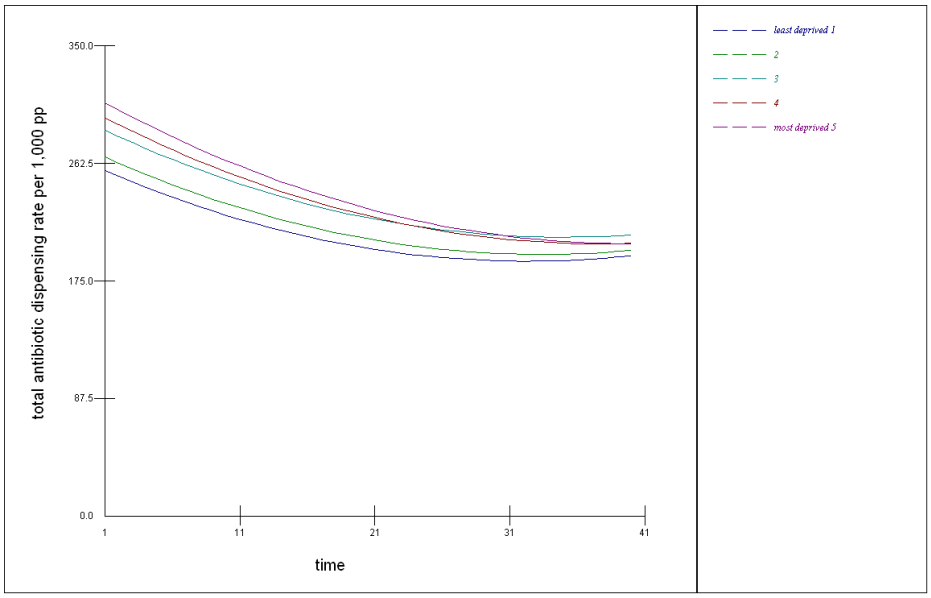


Figure 5.29 Fitted total antibiotic dispensing rates from the fitted three-level model by practice deprivation quintile



When all of the practice characteristics were included in a multivariate model, (adjusted for time, the quadratic time term, seasonality, and the interaction between time and the practice characteristic), the average age of the GP, single-handed status and deprivation remained independently associated with total antibiotic dispensing (Table 5.6). The addition of practice characteristics to the model only explained a

further 6% of total variation in antibiotic dispensing due to practice differences (from 78% to 84%) and reduced the variation due to LHB differences by 10% (from 17% to 7%).

For separate antibiotic groups, the results of each multivariate analysis are shown in Table 5.6. Factors associated with dispensing of these antibiotics varied by antibiotic group. Similarly to total antibiotic dispensing, higher levels of broad-spectrum penicillin dispensing were independently associated with practices with older GPs, practices from a more deprived area and those that were run single-handedly.

Phenoxymethylpenicillin and flucloxacillin dispensing were initially negatively associated with the average age of the GP (β=-0.175, SE=0.047, $p<0.001$ and β =-0.102, SE=0.040, p=0.011 respectively), with practices run by younger GPs dispensing a higher quantity of these antibiotics. In both cases, after adjusting for the interaction term (time x age), both of these associations became non-significant (β=-0.109, SE=0.082 and β=-0.035, SE=0.048 respectively). No practice characteristics were associated with the dispensing of cephalosporins and tetracylines after adjusting for time and seasonality.

Higher levels of macrolide and trimethoprim dispensing were both associated with practices from more deprived areas. Higher levels of trimethoprim dispensing were additionally independently associated with practices that were run single-handedly (β=-3.607, SE=0.991, $p<0.001$). Higher levels of macrolide dispensing were associated with practices with older GPs (β =0.312, SE=0.108, p=0.004) and higher levels of quinolones associated with practices with a higher proportion of male GPs (β=0.038, SE=0.011, p=0.001)

Table 5.6 Multivariate analysis for antibiotic dispensing and practice characteristics by antibiotic group (estimated by MCMC methods) (parameter estimates β (SE) for significant practice characteristics shown only[i])

Antibiotic	Average age of GP per practice	Proportion of male GPs per practice	Multi-handed practice[ii]	Deprivation quintile of practice[iii]			
				2	3	4	5 (most deprived)
Penicillin	-	-	-	-	-	-	-
Flucloxacillin	-	-	-	-	-	-	-
BSPs	1.95 (0.33)	-	-10.39 (5.51)	6.70 (5.66)	15.16 (5.71)	25.43 (5.52)	29.93 (6.52)
Trimethoprim	-	-	-3.61 (0.99)	0.43 (1.00)	1.03 (1.13)	2.04 (1.05)	3.16 (1.31)
Macrolides	0.32 (0.11)	-	-	3.07 (2.20)	5.71 (2.15)	5.76 (2.01)	7.66 (2.28)
Cephalosporins	-	-	-	-	-	-	-
Quinolones	-	0.04 (0.01)	-	-	-	-	-
Tetracyclines	-	-	-	-	-	-	-
Total antibiotics	1.88 (0.46)	-	-22.00 (9.81)	11.94 (9.62)	24.86 (12.25)	36.59 (9.32)	42.25 (10.14)

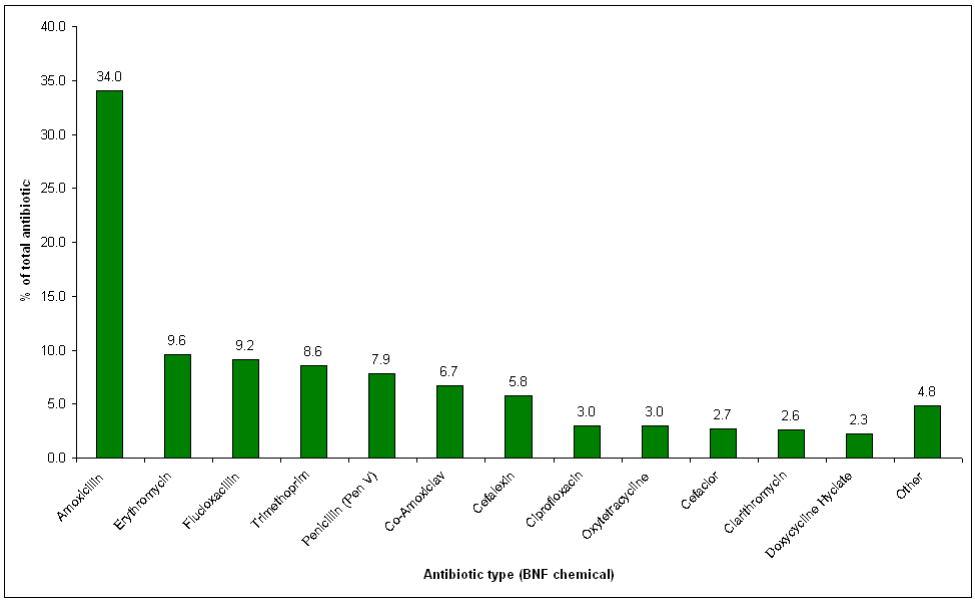
[i] *Adjusted for time, quadratic time term, seasonality and the interaction between time and practice characteristics*
[ii] *Single-handed practice= reference category*
[iii] *Deprivation quintile 1 (least deprived) = reference category*

5.4.2 Antibiotic dispensing in Wales: 2000 to 2006 (monthly data)

This section examines the variation in monthly antibiotic dispensing rates by detailed type of antibiotic in our nine groups of antibiotic. In total, 454 practices with a total population of 2,902,920 patients (97.9% of the Welsh population) were available for analysis and a total of 12,032,078 antibiotic items were dispensed over the six year period (April 2000-March 2006).

Figure 5.30 illustrates the most commonly dispensed antibiotics in Welsh general practices between 2000 and 2006, by antibiotic type (BNF chemical group). Amoxicillin was the most commonly dispensed antibiotic in primary care, accounting for 34.0% (N=4,093,204) and 9.6% (N=1,151,542) of total dispensing was accounted for by erythromycin. Other antibiotics included minocycline hydrochloride (1.4%), lymecycline (0.6%) and cefradine (0.6%).

Figure 5.30 Most commonly dispensed antibiotics in primary care from 2000 to 2006 by antibiotic type (BNF chemical)

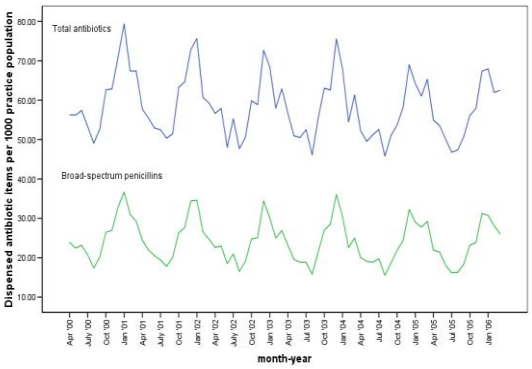


5.4.2.1 *Monthly time trends in antibiotic dispensing*

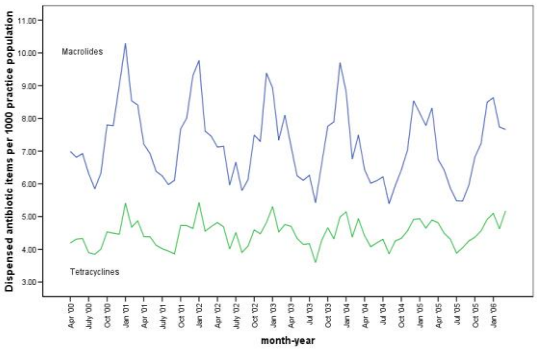
Figures 5.31a to e show detailed trends in monthly dispensing for antibiotics specifically used in the treatment of RTIs. As before, there was significant seasonal variation, with peak antibiotic use over the winter months (mainly December) and troughs in August. Flucloxacillin is the exception, where the highest rate of dispensing was in the summer months and lowest in the winter months (Figure 5.32).

Figure 5.31 Monthly trends in antibiotic dispensing rates by antibiotic group: April 2000 to March 2006

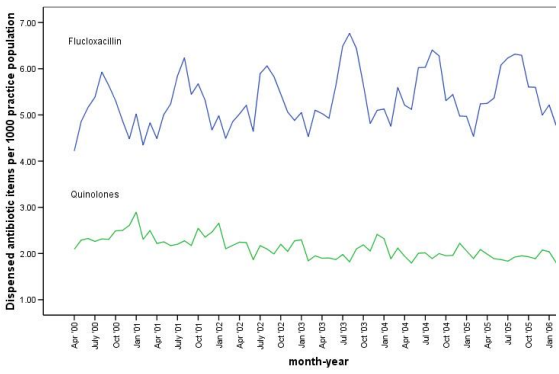
a. Total antibiotics and BSPs



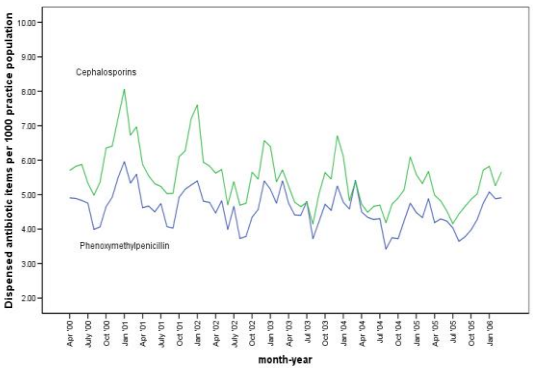
b. Macrolides and Tetracyclines



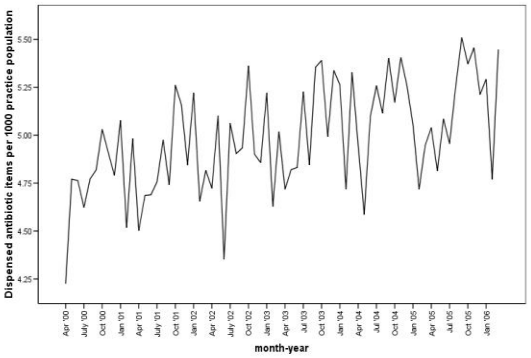
c. Flucloxacillin and Quinolones



d. Cephalosporins and Penicillin

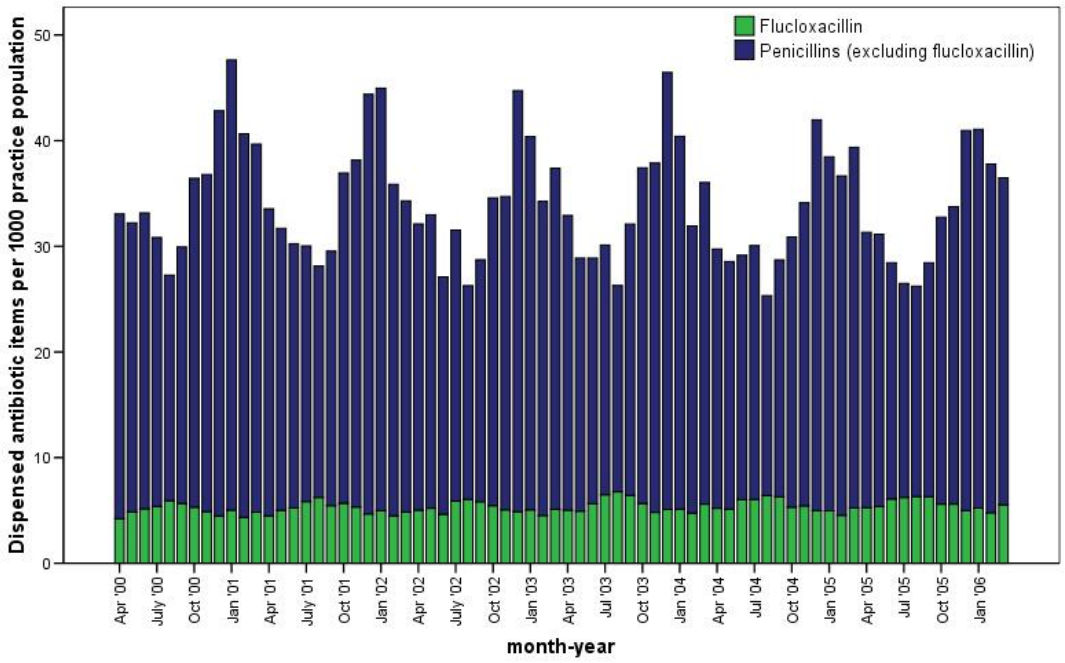


e. Trimethoprim



NB: Scales differ by antibiotic group

Figure 5.32 Monthly trends for flucloxacillin dispensing rates compared to remaining penicillins



Three-level (LHB, practice, time) quadratic models were fitted for each of the antibiotic groups. For some antibiotics, the variations in the linear and quadratic terms (β_1 and β_5) at the LHB level were small and improved the goodness of fit of the model by an insignificant amount. In these cases, both the linear and quadratic term were fixed at the LHB level. Parameter estimates were converted from monthly change to quarterly change to aid comparison with Table 5.3.

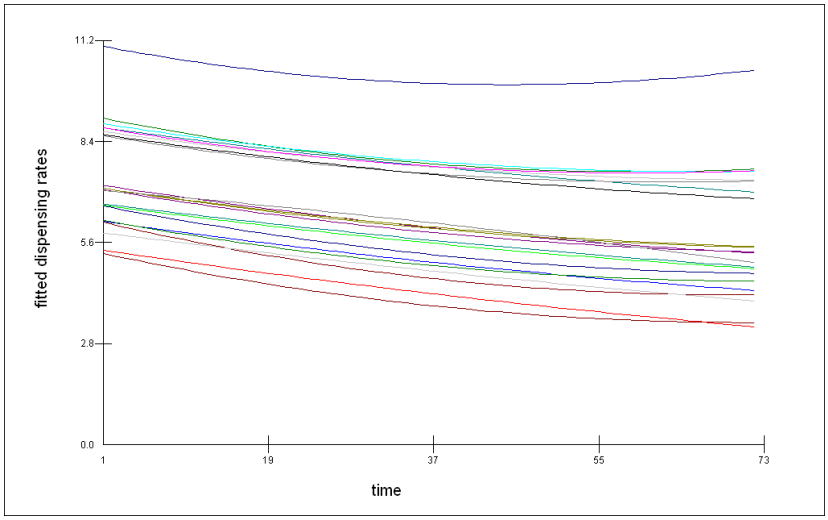
Table 5.7 Parameter estimates for quarterly antibiotic dispensing rates per 1,000 pp, by antibiotic group: 2000 to 2006 (estimated by MCMC methods)

Antibiotic	Parameter estimates			p-value		Median (25th to 75th quartile) dispensing rates per 1,000 pp per annum	
	Intercept (SE) β_0	Time (slope) (SE) β_1	Time^2 (SE) β_5	β_1	β_5	2000	2005
Penicillin	16.08	-0.034	0.0006	<0.001	0.689	54	47.28
	(0.42)	(0.004)	(0.0015)			(34.56 to 76.32)	(31.68 to 65.04)
Flucloxacillin	14.04	0.026	-0.0005	<0.001	<0.001	56.64	65.28
	(0.39)	(0.005)	(0.0001)			(39.6 to 75.96)	(48.6 to 83.4)
BSPs	96.96	-0.177	0.0017	<0.001	0.027	299.16	269.28
	(2.94)	(0.026)	(0.0008)			224.76 to 405.24)	(201.36 to 353.76)
Trimethoprim	14.67	0.009	0.000006	0.171	0.972	55.56	61.2
	(0.51)	(0.007)	(0.0002)			(42.6 to 70.32)	(48.36 to 73.92)
Macrolides	26.85	-0.047	0.000015	<0.001	0.957	82.68	75.24
	(0.72)	(0.012)	(0.0003)			(57.72 to 116.52)	(54.36 to 102.36)
Cephalosporins	21.18	-0.072	0.0007	<0.001	0.013	60.24	47.04
	(1.20)	(0.009)	(0.0003)			(32.88 to 99.72)	(26.04 to 78.00)
Quinolones	7.59	-0.023	0.0002	<0.001	0.065	24	20.28
	(0.48)	(0.02)	(0.0001)			(14.16 to 38.16)	(12.6 to 31.32)
Tetracyclines	14.49	0.002	-0.000005	0.669	0.978	48	50.28
	(0.48)	(0.005)	(0.0002)			(35.16 to 63.72)	(37.44 to 66.00)
Total antibiotics	212.41	-0.315	0.0026	<0.001	0.003	726.24	663.96
	(3.07)	(0.032)	(0.0009)			(593.16 to 894.12)	(550.32 to 803.16)

In this period (2000 to 2006), dispensing for most antibiotics was still decreasing over time albeit at a much lower rate than before, the exception being flucloxacillin, with an annual rate of increase of 0.10 per 1,000 pp ($p<0.001$). Tetracyclines and trimethoprim were more stable from April 2000 onwards (Annual rate $\beta_1=0.008$, $p=0.669$ and $\beta_1=0.003$, $p=0.171$ respectively).

The quadratic term was significant only for flucloxacillin, cephalosporins and broad-spectrum penicillins ($p<0.001$, 0.013 and 0.027 respectively), indicating either a flattening of the downward trend or an upward curvature. The variation in trends of cephalosporin dispensing rates from the fitted model by LHB, are shown in Figure 5.33. In particular, one LHB's dispensing of cephalosporins was much higher with some indication of a slight increase over time.

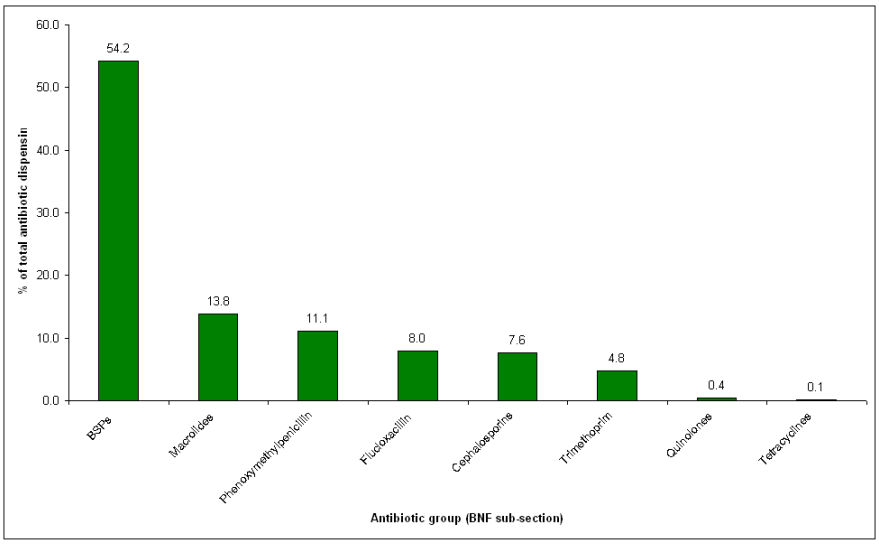
Figure 5.33 Fitted cephalosporin dispensing rates by Local Health Board



5.4.3 Antibiotic dispensing in Wales for children: 2000 to 2006

In total, 454 practices with a total population of 501,191 patients aged 0-15 were available for analysis and a total of 2,336,852 liquid oral antibiotic items (taken as a proxy for dispensing in children) were dispensed over the six year period (April 2000-March 2006), making up 18% of all antibiotic items dispensed. When total antibiotic dispensing was broken down into antibiotic group (BNF sub-section), liquid oral broad-spectrum penicillins were most frequently dispensed in primary care (Figure 5.34).

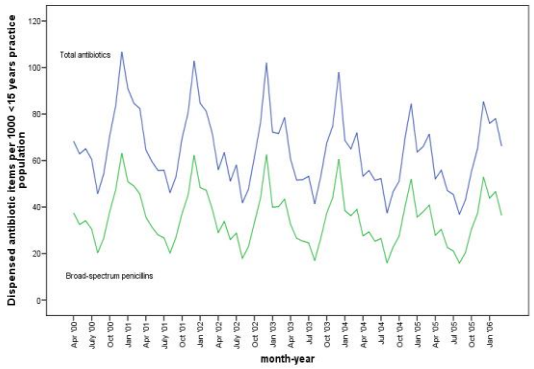
Figure 5.34 Most commonly dispensed liquid oral antibiotics in primary care from 2000 to 2006 by antibiotic group



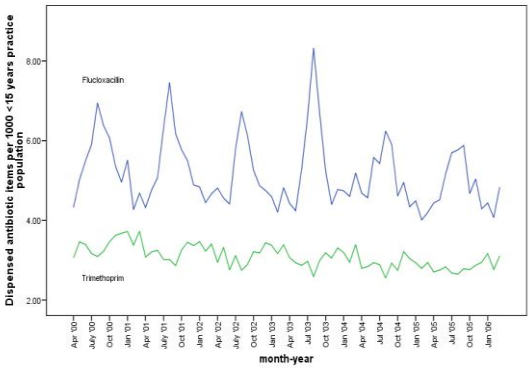
Figures 5.35a to f show the trends in dispensing for antibiotics in children more commonly used in the treatment of RTIs, with similar trends and seasonality to dispensed antibiotics for all ages. For most antibiotics, dispensing significantly decreased over time after April 2000 (Table 5.8). The exception to these decreasing trends was tetracyclines which increased, with an annual rate of change of 0.01 per 1,000 <15 years practice population (pp) (p=0.041).

Figure 5.35 Monthly trends in antibiotic dispensing in children by antibiotic group

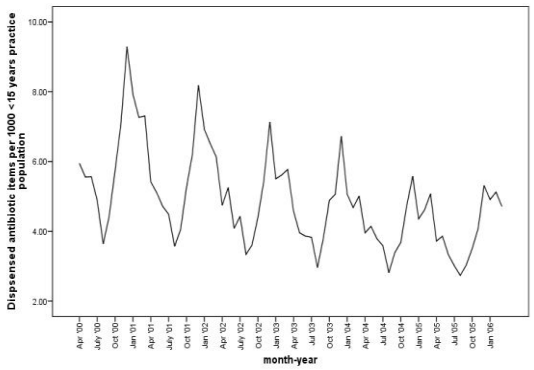
a. Total antibiotics and BSPs



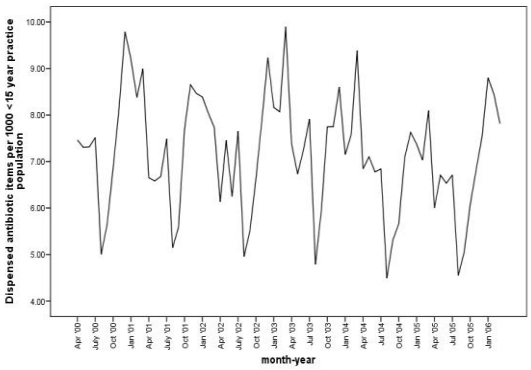
b. Flucloxacillin and Trimethoprim



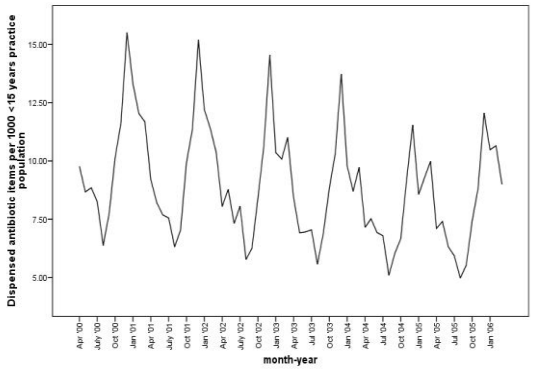
c. Cephalosporins



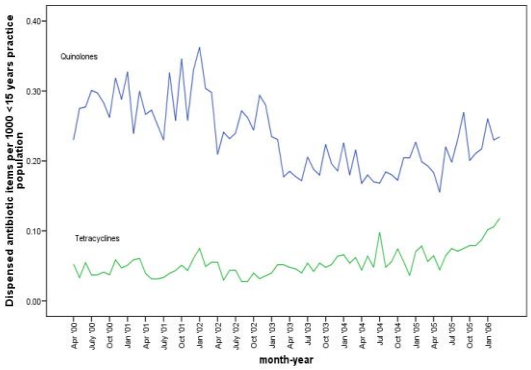
d. Penicillin



e. Macrolides



f. Tetracyclines and Quinolones



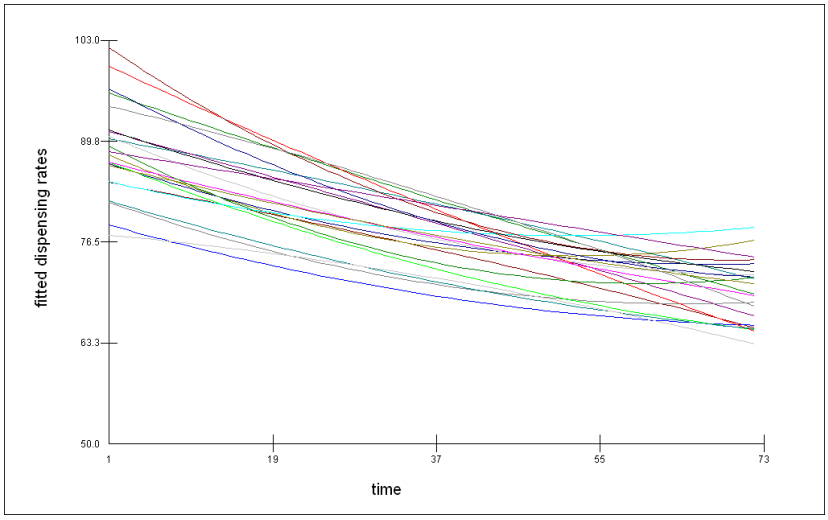
NB: Vertical scales differ by antibiotic group

Table 5.8 Parameter estimates for quarterly antibiotic dispensing rates for children per 1,000 pp, by antibiotic group: 2000 to 2006 (estimated by MCMC methods)

	Parameter estimates			p-value		Median (25th to 75th quartile) dispensing rates per 1,000 pp per annum	
Antibiotic	**Intercept (SE) β_0**	**Time (slope) (SE) β_1**	**Time^2 (SE) β_5**	**β_1**	**β_5**	**2000**	**2005**
Penicillin	25.23	-0.039	-0.0005	<0.001	0.194	72.6	65.04
	(0.81)	(0.009)	(0.0004)			(33.36 to 122.16)	(31.8 to 105.96)
Flucloxacillin	14.31	-0.028	-0.0003	<0.001	0.112	55.32	51.84
	(0.54)	(0.006)	(0.0002)			(29.16 to 85.2)	(27.96 to 78.24)
BSPs	148.53	-0.440	0.0043	<0.001	0.004	437.52	346.92
	(5.19)	(0.056)	(0.0015)			(286.92 to 639.48)	(228.12 to 522.24)
Trimethoprim	10.77	-0.035	0.0002	<0.001	0.281	34.08	29.76
	(0.51)	(0.006)	(0.0002)			(16.92 to 56.28)	(13.8 to 46.68)
Macrolides	37.68	-0.140	0.0009	<0.001	0.053	98.64	71.52
	(1.17)	(0.014)	(0.0004)			(51.48 to 169.2)	(37.44 to 124.8)
Cephalosporins	22.74	-0.122	0.0009	<0.001	0.013	47.16	27.48
	(1.65)	(0.012)	(0.0004)			(18.84 to 97.2)	(6.84 to 62.16)
Quinolones	0.93	-0.005	0.0001	0.001	0.124	0.00	0.00
	(0.09)	(0.001)	(0.00004)			(0.00 to 0.00)	(0.00 to 0.00)
Tetracyclines	0.15	0.0014	0.00004	0.041	0.111	0.00	0.00
	(0.03)	(0.0007)	(0.00003)			(0.00 to 0.00)	(0.00 to 0.00)
Total antibiotics	259.56	-0.801	0.0055	<0.001	0.026	825.36	659.4
	(6.69)	(0.090)	(0.0024)			(600.96 to 1120.56)	(480 to 896.88)

The quadratic terms for most of the antibiotic groups were not significant. The exceptions were broad-spectrum penicillins (BSPs), cephalosporins and total antibiotics (due to the high proportion of BSPs), which had positive parameters for the quadratic term (p=0.004, 0.013 and 0.026 respectively). This upwards curvature might represent a slowing down of the rate of decrease or even an increase. Figure 5.36 shows the variation in total antibiotic dispensing over time by LHB.

Figure 5.36 Fitted total antibiotic dispensing rates for children from the fitted three-level model by Local Health Board



5.4.4 Comparisons in trends between the two datasets: antibiotic dispensing for all ages vs. children, 2000 to 2006

For the period 2000 to 2006, in comparison with trends in antibiotic dispensing for all ages, the trends in dispensing for children were very similar, with decreases over time for phenoxymethylpenicillin, BSPs, macrolides, cephalosporins, and quinolones (Table 5.9). Relating the annual rate of change figures to dispensing in 2000, an annual fall in BSPs of 0.71 per annum (dispensing for all ages) and of 1.76 per annum (dispensing for children) can be equated to around 0.24% and 0.40% of BSP dispensing in 2000. The exception to these decreasing trends was flucloxacillin which increased significantly over time for all formulations (all ages) but significantly decreased for liquid oral formulations (children). Trimethoprim dispensing was stable for all formulations but a decrease was seen for liquid oral formulations (annual rate of change of 0.04 and -0.14 per 1,000 pp respectively).

Again, variation due to inter-practice differences was greater than inter-LHB (where three-level models were used) and intra-practice differences for all antibiotic groups (Table 5.10). Variation in quinolones and tetracycline dispensing was very low mainly due to low dispensing rates in children (75^{th} quartile=0). The variation due to inter-LHB differences ranged from 2% in flucloxacillin and trimethoprim dispensing to 10% in BSPs dispensing. The dispensing of cephalosporins had the highest between practice variation (70%) and quinolones the least variation (40%). Intra-practice variation was higher in children than for all ages but this could be accounted for by smaller numbers of dispensed antibiotics resulting in less stable rates.

Table 5.9 Comparison of annual rate of change (per 1,000 pp) between antibiotics dispensed for all ages and for children: 2000 to 2006

Antibiotic	All ages Annual rate of change	p-value	Children Annual rate of change[i]	p-value	All ages Median (25th to 75th quartile) Dispensing rates in 2000 per 1,000 pp	Children Median (25th to 75th quartile) Dispensing rates in 2000 per 1,000 pp
Penicillin	-0.14	<0.001	-0.16	<0.001	54.00 (34.56 to 76.32)	72.60 (33.36 to 122.16)
Flucloxacillin	0.11	<0.001	-0.11	<0.001	56.64 (39.60 to 75.96)	55.32 (29.16 to 85.20)
BSPs	-0.71	<0.001	-1.76	<0.001	299.16 (224.76 to 405.24)	437.52 (286.92 to 639.48)
Trimethoprim	0.04	0.171	-0.14	<0.001	55.56 (42.60 to 70.32)	34.08 (16.92 to 56.28)
Macrolides	-0.19	<0.001	-0.56	<0.001	82.68 (57.72 to 116.52)	98.64 (51.48 to 169.20)
Cephalosporins	-0.29	<0.001	-0.49	<0.001	60.24 (32.88 to 99.72)	47.16 (18.84 to 97.20)
Quinolones	-0.09	<0.001	-0.02	0.001	24.00 (14.16 to 38.16)	0.00 (0.00 to 0.00)
Tetracyclines	0.01	0.669	0.01	0.041	48.00 (35.16 to 63.72)	0.00 (0.00 to 0.00)
Total antibiotics	-1.25	<0.001	-3.20	<0.001	726.24 (593.16 to 894.12)	825.36 (600.96 to 1120.56)

[i] *practice population <15 years of age*

Table 5.10 Local Health Board and practice variation for dispensing rates in children by antibiotic groups (estimated by MCMC methods)

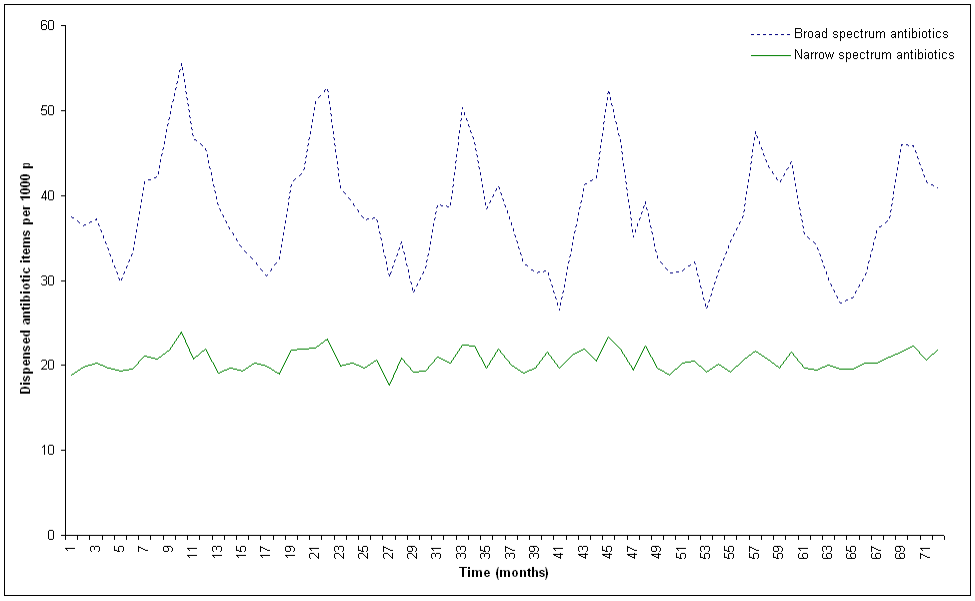
	Between LHB variation			Between practice variation			Within practice variation σ^2_{e0}	ICC[i] (LHB/ Practice)
	Intercept σ^2_{v0}	Time σ^2_{v1}	Time^2 σ^2_{v5}	Intercept σ^2_{u0}	Time σ^2_{u1}	Time^2 σ^2_{v5}		
Penicillin	1.19	*NA*	*NA*	25.44	0.003	<0.001	16.99	3%/58%
Flucloxacillin	0.30	*NA*	*NA*	8.93	0.002	<0.001	8.81	2%/50%
BSPs	51.17	0.005	<0.001	297.56	0.039	<0.001	171.10	10%/57%
Trimethoprim	0.28	*NA*	*NA*	7.40	0.002	<0.001	4.86	2%/59%
Macrolides (2-level model)	-	-	-	67.50	0.001	<0.001	27.45	- / 71%
Cephalosporins	5.78	*NA*	*NA*	52.20	0.007	<0.001	16.36	8%/70%
Quinolones	0.0015	*NA*	*NA*	0.30	<0.001	<0.001	0.46	0.2%/40%
Tetracyclines	0.0013	*NA*	*NA*	0.02	<0.001	<0.001	0.13	1%/13%
Total antibiotics	73.11	0.01	<0.001	695.10	0.10	<0.001	331.01	7%/63%

[i] *ICC = Intra-class correlation;*
NA = Not applicable. Time and time squared terms are fixed at LHB level since variation between LHBs is not significant.

5.4.5 Broad- vs. narrow-spectrum antibiotic dispensing

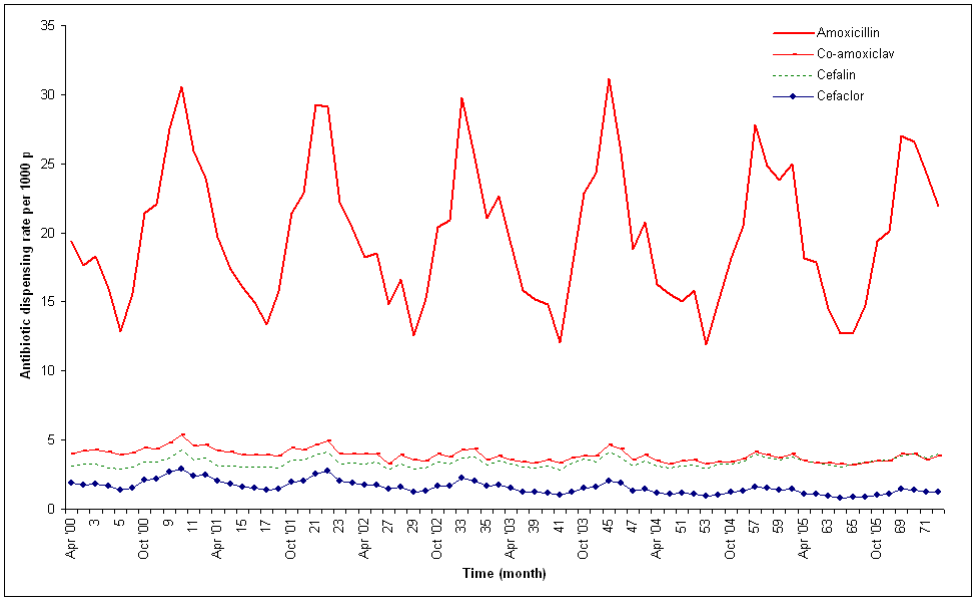
In total, 7,803,395 (64.9%) and 4,228,683 (35.1%) broad- and narrow-spectrum antibiotics respectively were dispensed over the six-year period for the 454 practices (total of 12,032,078 antibiotics dispensed for antibiotics most commonly used in RTIs). Figure 5.37 shows the monthly trend in dispensing of these two categories of antibiotics. It appears that narrow-spectrum dispensing is static over the period, with some indication of a decline in dispensing of broad-spectrum antibiotics, although seasonality is the same as for total antibiotics (mainly because of the high proportion of broad-spectrum penicillins) with peaks in dispensing over the winter period and troughs during summer.

Figure 5.37 Broad- and narrow-spectrum antibiotic dispensing monthly rates over time (April 2000 to March 2006)



Of the broad-spectrum antibiotics, 52.5% (n=4,093,204) were made up of amoxicillin, 10.3% (800,424) of co-amoxiclav and 8.9% (696,402) of Cefalexin (Figure 5.38). For narrow spectrum antibiotics, 27% (1,151,542) were made up of erythromycin, 26% of flucloxacillin (1,101,852), 24% of trimethoprim (1,028,770) and 22% of penicillin (benzathinepenicillin, penicillin V and G and procaine benzylpenicillin) (946,518).

Figure 5.38. Monthly broad-spectrum antibiotic dispensing per 1,000 practice population (April 2000 to March 2006)



A three-level quadratic repeated measures model for broad-spectrum antibiotic dispensing, after adjusting for seasonality, showed an average slope (β_1) of -0.37 (SE=0.044, 95% CI=-0.46 to -0.28) (per 1,000 practice population per quarter) indicating a general decrease in rates over time. The model showed a significant quadratic term (β_5=0.00096 (0.00041)) indicating an upwards curvature. This term varied significantly between LHBs and practices (SD=σ_{v5}=0.0014 and σ_{u5}=0.004 respectively). Figure 5.39 shows the variation in practices' dispensing of broad-spectrum antibiotics. In particular, one practice had a very high intercept (highlighted in red) and had the steepest decline over time and a greater upwards curvature to the trend.

Figure 5.40 shows the fitted values from the fitted model for each of the 22 LHBs. There was more than three times as much variability due to inter-practice differences within LHBs (SD=σ_{u0}=0.141) as there was between LHBs (SD=σ_{v0}=0.042). However, a total of 7% of variation was explained by inter-LHB differences and 73% by inter-practice variation.

Figure 5.39 Caterpillar plots: practice-level residuals for broad-spectrum dispensing rates (± 1.96SD) vs. rank

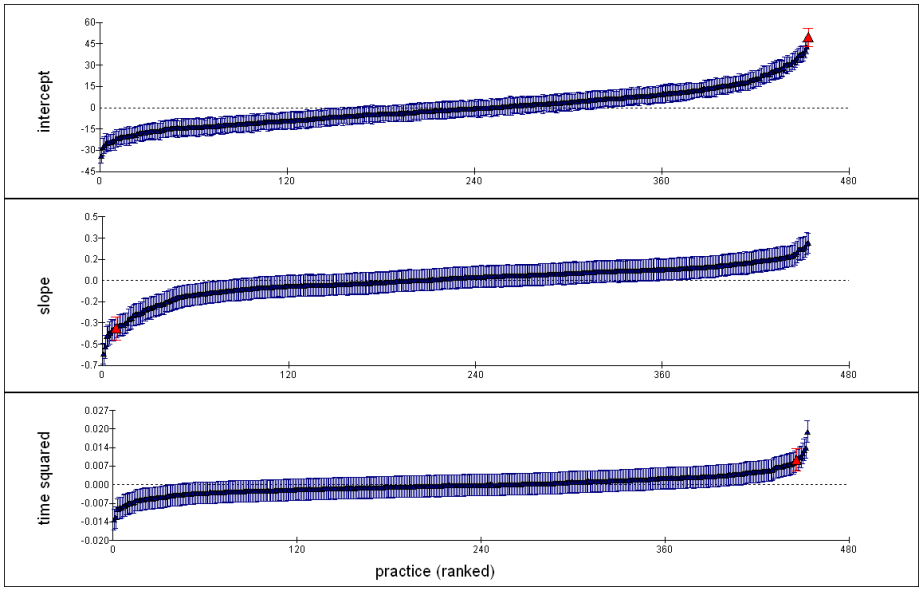
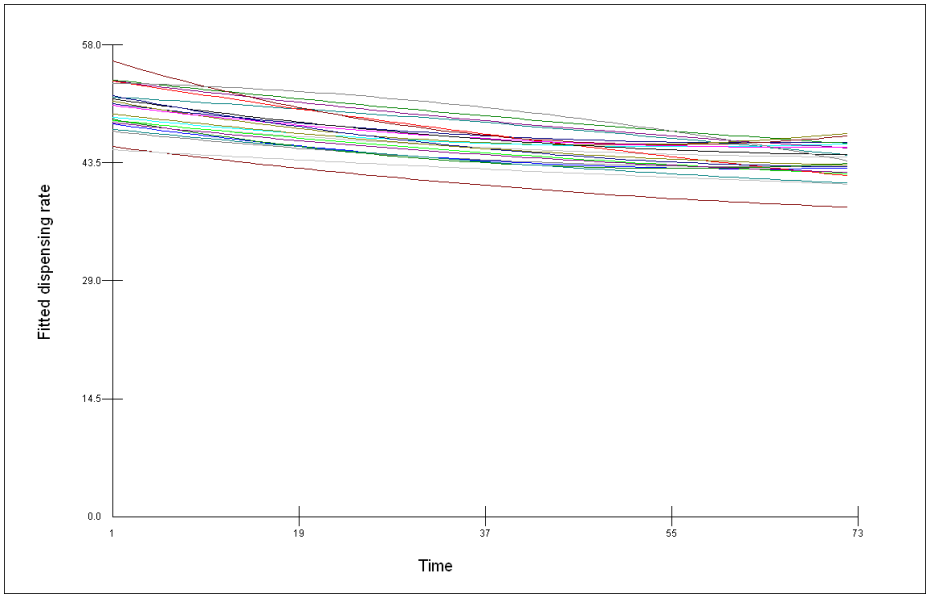


Figure 5.40 Fitted monthly broad-spectrum dispensing rates by Local Health Board



A three-level linear repeated measures model for narrow-spectrum antibiotic dispensing after adjusting for seasonality, showed an average slope (β_1) of -0.048 (SE=0.028, 95% CI=-0.104 to 0.001) (per 1,000 practice population per quarter) indicating no general trend in rates. The model showed a non-significant quadratic term (β_5=-0.00013 (0.00018)).

Although there was no general trend in overall dispensing of narrow-spectrum antibiotics there was still considerable variation between LHBs (SD=σ_{v1}=0.027) and practices (SD=σ_{u1}=0.079). The variation in practice dispensing can be seen in the caterpillar plot with great variation in the practices' slopes with one practice initially with a high rate of dispensing and reducing the most over time (Figure 5.41). Figure 5.42 shows the predicted dispensing rates from the fitted model by LHBs.

Figure 5.41 Caterpillar plots: practice-level residuals for narrow-spectrum antibiotic dispensing rates (± 1.96SD) vs. rank

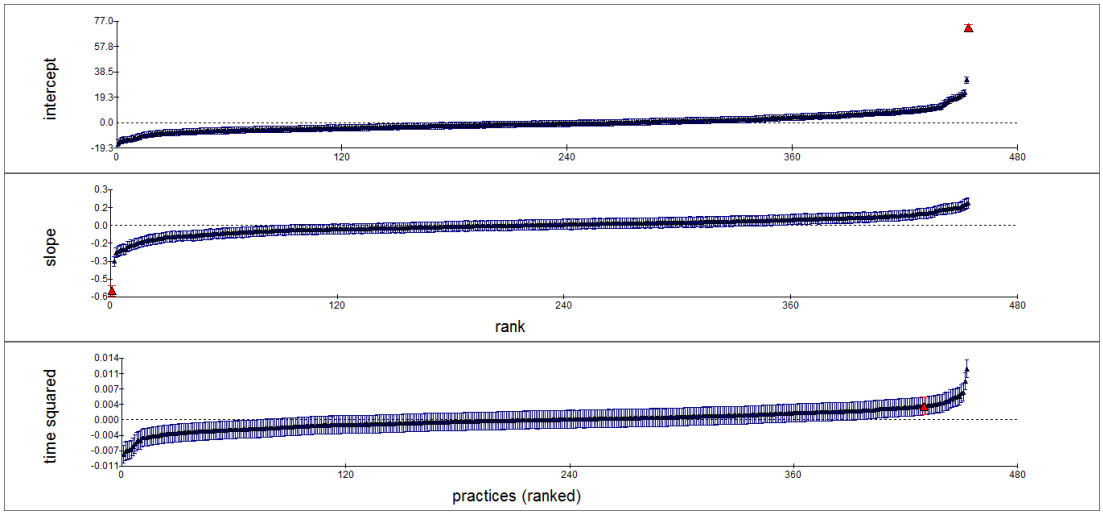
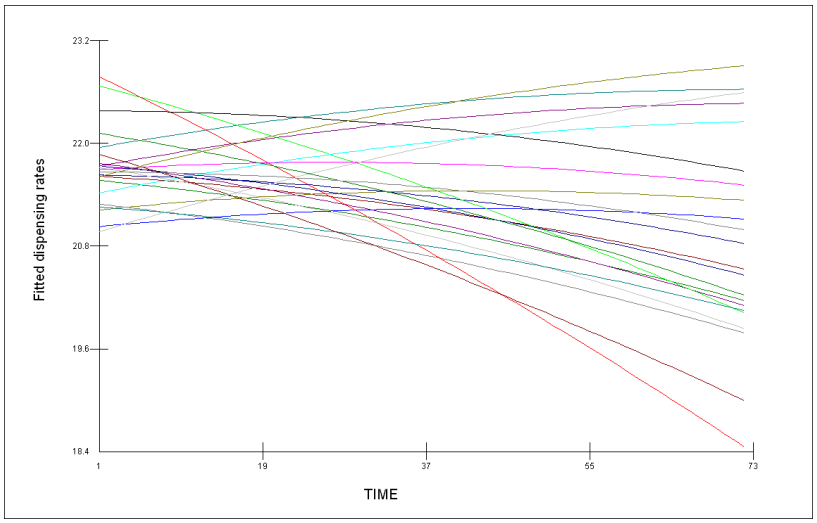


Figure 5.42 Fitted monthly narrow-spectrum dispensing rates from the fitted three-level model by Local Health Board



5.5 Discussion

5.5.1 Main findings

In Wales, overall levels of community dispensing of antibiotics most commonly used to treat RTIs decreased between the study years 1996 and 2005, with the majority of the reduction seen in the early period. There was some indication that this reduction had slowed down in later years. These reductions were observed across all antibiotic groups with the exception of flucloxacillin, which increased over the study period. Seasonality was also evident with peaks in the winter periods (October to March) and troughs in the summer period, again with the exception of flucloxacillin where dispensing rates peaked in quarter 3 (July-September). General trends in the dispensing of broad-spectrum antibiotics were also downwards but there were no notable trends in the dispensing of narrow-spectrum antibiotics.

Trends and seasonality in the dispensing of liquid oral antibiotics (a proxy for dispensing in children) between 2000 and 2006 were similar to those seen for dispensing for the whole practice population. However, the dispensing of liquid oral flucloxacillin significantly decreased over time, and there was a notable decline in the dispensing of trimethoprim. The low dispensing of both tetracyclines and quinolones can be explained by these antibiotics being contraindicated in children as they may result in permanent staining of teeth and increase the risk of damage to the musculoskeletal system.

To date this is one of the few studies to examine the variation in trends of antibiotic dispensing between general practices and on such a large scale and over a large period of time. Although conclusions based on the whole dataset identified that overall antibiotic dispensing had decreased over time (by 29% between 1996 and 2005), this did not happen for all practices (although it did for most). Antibiotic dispensing not only varied greatly between practices, with a six-fold difference in total antibiotic dispensing rates at the extremes in 2005, but also over time with some practices increasing their dispensing over the study period. Practices with the highest dispensing rates initially, tended to decrease their dispensing the most, perhaps as there was more scope for reduction. There was also some variation between the 22

Local Health Boards (LHBs), but they all decreased their dispensing over time. Practices with older general practitioners (GPs) and who served more deprived areas were more likely to dispense a higher number of overall antibiotics, after adjusting for any effect of time and seasonality.

5.5.2 Strengths and weaknesses of the study

The data that informs this analysis was obtained from the PSU in NWIS and is equivalent to the Prescription Pricing Authority's Prescribing Analysis and Cost Tabulation (PACT) data in England. This data covers all practices that existed in Wales between 1996 and 2006; therefore a large amount of detailed antibiotic dispensing data was analysed at a general practice level over time. In this study, monthly and quarterly trends were examined for specific antibiotics most commonly used in the treatment of respiratory tract infections, and also for a proxy for children's prescribing, namely liquid oral antibiotics. Broad and narrow spectrum antibiotic dispensing was also examined but it was not possible to examine whether prescriptions were appropriate, since no information was available on the dosage, duration or indication of the drug or on patient characteristics.

Although data for a total of 533 practices were initially obtained, 107 practices were excluded on the basis of having unstable or small practice populations for the study period. The remaining 426 practices covered a total of 94.5% (2,802,319 of the Welsh population). It is likely that the excluded practices either stopped practising or merged with another practice, and due to anonymisation their data could not be combined. Including these practices would have introduced bias into the dispensing data. Excluded practices were more likely to be single-handed and from a more deprived area and this possible bias should be taken into consideration when interpreting the results.

Many of the weaknesses of the dispensing data have already been covered in Chapter 4. Results are for overall antibiotic dispensing for all indications, not specifically for RTIs, dispensing data do not represent consumption, and there is possible underestimation of out-of-hours dispensing. Caution should be taken regarding the interpretation of dispensing of liquid oral antibiotics as a proxy for dispensing in

children. Since amoxicillin liquid formulations are amongst the most frequently supplied medicines via out-of-hours services, they are likely to be under-represented in this dataset (Sharland 2007). Additionally, liquid oral antibiotics are not exclusively dispensed to children, but could also be given to elderly patients.

Whilst the variation in antibiotic dispensing attributable to differences in practices and LHBs (which accounted for over 78% of total variation) was examined, the practice demographics studied did not account for a great amount of the variation, only explaining an additional 2% of total antibiotic dispensing. Other factors therefore need to be examined as possible drivers of dispensing in primary care, perhaps not accounted for by variation in practice demographic factors or even variation in the incidence of infections. For example, it has been suggested that the widening of prescribing to healthcare professionals such as pharmacists or nurses could increase dispensing (Wise 2007). This data has been on dispensing at a practice level and does not take into account variation in antibiotic dispensing by individual GPs; this cannot be measured accurately at present.

The freezing (in April 2001) and reduction (between October 2004 and April 2007) (and then abolition) of prescribing charges in Wales could also have had an effect on dispensing rates in Wales. However, a recent study found a modest increase in dispensing rates (4%) between October 2003 and March 2008 for the most commonly dispensed antibiotics (combination of amoxicillin 250mg and 500mg, erythromycin 250mg, phenoxymethylpenicillin 250mg and trimethoprim 200mg) when compared to those in North East England (decrease of 7%) (Cohen *et al*. 2010).

5.5.3 Comparisons with existing literature

5.5.3.1 *Antibiotic prescribing for all ages*

The trends in antibiotic dispensing found in this study are similar to those found in other UK data studies (Majeed *et al*. 2004; Sharland *et al*. 2005; Fleming *et al*. 2005; Prescribing Review 2006). These studies suggested that most of the decrease in overall antibiotic prescribing in primary care had occurred by 2000 when rates reached a plateau. Data from the English Prescription Cost Analysis database

(covering all prescriptions dispensed in the community in England) demonstrate that antibiotic use fell from 44.5 million items in 1996 to 32.8 million in 2004, but had since risen slightly to 33.3 million in 2006. Trends in antibiotic prescribing in Wales between 1999 and 2005 in a primary care or outpatient setting saw a reduction in prescriptions per 1,000 inhabitants per day (PIDs) whereas an increase was found in DDD per 1,000 inhabitants per day (DIDs) (Davey *et al*. 2008). They also found a significant reduction in PIDs for England and Scotland. This suggests that the initiatives introduced in the late 1990s to reduce antibiotic usage did have an impact on antibiotic prescribing in primary care. Little evidence was found to support the finding of an increase of flucloxacillin dispensing but one study by Hayward *et al.* (2008) detected a 1.8-fold increase in flucloxacillin prescription rates between 1991 and 2006.

Decreases in antibiotic prescriptions in an outpatient setting have also been observed for the US (McCaig *et al*. 2003; Roumie *et al*. 2005), and Australia where prescribing rates fell by 24.3% between 1990 and 2002 (Pan *et al.* 2006). In Europe, data from the European Surveillance of Antimicrobial Consumption (ESAC) project provided DID data on outpatient antibiotic use in 34 European countries. A paper by Ferech *et al.* (2006) specifically examined trends between 1997 and 2003 and found that DIDs had increased in many of the countries, including Denmark, Portugal and Greece. Patterns varied between countries; in some countries such as France and Belgium, DIDs initially increased then decreased while in the UK and Spain DIDs initially decreased and then increased.

A number of studies have found that broad spectrum antibiotics and macrolides are prescribed most frequently in primary care in the UK (Ferech *et al*. 2006; Petersen and Hayward 2007) and specifically in acute cough (Butler *et al*. 2009). Meropol *et al.* (2009) found a decrease between 1990 and 2004 in the UK in both the overall antibiotic prescribing rate, and also that of broad spectrum antibiotics in acute RTIs, in the UK, a finding supported by US data (Vanderweil *et al*. 2007).

5.5.3.2 *Antibiotic prescribing in children*

A study by Sharland (2007), using data from the Prescription Pricing Authority's database (covering dispensing of antibiotic prescriptions from general practices in England), used the same proxy of oral liquid formulations of antibacterials for antibiotics in children. They similarly showed a decline in dispensed items between 1996 and 2004 and evidence of a slight increase after 2004 (an increase of 0.92% of items was seen between 2004 and 2005). Using monthly dispensed items, the same seasonal variations were seen with peaks in the winter months and troughs in the summer months for most antibiotics, with the exception of flucloxacillin where the reverse occurred. Another study using data from 125 UK practices (using data from the IMS Mediplus UK database), examined community antibiotic prescribing in 0-18 year olds between 1996 and 2006. They found that total antibiotic prescribing rates fell by 24% between 1996 and 2000 but rates were then stable until 2002 (Thompson *et al.* 2009b). Thereafter, prescribing increased by 10% between 2003 and 2006 with the increase being more marked between 2005 and 2006. More recently, Schneider-Lindner *et al*. (2011) observed a turn in the tide of antibiotic prescribing rates in children with rates at their lowest at 419 per 1000 pp in 2000 increasing to 568 per 1000 pp in 2007 (comparable to those in the late 1990s).

Similar reductions in dispensing for children have also been observed in the USA (McCaig *et al*. 2002; Finkelstein *et al*. 2003), and Europe (Otters *et al*. 2004). Sharland *et al.* (2007) additionally identified from Unicef data that certain European countries (France, Germany, Italy, Spain, UK) and the USA had decreased their prescribing for children between 2002/03 and 2004/05. Seasonal variation was observed in all countries with prescribing lowest in September and highest in March for all countries except the UK.

5.5.3.3 *Practice characteristics*

A number of studies have also found that certain prescriber and practice characteristics are associated with higher prescribing of antibiotics. The findings that male and older GPs were more likely to prescribe antibiotics were supported by several other studies from the UK, Europe, Canada and Taiwan (Gill and Roalfe

2001; Arnold *et al.* 2005; Fischer *et al.* 2005; Huang *et al.* 2005; Wang *et al.* 2009). Single-handed practices (Unsworth and Walley 2001; Wilson *et al*. 1999) and practices in areas of greater deprivation (Wilson *et al*. 1999; Unsworth and Walley 2001; Curtis and Marriott 2008) also had higher prescribing rates. Practices serving populations with greater morbidity were more likely to have higher prescribing of all drugs, not only antibiotics (Omar *et al.* 2008; Wang *et al.* 2009). Otters *et al.* (2004) found that a prescription of a broad spectrum antibiotic was associated with single-handed practices and having a high proportion of children registered with the practice.

5.5.4 Implications of findings for clinical practice and future research

Analysis of this general practice level dispensing data has been crucial to our understanding of antibiotic dispensing in primary care, how dispensing of specific types of antibiotics varies over time and between practices and health administrative area. Despite a number of limitations, this seems the best way to estimate reliably antibiotic prescribing in primary care, both at a macro level for the whole population of Wales and also at a micro level for LHBs and general practices.

Surveillance of national trends in antibiotic dispensing is important, firstly at a national level in order to monitor overall trends in antibiotic use and secondly to identify any problems or unexpected increases. For example, there is now a possibility that the reduction in antibiotic dispensing in Wales that was seen in the late 1990s was not sustained and that dispensing has since increased for most antibiotics (Welsh Antimicrobial Resistance Programme Surveillance Unit 2009). The factors associated with this change in dispensing patterns in general practice need to be investigated; are GPs not following guidelines or are patients asking for antibiotics more frequently or is the change due to diagnostic uncertainty?

Almost all practices decreased their dispensing rates over the study period but there were variations in decreases with those with the highest initial dispensing reducing the most. It would be useful to investigate these practices to determine whether they were reducing all antibiotic dispensing or just inappropriate dispensing and if there is a blanket reduction then could reducing prescribing have negative as well as positive

effects?

Trends could also be used to assess the effectiveness of interventions designed to change the dispensing of antibiotics such as nurse prescribing, devolution or free prescriptions (in Wales). At an LHB and practice level, it allows feedback and reflection on GP prescribing behaviours and gives an indication on whether guidelines are being followed. A study recently completed in Wales revealed to general practices both their own dispensing rates and also those of their LHB and of Wales; practices generally reported this as being really useful (Simpson *et al*. 2009). Even without the indication of why the antibiotic was given, guidance could be provided. For example, amoxicillin was the antibiotic most frequently prescribed by GPs. These are usually used in the treatment of RTIs, and for most patients are not useful. Guidance could then be given as to who would benefit the most from them. This could improve the quality of prescribing in general practice and would allow LHBs to introduce appropriate prescribing initiatives. Identifying certain practice characteristics that are associated with higher prescribing would give further insight into who should be targeted (for example single-handed practices).

The monitoring of antibiotic dispensing data by type of antibiotic is of great importance and should be continued, with timely reports which are relevant to both practitioners and policy makers. As already stated, one flaw of the dispensing data used here is that no patient level data exists and thus no patient identifiers such as age and gender. Thus analysis can only be done at an aggregate level over the practice population. Plans are underway to record this information, (using an identifier such as the NHS number) from scripts and this would allow more detailed analysis, including further research into antibiotic dispensing in children instead of using liquid oral antibiotics as a proxy. This would also allow the linkage via an NHS number of dispensing data to other datasets, such as antibiotic resistance, at an individual level. Further questions of interest include why dispensing of liquid oral tetracyclines is increasing and the reason for the increase in flucloxacillin over time for all ages. Flucloxacillin syrups, given mainly to children, could not explain the increase and one theory is that flucloxacillin may be being used as a substitute for co-amoxiclav.

Reassuringly, the direction of the trends in dispensing in the sample of Welsh practices in Chapter 4 mirrors that found at the all-Wales level, albeit a stronger decreasing trend due to the different study periods. It would therefore be of interest to examine the complications arising in primary care to see whether the same trends are found for all practices in Wales. Unfortunately, the General Practice Morbidity Database (GPMD) will not have 100% coverage in Wales and currently no other source routinely collects primary care data for all practices in Wales. Hospital admissions data however is a plausible source although it would be preferable to capture complications arising in both primary and secondary care.

5.6 Introduction to Welsh resistance data

In summary, this chapter uniquely used a large dataset at the general practice level and robust methods to examine recent trends in antibiotic dispensing in Wales. Overall dispensing decreased over time but at what consequence to antibiotic resistance and adverse outcomes such as hospital admissions of serious infections? Chapter 6 will explore patterns of antibiotic resistance in Wales by examining trends in community resistance rates for common respiratory pathogens using retrospective Welsh antibiotic resistance data. Chapter 7 will similarly examine the changing patterns of hospital admissions of complications arising from respiratory tract infections using Welsh hospital admissions data.

Chapter 6 Antibiotic resistance in Wales

6.1 Introduction

Chapter 5 showed that a decrease in community dispensing of antibiotics most commonly used to treat respiratory tract infections (RTIs) decreased between April 1996 and April 2006, with the majority of the reduction seen in the early period. With the increasing problems of antimicrobial resistance, and the mounting evidence of a link with antibiotic usage, it is important to ascertain whether this decrease in dispensing has had a beneficial effect on antibiotic resistance in the community with the hope that reducing usage of antibiotics might lead to a reduction in resistance rates.

The merging of regional microbiology laboratory databases in Wales has provided the opportunity of using routinely collected antibiotic resistance data for community and hospital infections with bacteria, parasites and viruses. The main intention of this dataset is for surveillance purposes, directed to monitor trends and changes in resistance in both community and hospital infections, and to provide current estimates of local resistance in infection. The aim of this chapter was not only to identify such trends in community resistance rates for common respiratory pathogens using retrospective Welsh antibiotic resistance data but to examine variations in these rates and trends at a local level (laboratory and general practice). The relation between resistance and antibiotic dispensing and any practice characteristics that may influence rates was also examined. In particular associations between changes in antibiotic dispensing and changes in antibiotic resistance at a general-practice level were investigated.

6.2 Methods

6.2.1 Microbiology data

Community microbiology data are derived from samples taken from patients presenting to a GP with a suspected infection. Patient samples and swabs are then sent to microbiology laboratories to identify an isolate (a sample with an identified

bacterium) and this is tested for resistance to a set of antibiotics. Routine antimicrobial resistance testing data is sent by laboratories to the Laboratory Information Management Systems (LIMS). All data stored on LIMS is extracted by each regional DataStore system and the information mapped into a pseudo-anonymised standardized format. This data is then held by the National Public Health Service for Wales (NPHS) for extraction and analysis.

For this study microbiological data for samples submitted by Welsh general practices were obtained from 11 of the 18 Welsh and Welsh border Public Health and NHS laboratories. Those included were Aberystwyth, Bangor, Bridgend, Cardiff, Carmarthen, Haverfordwest, Newport, Pontypridd, Rhyl, Swansea and Wrexham. Data from the practices served by the Merthyr and Abergavenny laboratories, and the practices served by the Welsh border laboratories (Chester, Hereford and Shrewsbury) were not included in this report as their LIMS were not linked to DataStore at the time of data extraction.

The dataset covered nine years of retrospective data (January 1998 to December 2006) and were based on samples sent by GPs for testing. Results were extracted for those identified with the following identified organisms: *Haemophilus influenzae* (*H. influenzae*), *Streptococcus pneumoniae* (*S. pneumoniae*) and *Streptococcus pyogenes* (*S. pyogenes)*. These organisms were examined since they are the main cause of bacterial RTIs; *H. influenzae* and *S. pneumoniae* both cause lower RTIs such as bronchitis and pneumonia, and also acute sinusitis and ear infections, whereas *S. pyogenes* are the causative bacteria in many upper RTIs such as sore throats, although they are known to also cause skin infections such as impetigo.

For each isolate reported as either *H. influenzae*, *S. pneumoniae* or *S. pyogenes*, the following information was obtained: patient identification number, age and gender of patient, address from where the sample was sent, laboratory, date of specimen collection, specimen type and site (e.g. ear, throat swab), specimen number, and result (R=Resistant, S=Sensitive, I =Intermediate, blank =not tested) for certain antibiotics (Table 6.1). The set of antibiotics for which resistance is tested varies between laboratories and isolates but those shown in the table are tested in the great majority of these isolates.

Table 6.1 Antibiotics commonly tested for resistance by organism

Antibiotic	Organism		
	S. pneumoniae	***S. pyogenes***	***H. influenzae***
Amoxicillin	✓	✓	✓
Augmentin/ Co-amoxiclav			✓
Cefuroxime			✓
Erythromycin	✓	✓	
Penicillin	✓	✓	✓
Quinolones[i]			✓
Tetracyclines	✓	✓	✓

[i] *All laboratories test Ciprofloxacin except for Bangor and Wrexham which test Norfloxacin and Levofloxacin respectively*

The proportion of results recorded as intermediate, varied between 0.1 and 0.5%, according to the organism and the antibiotic tested for resistance; these were included in the resistant category as is common practice (Heginbothom *et al*. 2004). The recording of specimen site varied by laboratory, with some laboratories providing more detail than others (e.g. Left nostril as opposed to Ear, Nose and Throat (ENT)). In order for the data to be pooled across laboratories, specimens were re-coded to the following groups: ENT, Sputum, Eye, Genital and Other (including blood, skin, wounds and urine).

6.2.2 Allocating practice codes to individual samples

For each isolate an address of the establishment that submitted the sample for testing was provided. Since our main aim was to examine the association between antibiotic consumption and resistance at a general practice level, all general practices from this list of establishments (n=811) were identified. Locations identified as non-general practice establishments (occupational health units, child health centres, family planning clinics, prisons, rehabilitation day units, private clinics and also English practices sending samples to Welsh laboratories), were excluded (n=75).

Each unique location was manually allocated a unique identification W-code (see section 3.2.3) using a variety of methods such as the NHS directory (http://www.wales.nhs.uk/directory.cfm) and internet searching tools (e.g. Google). W-codes were then cross-checked with a limited list of practice W-codes, names and addresses provided by DataStore. Any location names that could not reliably be

linked to a W-code were excluded (n=14). Codes were combined where the location name of the practice could not allow a definite match to a W-code, to ensure that it could be linked appropriately to dispensing data. For example, codes for practices were combined and data pooled if branches of a main practice merged over the time period or several separate practices within one area were indistinguishable and could not be reliably allocated to a unique W-code. This could happen due to ambiguous location names and because GPs were not identified by name.

In total, 722 general practice names were allocated a W-code. This number is greater than the number of actual practices in Wales because of duplication. Some practice names were recorded differently by the same laboratory or samples from practices were sent to more than one laboratory and they recorded the practice name differently. For example, samples from a practice in Llanrwst, North Wales were sent to the Bangor, Rhyl and Cardiff laboratories and the location name recorded differently in each, therefore creating three different location names for allocation of a W-code. After these were resolved, there were 437 unique general practices from which data could be analysed. Again, to ensure complete practice anonymity the Prescribing Services Unit (PSU) based in NWIS allocated the encrypted practice codes to replace the identifiable W-codes; all identifiable datasets were subsequent destroyed. This allowed the linkage of this data to antibiotic dispensing data and practice characteristics (practice deprivation quintile (based on Townsend scores), single-handed status of the practice (single or multi-handed)) used in Chapter 5.

Some practices (n=62 out of 438) were served by many laboratories (13 served by three laboratories, 49 served by two laboratories). In all cases, one laboratory processed the majority of samples with the other laboratories handling a small number. For the purpose of analysis, the laboratory in which the majority of samples were tested was used to ensure that practices were nested exclusively within one laboratory.

6.2.3 Data quality within laboratories

In the past, many methods of antimicrobial resistance testing were used in different laboratories leading to variations in laboratory definition of resistance (for example,

differing minimum inhibitory concentration (MIC) breakpoints). In 1998, the standardized method of disc testing was published by the British Society for Antimicrobial Chemotherapy (BSAC) Working Party on Susceptibility Testing, with a further update in 2000 (British Society for Antimicrobial Chemotherapy Working Party 2008). In the late 1990s, uptake of this method was variable in Wales but general adoption of the method was seen from early 2001. By 2006, all but one laboratory used a combination of the BSAC standardized disc sensitivity method, and the BD Phoenix automated AST/ID system. All laboratories involved participated in the United Kingdom National External Quality Assessment Service scheme and attained acceptable results. With laboratories using the same method there is a real opportunity to combine data, so that levels of resistance in Wales can be examined, and changes detected.

6.2.4 Potential bias in resistance data

Although methodologies used within Welsh microbiology laboratories have become standardised, allowing resistance rates to be compared, bias may still occur in resistance data. Two papers have been published on potential biasing/confounding effects in resistance data and their impact on regional surveillance of resistance (Magee *et al*. 2004; Heginbothom *et al*. 2004). They found that as a result of certain laboratory practices, published resistance rates may be biased and not representative of the true rate in the population. Therefore, to ensure appropriate interpretation of results, three potential sources of bias were examined: (1) variation between practices regarding submission of microbiological samples to laboratories for analysis; (2) variations in resistance testing by laboratories and (3) repeated testing of isolates with the same resistance pattern from the same patient.

6.2.4.1 *Selective sampling at practice level*

A GP will not submit for testing a sample from every patient presenting with a suspected bacterial infection or with symptoms of an infection. Routine resistance data only covers community infections in samples that are actually submitted by GPs and these are bound to be selective in some way. For example, one study found that GPs were more likely to send in urine samples from children and also from patients

who were young, pregnant or had recurrent infections/symptoms (Hillier *et al*. 2006). It is also believed that specimen submission strategies are biased, with more specimens submitted from patients with resistant pathogens and thus not responding to antibiotic therapy (Magee *et al*. 2004); if this is the case then there is a potential overestimation of true population resistance rates. The effects of bias caused by the selective submission of samples could partly be quantified by examining the relationship between the practices' resistance rates (number of resistant samples per 100 tested isolates) and sampling rates (number of samples per 100 practice population). Therefore, sampling data, consisting of the total number of samples sent to a laboratory by a practice during the period January 1998 to December 2006, was obtained from Datastore for 11 of the 18 Welsh and Welsh border laboratories serving Welsh practices. These gave the number of samples sent by the practice per month, subdivided by the site the specimen was taken from (ENT, Sputum, Eye, Genital and Other) and the laboratory to which it was sent for testing.

If the data do show sampling bias, there may be an association between sampling and resistance rates. To investigate this, an annual sampling rate per 100 practice population was calculated for each practice based on all samples submitted by the practice and the relationship between resistance and sampling was explored.

6.2.4.2 *Selective testing at laboratory level*

Selective testing could occur if a laboratory only tested resistance to a certain antibiotic against selected subgroups of an organism type. There are many reasons why a minority of isolates might have been tested for resistance to a particular antibiotic. For example, laboratories may have changed their policy on which antibiotics were tested and therefore the proportion of isolates tested may vary over time. Laboratories may also be more likely to test isolates if they came from a particular site (e.g. isolates from eyes given 'topical antibiotics'). Selective testing could also occur if isolates were tested with specific antibiotics due to lack of response to first-line antibiotics or because the antibiotic had been identified as having been prescribed to the patient.

To identify any possible biases occurring at laboratory level, and to reduce the effect of selective testing on the published rates, the proportion of isolates tested against an antibiotic by laboratory was chosen as a useful indicator of selective testing (number of isolates tested for resistance/total number of isolates submitted for testing x 100). For the purposes of this study, if a laboratory had <80% of isolates tested this would indicate possible selective testing. Resistance rates were pooled from the laboratories deemed as non-selective (≥80% isolates tested) for comparison with the selective laboratory resistance rate.

If a laboratory demonstrated possible selective testing for an antibiotic/organism combination and had a higher resistance rate than the pooled non-selective laboratory estimate, then further investigations were carried out to examine what reasons may account for selective testing. Inconsistent patterns were sought in the percentage of isolates tested by year of specimen submission (testing due to policy changes), specimen group (site-specific testing) and multiple-resistance to other antibiotics (second-line testing). For laboratories demonstrating higher resistance rates and evidence of selective testing then the relevant data were excluded.

If a laboratory had <80% of isolates tested and had a lower resistance rate than the pooled non-selective laboratory estimate, then no further examination was carried out and that particular laboratory/organism/antibiotic combination was included for analysis. No further analysis was undertaken if a laboratory had <80% of isolates tested but only a small number of isolates submitted for testing (<10).

6.2.4.3 *Duplicate testing*

Repeat testing occurred if a patient had multiple specimens submitted and tested from a single infection episode, possibly because initial treatment failed or because the infection resolved slowly despite appropriate therapy. Duplicate isolates were defined as multiple isolates of the same organism with the same resistance pattern from the same patient and were flagged by Datastore. Matching on resistance pattern was carried out using soft matching so resistance did not match if an antibiotic for the first isolate was R and the second isolate was S (or vice-versa). They would

match however if the resistance combinations were R-I or S-I, and a blank result (indicating that it was not tested) would be matched with any other result. Duplicates could potentially lead to a biased estimate of the prevalence of resistance in a population, although previous work in this area showed that the inclusion of repeat isolates made little difference to resistance estimates (Magee *et al*. 2004). To ensure that only new infections were included, duplicates that occurred within 91 days of the initial isolate were removed from the dataset. The cut-off of 91 days was taken to reflect the maximum duration between two samples being part of the same infection or organism and this threshold is recommended for distinction of continuing from repeat infections for infectious diseases in Wales (Wales Office of Research and Development for Health and Social Care Report 2005; Magee *et al*. 2004).

6.3 Statistical analysis

For the purpose of all analyses the following organism/antibiotics were considered due to their high level of resistance and/or clinical importance because of usage for these infections:

- *H. influenzae* and amoxicillin resistance
- *H. influenzae* and tetracycline resistance
- *S. pneumoniae* and penicillin (including amoxicillin) resistance
- *S. pneumoniae* and erythromycin resistance
- *S. pyogenes* and erythromycin resistance.

All analyses were restricted to "Up-to-Standard" (UTS) practices as defined in Chapter 5 that submitted an isolate. The representativeness of the UTS included practices were compared to those practices deemed as not UTS on practice based characteristics (e.g. single handed status, age of GPs, sampling rate) using t-tests, Mann Whitney test and χ^2 test depending on the type of outcome.

6.3.1 Trends in resistance rates

Resistance rates (number of resistant isolates / number of isolates tested) and testing rates (number of isolates tested / number of isolates submitted) were calculated per

annum. A basic single-level linear regression was undertaken initially to establish overall trends in resistance rates. Multilevel modelling was then used to ascertain trends in resistance rates (using the above organism/resistance combinations).

6.3.1.1 *Logistic regression*

A three-level logistic regression model using the result of testing resistance as a binary outcome variable (y_{ijk} = 1 if an isolate *i* in practice *j* and laboratory *k* was resistant, and 0 if sensitive) was used to account and correct for variation at the level of the laboratory, general practice, and individual isolate. The three-level random intercept model logit model takes the form:

$$y_{ijk} = logit(\pi_{ijk}) = log\left(\frac{\pi_{ijk}}{1-\pi_{ijk}}\right) = \beta_{0jk} + \beta_1 x_{ijk}$$

where

$$\beta_{0jk} = \beta_0 + v_{0k} + u_{0jk}$$

The intercept consists of three terms: a fixed component β_0 and a laboratory and general practice specific component, v_{0k} and u_{0jk}. As before, these are assumed to follow Normal distributions with mean zero and variances σ^2_{v0} and σ^2_{u0}.

For discrete response models, maximum likelihood estimation is computationally intensive and therefore quasi-likelihood methods are used (Rasbash *et al*. Centre for Multilevel Modelling, University of Bristol). These procedures use a linearisation method based on the Taylor series expansion which transforms a discrete response model to a continuous response model. After applying the linearisation, the model is then estimated using iterative generalised least squares (IGLS) or reweighted IGLS (RIGLS). The transformation to a linear model requires an approximation to be used. The types of approximation available in MLwiN are: marginal quasi-likelihood (MQL) and predictive (or penalized) quasi-likelihood (PQL). Both of these methods can include either 1st order terms or up to 2nd order terms of the Taylor series expansion. The 2nd order using a second order penalised quasi-likelihood (2nd order PQL) approach is preferred as the default of 1st order marginal quasi-likelihood (MQL) can sometimes give crude approximations that are biased downwards

especially if level 2 units are small or the response proportion is extreme. For this reason we began with the 1st order MQL procedure to obtain starting values for the 2nd order PQL procedure.

6.3.1.1.1 *Interpretation of coefficients*

Given:

$$y_{ijk} = logit(\pi_{ijk}) = log\left(\frac{\pi_{ijk}}{1-\pi_{ijk}}\right) = \beta_{0jk} + \beta_1 x_{ijk}$$

Taking exponentials of each side then:

$$\left(\frac{\pi_{ijk}}{1-\pi_{ijk}}\right) = exp^{\beta_{0jk}} \times exp^{\beta_1 x_{ijk}}$$

If x is increased by 1 unit then:

$$\left(\frac{\pi_{ijk}}{1-\pi_{ijk}}\right) = exp^{\beta_{0jk}} \times exp^{\beta_1 (x_{ijk}+1)} = exp^{\beta_{0jk}} \times exp^{\beta_1 x_{ijk}} \times exp^{\beta_1}$$

This can be interpreted as the multiplicative effect on the odds for a 1-unit increase in x. If x is binary then exp^{β_1} can be interpreted as the odds ratio (OR), comparing the odds for units with x=1 relative to the odds for units with x=0. Parameter estimates and standard errors (SEs) are presented alongside the ORs and 95% confidence interval (CIs).

For the multilevel modelling, time was recalculated as study years (from April to March) to reflect the study period used by the dispensing data. Therefore the study period ran from April 1998 to March 2006, thus covering 8 years (for example April 1998 to March 1999 is referred to as 1998 for simplicity). The model also included the following important individual sample and practice characteristics as explanatory variables: age group (0-4, 5-15, 15-64, 65-84, 95+ years) and gender of the person from whom the sample was taken, site where the specimen was taken (sputum, ENT, eye, genitalia, other), the year the specimen was submitted (study year), practice deprivation quintile (based on Townsend scores), single-handed status of the practice (single or multi-handed), the average age of GPs and the percentage of male GPs

within a practice, and sampling rate (as described in section 6.2.4.1).

6.3.2 Association between antibiotic dispensing and resistance

Associations between resistance (using the above organism/resistance combinations) and antibiotic dispensing (using broad spectrum penicillin (BSP), beta-lactams, macrolides, tetracyclines) were analysed. Lagged dispensing is calculated as the sum of items dispensed in the quarter that the isolate was submitted plus the three quarters prior to that. As before, a three-level logistic regression model was used and where there were significant associations between resistance and lagged antibiotic dispensing, significant individual and practice characteristics were also incorporated in the model. Interactions between the study year and lagged dispensing were modelled to allow for different associations between resistance and lagged dispensing in different study years. Again parameter estimates and SEs are presented alongside ORs with 95% CIs. The ORs presented show the odds of resistance at the 75^{th} percentile of the lagged dispensing distribution compared to the 25^{th} percentile.

6.3.3 Duplicate isolates

Duplicate isolates were excluded from all main analyses but were also compared to non-duplicate isolates to explore any differences with regards to resistance, dispensing and individual patient and practice characteristics. A three-level logistic regression model was fitted with the individual binary outcome (duplicate or not) as the outcome and included study year, individual patient, isolate (including resistance) and practice characteristics. All significant variables were included in the final multivariate model.

6.3.4 Changes in antibiotic dispensing and resistance

Practices that submitted isolates in both 1998 and 2005 were included in a separate analysis to explore the relationship between practice level changes in total antibiotic dispensing and changes in antibiotic resistance. Practices were grouped into quartiles based on their change in total antibiotic dispensing data between 1998 and 2005. Resistance rates for 1998, 2005 and the actual change in rates (with 95% CIs) were compared between these quartiles. Additionally practices were also grouped into

quartiles based on their separate changes of BSP, tetracycline and macrolide dispensing, and these were compared to changes in resistance for appropriate isolates. For example, in *S. pneumoniae*, change in erythromycin resistance was compared between quartiles based on the reduction of both total antibiotic and macrolide dispensing.

6.3.5 Sensitivity analyses

Since the main aim of this thesis was to examine RTIs, all models were fitted using data on all isolates (from all specimen sites) and separately on isolates from sputum samples (taken to determine a chest infection) and swabs taken from ENT regions. Statistical analyses were undertaken using SPSS for Windows (version 16.0) and MLwiN (version 2.11) after transfer of data as Access and Excel files.

6.4 Results

6.4.1 Microbiology data

Over the nine year study period (January 1998 to December 2006) the eleven Welsh laboratories received 27,614 *H. influenzae* isolates from 431 practices, 13,307 *S. pneumoniae* isolates from 422 practices and 19,640 *S. pyogenes* isolates from 423 practices. These three datasets were restricted to isolate data from practices deemed to have reliable populations, previously identified during the quality process of dispensing data (section 5.2.4). Although around 65 practices had been excluded from each dataset (accounting for 16% of practices), on average only 8% of isolates were excluded.

A total of 25,453 *H. influenzae* isolates remained from 363 UTS practices (covering 84% of the Welsh population), 12,256 *S. pneumoniae* isolates from 358 practices and 17,927 *S. pyogenes* isolates from 360 practices. Table 6.2 shows the practice characteristics for practices included in, and excluded from, the main analyses for *H. influenzae* isolates.

Table 6.2 Practice characteristics for included and excluded practices for *H. influenzae* isolates

	Included N=363	**Excluded N=68**	**Test statistic, p-value**
Practice population Total (% of Welsh population[i])	2,481,342 (84%)	228,060 (8%)	-
Practice population Median (25^{th} to 75^{th} percentile)	6,422 (4,303 to 8,783)	4,216 (2,190 to 6,555)	MW, p<0.001
Single-handed N (%)	49/359 (13.6)	14/51 (27.5)	χ^2=6.54,p=0.011
Practice deprivation[ii] Mean (sd)	0.12 (1.86)	0.59 (2.14)	t=1.57, p=0.116
Age of GPs (years) Mean (sd)	49.81 (6.37)	49.38 (6.84)	t=0.44, p=0.657
% of male GPs Median (25^{th} to 75^{th} percentile)	66.67 (50-100)	62.50 (50-100)	MW, p=0.238
Average sampling per 100 practice population (98-06) Median (25^{th} to 75^{th} percentile)	18.14 (12.85 to 23.13)	13.17 (2.40 to 22.51)	MW, p<0.001

[i] *Official estimated Welsh population was 2,965,900 (taken on June 2006) (Welsh Assembly Government Aug 2007),* [ii] *Practice deprivation based on Townsend 2001 scores*
All other practice characteristics taken as practice's current state (June 2007)

As found previously, excluded practices were more likely to have been single-handed and hence have a lower practice population ($p=0.011$ and $p<0.001$ respectively) than included practices. They also did not submit as many samples over the total period. Although only results for *H. influenzae* isolates are displayed, the results for both *S. pneumoniae* and *S. pyogenes* isolates are similar. Some practices were not included in these analyses since they either did not submit any samples to a laboratory using Datastore. This will be taken into consideration in the discussion. Table 6.3 shows the characteristics of the patients from whom these isolates were obtained and at a practice level.

Table 6.3 Characteristics of the patients with *H. influenzae, S. pneumoniae and S. pyogenes* infections

	H. influenzae	***S. pneumoniae***	***S. pyogenes***
Total isolates submitted (number of practices)	25,453 (363)	12,256 (358)	17,927 (360)
Average number of isolates submitted per annum	2,822	1,362	1,992
Average number of isolates submitted per annum, range by laboratory	100 to 457	33 to 231	77 to 379
Age group (years) N (%)			
0-4	7,007 (27.7)	5,170 (42.5)	2717 (15.3)
5-15	918 (3.6)	970 (8.0)	4595 (25.8)
16-24	494 (2.0)	206 (1.7)	2075 (11.7)
25-44	2,512 (9.9)	1,113 (9.1)	4643 (26.1)
45-64	6,971 (27.5)	2,171 (17.8)	2158 (12.1)
65-84	6,884 (27.2)	2,303 (18.9)	1290 (7.2)
85+	528 (2.1)	243 (2.0)	328 (1.8)
Gender N (%) Male	11,610 (46.4)	5,762 (48.3)	6,072 (34.7)
Specimen N (%)			
Sputa	17,081 (67.1)	4,997 (40.8)	150 (0.8)
ENT	2,187 (8.6)	2,220 (18.1)	7977 (44.5)
Eye	4,329 (17.0)	3,358 (27.4)	114 (0.6)
Genitalia	487 (1.9)	160 (1.3)	2528 (14.1)
Other	1,369 (5.4)	1,521 (12.4)	7158 (39.9)
Duplicates (≤91 days between samples) N (%)	2,368 (9.3)	964 (7.9)	973 (5.4)

H. influenzae isolates tended to be submitted from older patients (median age 52 years old) whereas *S. pyogenes* and *S. pneumoniae* isolates were submitted from younger patients (median ages of 21 and 19 years old respectively). The majority of *H. influenzae* and *S. pneumoniae* isolates were found in sputum samples whereas *S. pyogenes* isolates were found in ENT sites and the other category (around 35% were

taken from wound swabs). The proportion of duplicates identified varied by organism; duplicates were excluded from the main analyses. All laboratories continuously supplied data over the 9 year period apart from one which contributed data only from 2001.

6.4.2 Selective testing at laboratory level

For the five organism/antibiotic combinations of interest, a minimal amount of selective testing (<80% of isolates tested) was seen by laboratories. Where ≥80% of isolates were tested by laboratory and year of sample, inter-laboratory variation estimates were likely to have been attributed to other effects, e.g. methodology or real variation in resistance levels. For *H. influenzae* isolates, selective testing for resistance to tetracycline was practised in one laboratory in 2002 and 2003, resulting in the exclusion of 3103 (12.2%) isolates (275 were also duplicates). For *S. pneumoniae* isolates, selective testing of resistance to penicillin was practised in one laboratory in 2002 resulting in the exclusion of 168 (1.4%) isolates (13 were also duplicates). These isolates were excluded since the percentage of tested samples was low and resistance was higher than the overall average. They were excluded from any further analyses to avoid potential bias to resistance rates. There was no evidence of selective testing in *S. pyogenes* isolates. The final numbers of submitted isolates available for analysis are shown in Table 6.4.

Table 6.4 Summary of testing and resistance incidence (N) and rates (%) by year of isolate - submission for all isolates (excluding duplicates and selectivity)

Organism – Antibiotic resistant to		**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**Total**	**Change**[i]
***H. influenzae* – Amoxicillin**	*N isolates*	2,447	2,393	2,476	2,643	2,784	2,784	2,525	2,526	2,507	**23,085**	
	N tested	2,328	2,275	2,382	2,511	2,664	2,657	2,412	2,416	2,386	**22,031**	
	N resistant	500	442	515	512	543	479	404	395	460	**4,250**	
	% tested[ii]	95.1	95.1	96.2	95.0	95.7	95.4	95.5	95.6	95.2	**95.4**	0.1
	% resistant[iii]	21.5	19.4	21.6	20.4	20.4	18.0	16.7	16.3	19.3	**19.3**	-2.2
***H. influenzae* – Tetracyclines**	*N isolates*	2,140	2,091	2,146	2,359	2,463	2,462	2,232	2,196	2,168	**20,257**	
	N tested	1,563	1,514	1,506	1,703	1,716	1,596	1,383	1,389	1,093	**13,463**	
	N resistant	39	37	26	26	20	17	14	15	17	**211**	
	% tested	73.0	72.4	70.2	72.2	69.7	64.8	62.0	63.3	50.4	**66.5**	-22.6
	%resistant	2.5	2.4	1.7	1.5	1.2	1.1	1.0	1.1	1.6	**1.6**	-0.9
***S. pneumoniae* – Erythromycin**	*N isolates*	1,224	1,107	1,116	1,259	1,293	1,334	1,260	1,341	1,358	**11,292**	
	N tested	1,071	974	1,029	1,163	1,221	1,256	1,186	1,258	1,296	**10,454**	
	N resistant	81	75	70	80	88	131	103	128	152	**908**	
	% tested	87.5	88.0	92.2	92.4	94.4	94.2	94.1	93.8	95.4	**92.6**	7.9
	%resistant	7.6	7.7	6.8	6.9	7.2	10.4	8.7	10.2	11.7	**8.7**	4.1
***S. pneumoniae* – Penicillin**	*N isolates*	1,224	1,108	1,116	1,259	1,138	1,334	1,260	1,341	1,358	**11,138**	
	N tested	1,178	1,081	1,088	1,225	1,114	1,304	1,220	1,313	1,335	**10,858**	
	N resistant	50	35	28	30	30	47	46	45	51	**362**	
	% tested	96.2	97.6	97.5	97.3	97.9	97.8	96.8	97.9	98.3	**97.5**	2.1
	%resistant	4.2	3.2	2.6	2.4	2.7	3.6	3.8	3.4	3.8	**3.3**	-0.4
***S. pyogenes* – Erythromycin**	*N isolates*	1,839	1,790	2,093	2,019	1,853	2,068	1,933	1,655	1,704	**16,954**	
	N tested	1,798	1,732	2,047	1,987	1,833	2,047	1,913	1,641	1,680	**16,678**	
	N resistant	72	44	66	92	70	85	75	63	75	**642**	
	% tested	97.8	96.8	97.8	98.4	98.9	99.0	99.0	99.2	98.6	**98.4**	0.8
	%resistant	4.0	2.5	3.2	4.6	3.8	4.2	3.9	3.8	4.5	**3.8**	0.5

[i] *Change between 1998 and 2006,* [ii] *Percentage tested for resistance from all isolates (samples with identified organism) submitted for testing*
[iii] *Percentage of resistant samples from all tested isolates*

6.4.3 Trends in isolate testing and resistance data

For all isolates (from all sites), the proportion of organisms tested and proportion resistant were calculated for all organism/antibiotic combinations of interest excluding duplicates and selective testing (Table 6.4). Although testing differed between laboratories, 99.0% of *H. influenzae* isolates were tested for resistance to amoxicillin and this percentage remained static over the study period (0.7% change between 1998 and 2006). Overall, 19.1% of all tested *H. influenzae* isolates were resistant to amoxicillin and resistance decreased by 2.1% over the study period (from 21.2% to 19.1%). After fitting a single level linear regression, the trend indicated a decrease in resistance rates of 0.51% per annum (95% CI =0.06 to 0.95%, p=0.031). Over time, resistance to amoxicillin in *H. influenzae* appeared to be falling until 2004/05 with a rise in 2006 (Figure 6.1).

Only 70.5% of *H. influenzae* isolates were tested for resistance to tetracycline, and testing decreased by 19.6% between 1998 and 2006 (from 73.0% to 53.4% respectively). Overall, 1.6% of all *H. influenzae* isolates were resistant to tetracyclines and resistance significantly decreased over the study period by 0.16% per annum (95% CI=0.04 to 0.27%, p=0.017).

Overall, 97.5% and 99.3% of *S. pneumoniae* isolates were tested for resistance to erythromycin and penicillin (including amoxicillin) respectively, both of which increased slightly over time. Overall, 9.4% of tested *S. pneumoniae* isolates were resistant to erythromycin and resistance increased significantly over time by 0.52% per annum (β=0.52%, 95% CI=0.17 to 0.87%, p=0.010) with a slight peak in 2003. Resistance to penicillin was lower and stable with only 4.0% of isolates resistant. Overall, 98.7% of *S. pyogenes* isolates were tested for resistance to erythromycin, and testing increased by 1.0% between 1998 and 2006. Overall, 3.9% of tested *S. pyogenes* isolates were resistant to erythromycin with no significant change in rates over time.

Similar trends were seen across all organism/ antibiotic combinations of interest when only sputum and ENT samples were considered (Table 6.5 and Figure 6.2).

Figure 6.1 Trends in resistance rates by organism (excluding duplicates and selectivity) - All isolates

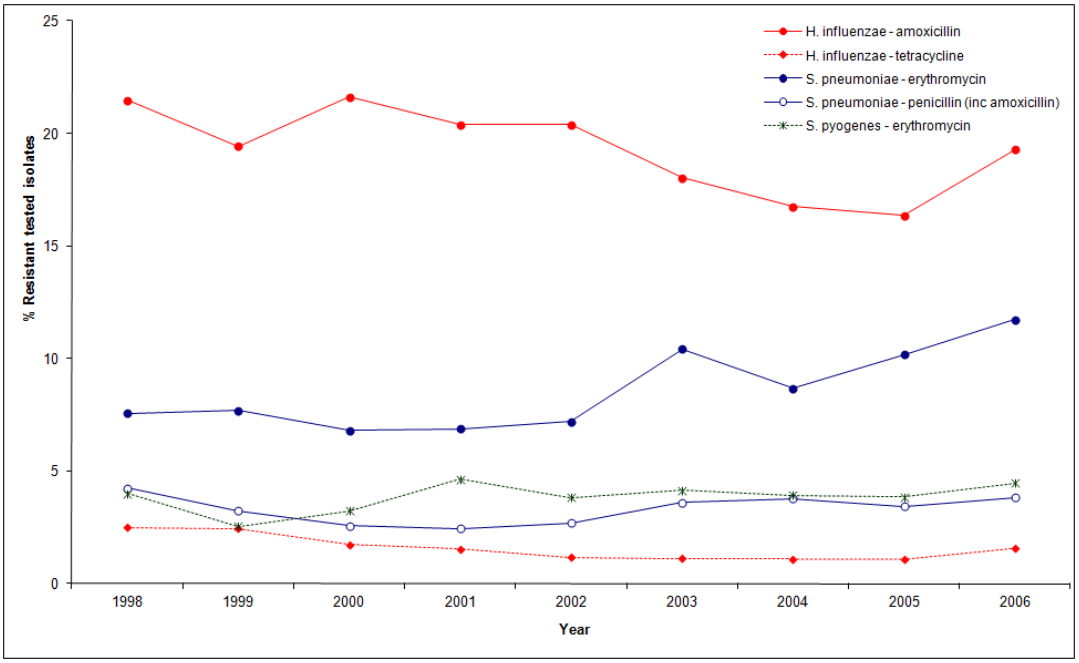


Figure 6.2 Trends in resistance rates by organism (excluding duplicates and selectivity) - Sputum and ENT isolates

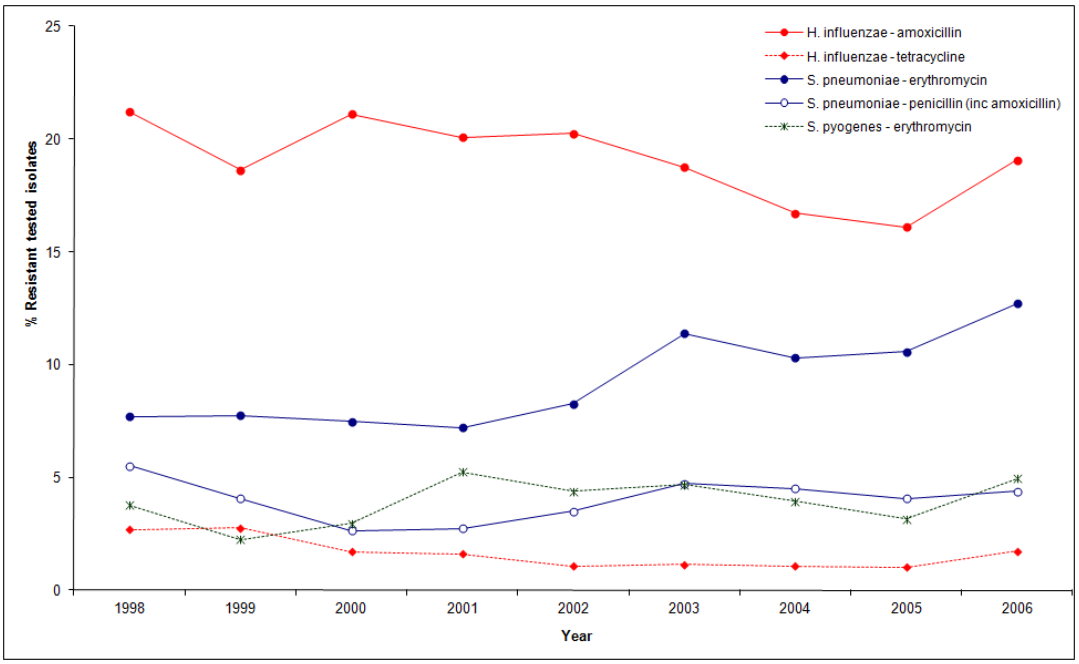


Table 6.5 Summary of testing and resistance incidence (N) and rates (%) by year of isolate - submission for Sputum and ENT samples (excluding duplicates and selectivity)

Organism – Antibiotic resistant to		1998	1999	2000	2001	2002	2003	2004	2005	2006	Total	Change[i]
***H. influenzae* – Amoxicillin**	*N isolates*	1,834	1,810	1,918	2,038	2,121	2,097	1,909	1,898	1,829	**17,454**	
	N tested	1,816	1,788	1,895	2,002	2,110	2,086	1,898	1,888	1,798	**17,281**	
	N resistant	385	333	400	402	427	391	317	304	343	**3302**	
	% tested[ii]	99.0	98.8	98.8	98.2	99.5	99.5	99.4	99.5	98.3	**99.0**	-0.7
	% resistant[iii]	21.2	18.6	21.1	20.1	20.2	18.7	16.7	16.1	19.1	**19.1**	-2.1
***H. influenzae* – Tetracyclines**	*N isolates*	1,636	1,608	1,684	1,844	1,907	1,864	1,692	1,668	1,625	**15,528**	
	N tested	1,194	1,192	1,237	1,421	1,418	1,312	1,134	1,167	867	**10,942**	
	N resistant	32	33	21	23	15	15	12	12	15	**178**	
	% tested	73.0	74.1	73.5	77.1	74.4	70.4	67.0	70.0	53.4	**70.5**	-19.6
	%resistant	2.7	2.8	1.7	1.6	1.1	1.1	1.1	1.0	1.7	**1.6**	-1.0
***S. pneumoniae* – Erythromycin**	*N isolates*	755	694	652	771	803	806	760	766	802	**6,809**	
	N tested	727	659	628	749	786	790	747	757	794	**6,637**	
	N resistant	56	51	47	54	65	90	77	80	101	**621**	
	% tested	96.3	95.0	96.3	97.1	97.9	98.0	98.3	98.8	99.0	**97.5**	2.7
	%resistant	7.7	7.7	7.5	7.2	8.3	11.4	10.3	10.6	12.7	**9.4**	5.0
***S. pneumoniae* – Penicillin**	*N isolates*	755	694	652	771	803	806	760	766	802	**6,809**	
	N tested	743	688	644	765	800	804	755	763	798	**6,760**	
	N resistant	41	28	17	21	28	38	34	31	35	**273**	
	% tested	98.4	99.1	98.8	99.2	99.6	99.8	99.3	99.6	99.5	**99.3**	1.1
	%resistant	5.5	4.1	2.6	2.7	3.5	4.7	4.5	4.1	4.4	**4.0**	-1.1
***S. pyogenes* – Erythromycin**	*N isolates*	890	914	929	928	896	930	918	734	754	**7,893**	
	N tested	873	889	914	916	889	918	911	730	747	**7,787**	
	N resistant	33	20	27	48	39	43	36	23	37	**306**	
	% tested	98.1	97.3	98.4	98.7	99.2	98.7	99.2	99.5	99.1	98.7	1.0
	%resistant	3.8	2.2	3.0	5.2	4.4	4.7	4.0	3.2	5.0	3.9	1.2

[i] *Change between 1998 and 2006,* [ii] *Percentage tested for resistance from all isolates (samples with identified organism) submitted for testing*
[iii] *Percentage of resistant samples from all tested isolates*

6.4.4 Multilevel modelling of all isolates

6.4.4.1 *Trends and characteristics of resistance*

A three-level logistic regression model using resistance or sensitive as a binary outcome variable was used to account for variation at the level of the laboratory, general practice, and individual. Univariate analyses were performed for each of the organism/resistance combinations to examine the trends in resistance data. Also examined were the possible explanatory variables of resistance data in relation to the patient characteristics of the submitted sample (age, gender, site) and the practice that submitted it (deprivation, single or multi-handed status, % male GPs, average age of the GPs, sampling rate per 100 practice population). Significant predictors were retained in the multivariate analysis to ascertain which variables independently predicted resistance.

6.4.4.1.1 *H. influenzae isolates and resistance to amoxicillin*

Over the whole study period, from 23,085 samples submitted with a *H. influenzae* isolate, 22,031 (95.4%) were tested. From those tested 4,250 (19.3%) were resistant to amoxicillin and 17,781 (80.7%) were sensitive. Univariate level analyses showed that resistance to amoxicillin was significantly lower between 2003 and 2005 (when compared to 1998) (Table 6.6). Resistance was also significantly lower in the 5-15 and 16-24 year old age group than in the 0-4 year age group and samples sent from the ENT and genitalia area had significantly lower resistance to amoxicillin than those sent from sputum samples. There was significant unexplained variation in resistance rates between laboratories (σ^2_{v0}=0.047 (SE=0.023)) but not between practices. When these significant variables were included in a single model, all remained independently significant predictors of resistance although the association between ENT and 16-24 year olds disappeared.

No associations were found between resistance and gender (β=0.014 (SE=0.035)), practice level deprivation tertile, single-handed status (β=-0.077 (SE=0.077)) average age of GPs (β=0.005 (SE=0.004)), percentage of male GPs (β=0.0006 (SE=0.0010)) or sampling rate (β=-0.034 (SE=0.026).

Table 6.6 Univariate models between amoxicillin resistance and sample characteristics in *H. influenzae* isolates

					95% CI	
		Log_e parameter estimate	**SE**	**OR**	**Lower limit**	**Upper limit**
Year sample collected	1998	Ref	-	-	-	-
	1999	-0.041	0.074	0.96	0.83	1.11
	2000	0.084	0.072	1.09	0.94	1.25
	2001	0.038	0.072	1.04	0.90	1.20
	2002	-0.061	0.072	0.94	0.82	1.08
	2003	-0.215	0.074	0.81	0.70	0.93
	2004	-0.278	0.077	0.76	0.65	0.88
	2005	-0.206	0.075	0.81	0.70	0.94
Age group	0-4	Ref	-	-	-	-
	5-15	-0.349	0.106	0.71	0.57	0.87
	16-24	-0.308	0.136	0.73	0.56	0.96
	25-44	0.049	0.064	1.05	0.93	1.19
	45-64	0.045	0.048	1.05	0.95	1.15
	65-84	0.080	0.048	1.08	0.99	1.19
	85+	0.027	0.123	1.03	0.81	1.31
Specimen	Sputa	Ref	-	-	-	-
	ENT	-0.244	0.068	0.78	0.69	0.90
	Eye	0.065	0.050	1.07	0.97	1.18
	Genitalia	-0.662	0.149	0.52	0.39	0.69
	Other (inc. wound)	0.096	0.084	1.10	0.93	1.30

6.4.4.1.2 *H. influenzae isolates and resistance to tetracyclines*

For the purposes of the multilevel modelling, one laboratory had only one practice that submitted only 3 samples; these were excluded. A total of 20,254 isolates remained after selectivity to testing for tetracycline resistance had been taken into account. Over the whole study period, 13,460 (67%) isolates were tested with 211 (1.6%) testing resistant to tetracycline (and 13,249 (98.4%) sensitive). At a univariate level, resistance was significantly lower from 2000 to 2005 when compared to resistance for 1998 and samples submitted from the 25-84 age groups had significantly higher resistance to tetracyclines than samples submitted from the 0-4 age group (Table 6.7). There was no significant variation in tetracycline resistance between laboratories or practices. When these significant variables were put in a single model, all remained independently significant predictors of resistance.

Table 6.7 Univariate models for tetracycline resistance and sample characteristics in *H. influenzae* isolates

					95% CI	
		Log_e parameter estimate	**SE**	**OR**	**Lower limit**	**Upper limit**
Year collected	1998	Ref	-	-	-	-
	1999	-0.044	0.235	0.96	0.60	1.52
	2000	-0.652	0.279	0.52	0.30	0.90
	2001	-0.572	0.269	0.56	0.33	0.96
	2002	-1.133	0.327	0.32	0.17	0.61
	2003	-0.786	0.299	0.46	0.25	0.82
	2004	-0.796	0.312	0.45	0.24	0.83
	2005	-0.616	0.301	0.54	0.30	0.97
Age group	0-4	Ref	-	-	-	-
	5-15	0.149	0.468	1.16	0.46	2.90
	16-24	0.632	0.470	1.88	0.75	4.73
	25-44	0.684	0.268	1.98	1.17	3.35
	45-64	0.516	0.230	1.68	1.07	2.63
	65-84	0.483	0.232	1.62	1.03	2.55
	85+	1.188	1.066	3.28	0.41	26.51

6.4.4.1.3 *S. pneumoniae isolates and resistance to erythromycin*

Over the study period, from 11,292 reliable *S. pneumoniae* isolates, 10,454 (93%) were tested for resistance. From these a total of 908 (8%) tested resistant to erythromycin and 9,546 (92%) tested as sensitive. Resistance to erythromycin was marginally significantly higher in 2005 when compared to 1998, and there was an age effect with the 5-15 and 25-44 age groups having lower levels of resistance when compared to the 0-4 age group (Table 6.8). Most specimen types had significantly lower resistance level than sputum samples, apart from samples taken from genitalia, and multi-handed practices were more likely to have higher resistance to erythromycin. When these significant variables were put in a single model, all remained independent predictors of resistance apart from single-handed status.

Table 6.8 Univariate models between erythromycin resistance and sample and practice characteristics in *S. pneumoniae* isolates

					95% CI	
		Log_e parameter estimate	**SE**	**OR**	**Lower limit**	**Upper limit**
Year collected	1998	Ref	-	-	-	-
	1999	-0.109	0.168	0.90	0.65	1.25
	2000	-0.148	0.163	0.86	0.63	1.19
	2001	-0.178	0.164	0.84	0.61	1.15
	2002	0.033	0.154	1.03	0.76	1.40
	2003	0.135	0.151	1.14	0.85	1.54
	2004	0.117	0.152	1.12	0.83	1.51
	2005	0.288	0.145	1.33	1.00	1.77
Age group	0-4	Ref	-	-	-	-
	5-15	-0.888	0.186	0.41	0.29	0.59
	16-24	-0.217	0.286	0.80	0.46	1.41
	25-44	-0.342	0.141	0.71	0.54	0.94
	45-64	0.075	0.096	1.08	0.89	1.30
	65-84	0.137	0.093	1.15	0.96	1.38
	85+	0.28	0.218	1.32	0.86	2.03
Specimen	Sputa	Ref	-	-	-	-
	ENT	-0.330	0.101	0.72	0.59	0.88
	Eye	-0.308	0.095	0.73	0.61	0.89
	Genitalia	-0.314	0.31	0.73	0.40	1.34
	Other (inc. wound)	-0.481	0.131	0.62	0.48	0.80
Single-handed status	Single	Ref	-	-	-	-
	Multi	0.339	0.167	1.40	1.01	1.95

6.4.4.1.4 *S. pneumoniae isolates and resistance to penicillin*

Over the study period, from 11,138 reliable *S. pneumoniae* isolates (after selectivity to testing for penicillin resistance had been taken into account), 10,857 (97.5%) were tested for resistance. From these, 361 (3%) tested resistant to penicillin and 10,496 (97%) as sensitive. Resistance to penicillin was significantly lower in 2001 (when compared to 1998), significantly lower in the 5-15 age group and significantly higher in the 45 years plus (when compared to the 0-4 year age group) (Table 6.9). Additionally, samples sent from ENT sites, eye, genitalia and other sites had significantly lower resistance than those sent from sputum samples. There was significant unexplained variation in resistance rates between practices (σ^2_{v0}=0.211 (SE=0.093)) but not between laboratories. Again when these significant variables were put in a single model, all remained independently significant predictors of penicillin resistance.

Table 6.9 Univariate models between penicillin resistance and sample characteristics in *S. pneumoniae* isolates

		Log_e parameter estimate	**SE**	**OR**	**95% Confidence interval**	
					Lower limit	**Upper limit**
Year collected	1998	Ref	-	-	-	-
	1999	-0.284	0.237	0.75	0.47	1.20
	2000	-0.296	0.231	0.74	0.47	1.17
	2001	-0.706	0.261	0.49	0.30	0.82
	2002	-0.356	0.236	0.70	0.44	1.11
	2003	-0.210	0.221	0.81	0.53	1.25
	2004	-0.123	0.219	0.88	0.58	1.36
	2005	-0.125	0.214	0.88	0.58	1.34
Age group	0-4	Ref	-	-	-	-
	5-15	-0.893	0.346	0.41	0.21	0.81
	16-24	-0.015	0.483	0.99	0.38	2.54
	25-44	-0.200	0.209	0.82	0.54	1.23
	45-64	0.484	0.153	1.62	1.20	2.19
	65-84	0.537	0.15	1.71	1.28	2.30
	85+	1.08	0.281	2.94	1.70	5.11
Specimen	Sputa	Ref	-	-	-	-
	ENT	-0.600	0.161	0.55	0.40	0.75
	Eye	-0.838	0.158	0.43	0.32	0.59
	Genitalia	-2.128	1.055	0.12	0.02	0.94
	Other (inc. wound)	-0.813	0.237	0.44	0.28	0.71

6.4.4.1.5 *S. pyogenes isolates and resistance to erythromycin*

No trend existed in resistance to erythromycin in *S. pyogenes* isolates and no sample or practice characteristics were associated with resistance. No other variables were significantly associated with resistance. There was significant unexplained variation in resistance rates between practices (σ^2_{v0}=0.238 (se=0.067)) but not between laboratories.

6.4.4.2 *The relationship between antibiotic resistance and dispensing*

A three-level multilevel logistic regression model was fitted with the individual binary resistance as the outcome and in the first instance included lagged antibiotic dispensing as an explanatory variable. The model was then adjusted for study year and any significant factors identified in the previous section. Table 6.10 shows the initial results from the univariate multilevel model examining the association between antibiotic resistance and lagged dispensing for isolates from all specimens (using ORs and 95% CIs). For any significant associations, the adjusted ORs are also shown.

For *H. influenzae isolates*, there was a significant positive association between amoxicillin resistance and lagged dispensing of BSPs, macrolides, and beta-lactams. For BSPs, resistance was 8% (95% CI=3% to 13%) higher in practices with a lagged dispensing rate at the 75th percentile (3089 dispensed items in the previous year) compared to practices with a lagged dispensing rate at the 25th percentile (1428 dispensed items per annum). Similarly in macrolides, resistance was 5% (0% to 10%) higher for practices that dispensed at the 75th percentile (979 dispensed items) compared to practices that dispensed at the 25th percentile (407 dispensed items). Resistance to beta-lactams was 7% (2% to 13%) higher for practices that dispensed at the 75th percentile (5118 dispensed items respectively) compared to practices that dispensed at the 25th percentile (2418 dispensed items respectively). There were no significant associations between amoxicillin resistance and tetracycline dispensing or between tetracycline resistance and dispensing in any of the antibiotics groups.

After adjusting for year, age and site of specimen the positive association between

resistance to amoxicillin and BSP dispensing remained. The resistance was 5% (0 to 11%) higher in practices that dispensed BSPs at the 75th percentile compared to practices that dispensed at the 25th percentile. For both macrolides and beta-lactams, the associations between dispensing and resistance to amoxicillin became non-significant on inclusion of confounders. More specifically it was the inclusion of the year in the model that diluted the effect and not the site of the specimen or age group.

For *S. pneumoniae* isolates there was a significant positive association between resistance to penicillin and dispensing of tetracyclines; the odds of resistance were 23% (OR=1.23, 95% CI=1.08 to 1.41) higher for practices dispensing at the 75th percentile (595 dispensed items per annum) compared to practices dispensing at the 25th percentile (262 dispensed items per annum). There were no significant associations between resistance to penicillin and BSP, macrolide and beta-lactam dispensing or between resistance to erythromycin and dispensing for any of the antibiotics. After adjusting for year, age and site of specimen, the relationship between penicillin resistance and tetracycline dispensing remained (1.19, 1.04 to 1.37).

For *S. pyogenes* isolates there were significant positive associations between penicillin resistance and dispensing of macrolides and beta-lactams. For macrolides, the odds of resistance were 17% (1.17, 1.05 to 1.31) higher in practices with a dispensing rate at the 75th percentile (1037 dispensed items per annum) compared to practices with dispensing rate at the 25th percentile (434 dispensed items per annum). For beta-lactams, the odds of resistance were 14% (1.14, 1.00 to 1.30) higher in practices with a dispensing rate at the 75th percentile (5061 dispensed items per annum) compared to practices with dispensing rate at the 25th percentile (2555 dispensed items per annum). After adjusting for year and age the relationship between erythromycin resistance and dispensing of macrolides and beta-lactams remained (1.28, 1.14 to 1.45 and 1.04, 1.04 to 1.40).

Table 6.10 Modelling for antibiotic resistance and lagged dispensing in *H. influenzae*, *S. pneumoniae* and *S. pyogenes* isolates for all isolates

Organism	Antibiotic resistance	Lagged antibiotic dispensing	Log_e parameter estimate	SE	Dispensing rate IQR[i]	OR (IQR)[ii] (95% CI)	Adjusted[iii] OR (IQR) (95% CI)
H. influenzae	Amoxicillin	BSPs	0.62	0.18	0.12	1.08 (1.03 to 1.13)	1.05 (1.00 to 1.11)
		Tetracyclines	-0.18	1.15	0.02	1.00 (0.95 to 1.05)	-
		Macrolides	1.02	0.51	0.05	1.05 (1.00 to 1.10)	1.03 (0.98 to 1.08)
		Beta-lactams	0.37	0.14	0.19	1.07 (1.02 to 1.13)	1.04 (0.98 to 1.10)
H. influenzae	Tetracycline	BSPs	1.16	0.68	0.12	1.15 (0.98 to 1.35)	-
		Tetracyclines	5.46	4.04	0.02	1.12 (0.95 to 1.33)	-
		Macrolides	2.14	1.87	0.05	1.11 (0.93 to 1.31)	-
		Beta-lactams	0.52	0.51	0.19	1.10 (0.92 to 1.33)	-
S. pneumoniae	Erythromycin	BSPs	-0.36	0.38	0.12	0.96 (0.87 to 1.05)	-
		Tetracyclines	-0.07	2.32	0.02	1.00 (0.91 to 1.10)	-
		Macrolides	-0.56	1.02	0.05	0.97 (0.89 to 1.07)	-
		Beta-lactams	-0.34	0.29	0.19	0.94 (0.85 to 1.04)	-
S. pneumoniae	Penicillin	BSPs	0.94	0.54	0.12	1.12 (0.99 to 1.28)	-
		Tetracyclines	9.78	3.14	0.02	1.23 (1.08 to 1.41)	1.19 (1.04 to 1.37)
		Macrolides	1.69	1.50	0.05	1.08 (0.94 to 1.24)	-
		Beta-lactams	0.28	0.42	0.19	1.05 (0.90 to 1.23)	-
S. pyogenes	Erythromycin	BSPs	0.77	0.50	0.12	1.10 (0.98 to 1.24)	-
		Tetracyclines	0.70	2.89	0.02	1.02 (0.90 to 1.15)	-
		Macrolides	3.32	1.21	0.05	1.17 (1.05 to 1.31)	1.28 (1.14 to 1.45)
		Beta-lactams	0.70	0.36	0.19	1.14 (1.00 to 1.30)	1.21 (1.04 to 1.40)

[i] *Inter quartile range (IQR) is the difference between the 75th and 25th percentile of the dispensing rate distribution*
[ii] *Odds Ratio (OR) is the odds of resistance at 75th percentile of lagged dispensing distribution compared to the 25th percentile*
[iii] *Adjusted for year sample collected, age group and site of sample*

6.4.5 Multilevel modelling for sputum and ENT samples

The analyses were re-run for sputum and ENT samples only, to examine how associations would differ for the subset of samples which were more relevant to RTIs than all infections.

For *H. influenzae* isolates, resistance to amoxicillin was significantly lower in samples collected in 2004 and 2005 when compared to 1998 (a similar trend to that seen in all samples). Resistance was also lower in ages between 45-84 years old (rather than in the 5-15 age group for all samples). Resistance to tetracycline was comparable to that in all isolates. At the univariate level, the same positive associations held between amoxicillin resistance and dispensing of BSP (1.07, 1.02 to 1.13), macrolides (1.06, 1.00 to 1.12) and beta-lactams (1.07, 1.01 to 1.13) in *H. influenzae* isolates. After adjusting for age and year, only the positive association between BSP dispensing and resistance held (1.06, 1.01 to 1.12). These results are shown in Appendix V.

S. pneumoniae isolates submitted in 2003 were significantly more resistant to erythromycin than those in 1998 and resistance in isolates submitted by 5-15 and 25-44 year olds was significantly lower than in those submitted by 0-4 year olds. This differs from all isolates, where resistance was higher in 2005 and across all age groups (with the exception of those aged 85 and over). For penicillin resistance the same associations held; specimens collected in 2001 were significantly less resistant than those collected in 1998 and specimens submitted by 5-15year olds were significantly less resistant than those submitted by 0-4 year olds. There were no associations between antibiotic dispensing and erythromycin or penicillin resistance in *S. pneumoniae* sputum and ENT isolates.

For *S. pyogenes* isolates, resistance to erythromycin was higher in 2003 when compared to 1998. However, the same associations held between erythromycin resistance and macrolide dispensing in *S. pyogenes* isolates (1.29, 1.12 to 1.48).

There was no significant variation in the relationship between any lagged antibiotic dispensing and resistance at the laboratory and practice level.

6.4.6 Changes in antibiotic dispensing and resistance

6.4.6.1 *H. influenzae isolates*

Of the 363 UTS practices that submitted *H. influenzae* isolates during 1998 to 2005, 275 (76%) practices submitted *H. influenzae* isolates in both 1998 and 2005, with 249 (69%) practices submitting both sputum and ENT samples. Practices submitting samples in both years were included in the following analyses. These practices had significantly larger list sizes, were less likely to be run single-handedly and also had slightly higher sampling rates (Table 6.11). They also had slightly lower levels of antibiotic dispensing than excluded practices in both 1998 and 2005, but these differences were not significant.

Table 6.11 Practice characteristics for included and excluded practices

	Included practices N=275	**Excluded practices N=88**	**Test statistic, p-value**
Practice deprivation Mean (sd)	0.14 (1.80)	0.04 (2.07)	t=0.45, p=0.656
Average sampling rate (1996-2006) Mean (sd)	0.19 (0.07)	0.13 (0.08)	t=6.84, p<0.001
Sampling rate (2006) Mean (sd)	0.22 (0.10)	0.17 (0.11)	t=3.38, p=0.001
Single-handed N (%)	27 (9.9)	22 (25.6)	χ^2=13.66, p<0.001
Practice population (March 2007) Median (25^{th} to 75^{th} percentile)	6843 (5107 to 9339)	4338 (2604 to 6935)	MW, p<0.001
Total antibiotic dispensing rate per 1,000 Median (25^{th} to 75^{th} percentile) **1998**	798.55 (671.00 to 931.52)	834.40 (686.53 to 979.86)	MW, p=0.127
2005	674.61 (578.0 to 786.89)	684.94 (591.67 to 795.39)	MW, p=0.554

Four practices did not have any dispensing data for 1998 and 2005 and therefore 271 (all isolates) and 245 practices (sputum and ENT) were included in the analyses. During the study period, reductions in dispensing were found for all antibiotics except for flucloxacillin and trimethoprim (Table 6.12). Only 5% of the 271 practices increased their total antibiotic dispensing over the period, whilst 18% increased their

BSP dispensing and 36% increased their dispensing of tetracyclines.

Table 6.12 Median dispensed antibiotic items (per 1,000 practice population per annum) in 1998 and 2005 in 271 Welsh practices

Antibiotics	**1998**	**2005**	**Reduction (% decrease)**
Penicillin	62.6	51.4	11.2 (18)
BSPs	327.2	262.0	65.2 (20)
Flucloxacillin	54.3	67.8	-13.5 (-25)
Cephalosporins	72.0	49.6	22.4 (31)
Tetracyclines	52.8	52.3	0.5 (1)
Macrolides	94.9	77.1	17.8 (19)
Quinolones	26.4	21.6	4.8 (18)
Trimethoprim	58.0	62.7	-4.7 (-8)
Beta-lactams	537.8	459.3	78.5 (15)
Total antibiotics	795.0	674.0	121.0 (15)

Quartiles were calculated based on reductions in antibiotic dispensing rates with equal number of practices in each quartile and defined according to the values shown in the final row of Table 6.13. Quartile 1 (75^{th} to 100^{th} percentile) refers to practices that reduced their dispensing the most and quartile 4 (0 to 25^{th} percentile) refers to the practices that reduced it least, or increased their dispensing. For total antibiotics, quartile 1 reduced dispensing by at least 195 items per 1,000 practice population per annum; quartile 2 by between 93 and 195; quartile 3 by between 33 and 93; and quartile 4 by less than 33.

Table 6.13 Quartiles with 5^{th} and 95^{th} percentiles, for reductions in dispensed antibiotic rates (per 1,000 practice population per annum) between 1998 and 2005

	Percentile				
Antibiotics	**95^{th}**	**75^{th}**	**50^{th}**	**25^{th}**	**5^{th}**
Penicillin	42.3	22.1	9.3	-2.4	-21.1
BSPs	237.9	110.1	57.5	12.1	-49.6
Flucloxacillin	19.4	-2.4	-13.3	-24.9	-43.3
Cephalosporins	111.4	49.3	18.0	-3.0	-31.3
Tetracyclines	36.1	12.7	2.2	-9.1	-24.8
Macrolides	94.0	42.3	15.9	-1.2	-32.0
Quinolones	39.2	13.2	3.8	-2.5	-13.4
Trimethoprim	26.7	8.3	-3.7	-13.7	-31.2
Beta-lactams	307.9	147.3	81.1	27.0	-61.5
Total antibiotics	386.5	194.6	93.3	33.3	-61.3

Table 6.14 shows the reduction in amoxicillin and tetracycline resistance by change in dispensing (total, BSPs and tetracyclines) quartile for all isolates. Amoxicillin resistance significantly reduced overall but it fell non-significantly in all quartiles of total antibiotic and BSP dispensing. The differences between quartiles (fourth minus first practice quartiles) were also not significant. For total dispensing, the difference was 0.6% (95% CI= -6.0% to 7.0%); BSPs= 0.6% (95% CI=-6.3% to 7.4%)). For sputum and ENT isolates, the same patterns were seen although the second quartile saw a significant decrease in resistance over time (Appendix VI). Again there was no significant difference between quartiles (fourth minus first practice quartiles) (total dispensing=1.7% (95% CI=-5.7% to 9.1%); BSPs=2.6% (95% CI=-5.1% to 10.4%).

There was no pattern in reductions in tetracycline resistance and quartiles of total antibiotic dispensing reduction for all isolates or in sputum and ENT samples. For all isolates, in practices in the first quartile resistance increased over time whilst for practices in the fourth quartile, resistance fell. There was a significant difference between the change in tetracycline resistance in the first and fourth practice quartiles (3.3%,95% CI= 0.5% to 6.2%). The same pattern was seen in sputum and ENT samples but the difference between the change in tetracycline resistance in the first and fourth practice quartiles was no longer significant (3.0%,95% CI= -0.3% to 6.4%) (Appendix VI).

Tetracycline resistance significantly reduced overall but it fell non-significantly in all quartiles of tetracycline dispensing. The difference between decreases in tetracycline resistance in the first and fourth practice quartiles was also not significant (1.3% (-1.7% to 4.3%). The same pattern was seen in sputum and ENT samples and the difference between the change in tetracycline resistance in the first and fourth practice quartiles was 2.1% (-1.4% to 5.7%) (Appendix VI).

Table 6.14 Changes (%) in resistance to amoxicillin and tetracycline over an 8-year period, in all *H. influenzae* isolates, by quartile of reductions in:
(a) Total antibiotic dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Amoxicillin resistance					
1998, %	20.3	21.5	19.5	19.9	20.3
2005, %	18.4	17.3	15.7	17.5	17.3
Change, % (95% CI)	↓1.9 (-3.0 to 6.9)	↓4.2 (-0.4 to 8.9)	↓3.8 (-1.0 to 8.5)	↓2.5 (-1.8 to 6.7)	↓3.0 (0.8 to 5.4)
Tetracycline resistance					
1998, %	1.9	2.9	2.8	3.1	2.7
2005, %	2.5	0.3	2.1	0.3	1.3
Change, % (95% CI)	↑0.6 (-1.9 to 3.1)	↓2.5 (0.5 to 4.7)	↓0.7 (-2.2 to 3.3)	↓2.7 (0.8 to 4.8)	↓1.4 (0.3 to 2.5)

(b) Broad Spectrum Penicillin dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Amoxicillin resistance					
1998, %	22.4	18.8	20.2	20.4	20.3
2005, %	18.7	16.1	18.6	16.1	17.3
Change, % (95% CI)	↓3.7 (-1.5 to 9.0)	↓2.7 (-1.6 to 7.0)	↓1.6 (-3.1 to 6.2)	↓4.3 (-0.2 to 8.7)	↓3.1 (0.8 to 5.4)

(c) Tetracycline dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Tetracycline resistance					
1998, %	2.2	2.0	3.1	3.5	2.7
2005, %	1.3	1.4	1.3	1.3	1.3
Change, % (95% CI)	↓1.0 (-0.9 to 2.8)	↓0.6 (-2.3 to 3.4)	↓1.8 (-0.9 to 4.1)	↓2.3 (-0.6 to 5.1)	↓1.4 (0.3 to 2.5)

6.4.6.2 *S. pneumoniae isolates*

Resistance data for 1998 to 2005 were available for 245 practices for all submitted *S. pneumoniae* isolates and 193 practices for sputum and ENT samples. Characteristics of the practices included in the analysis were similar to those found in the *H. influenzae* isolates except that the total antibiotic dispensing rate in 2005 was slightly (but not significantly) higher in the included practices for *S. pneumoniae.* Two practices did not have any dispensing data and therefore 243 and 191 practices were included in the analyses.

Again reductions were seen in the dispensing of all antibiotics except for flucloxacillin and trimethoprim during the study period. Although the number of practices changed for each type of isolate examined the results are comparable with those found in submitted *H. influenzae* isolate samples (as seen in Table 6.12). Just over 6% of the 243 practices increased their total antibiotic dispensing over the period, whilst 19% increased their BSP prescribing and 30% increased their prescribing of tetracycline. Once again, quartiles were calculated based on change in total dispensing rates with equal number of practices in each quartile and defined according to the values shown in the final row of Table 6.15.

Table 6.15 Quartiles with 5th and 95th percentiles for decrease in dispensed antibiotics rates (per 1,000 practice population) between 1998 and 2005

	Percentile				
Antibiotics	**95th**	**75th**	**50th**	**25th**	**5th**
Penicillin	41.9	22.6	9.5	-2.0	-22.0
BSPs	231.2	107.4	56.7	12.2	-51.0
Flucloxacillin	12.6	-2.5	-12.8	-24.6	-42.8
Cephalosporins	109.9	47.9	14.9	-5.1	-33.0
Tetracyclines	35.5	12.1	2.6	-9.4	-24.1
Macrolides	88.6	40.2	15.9	1.0	-34.4
Quinolones	44.5	13.2	3.7	-2.9	-14.6
Trimethoprim	25.8	7.2	-4.6	-14.4	-31.4
Beta-lactams	294.8	142.5	76.7	21.8	-66.9
Total antibiotics	370.0	184.9	90.9	28.1	-73.2

Table 6.16(a) shows the reduction in erythromycin and penicillin resistance by change in total antibiotic dispensing quartile for all isolates. The results for sputum

and ENT samples are shown in Appendix VII(a).

For all isolates, most quartiles saw an increase in resistance to erythromycin between 1998 and 2005 with practices in the third quartile significantly increasing. The exception was the fourth practice quartile (practices reducing dispensing the least or increasing). The difference between the changes in erythromycin resistance in the first and fourth practice quartiles was 5.0% (-2.3 to 12.3%). Similar patterns were seen in sputum and ENT isolates with a change between the first and fourth quartiles of 1.7% (-7.3 to 10.8%). Erythromycin resistance was also examined alongside quartiles of change in macrolide dispensing (Table 6.16(b)). For all isolates, a reduction was only seen in the third quartile and quartile 4 had a significant increase in resistance of 7.5% (1.9 to 13.0%). The difference between changes in erythromycin resistance in the first and fourth practice quartiles was -7.3% (-15.0 to 0.4%). A similar difference was seen in sputum and ENT isolates (-6.7%, -16.4 to 3.1%) (Appendix VII(b))

There was no pattern in changes in penicillin resistance by quartiles of dispensing reduction for all isolates or in sputum and ENT samples. For all isolates, the difference between changes in penicillin resistance in the first and fourth practice quartiles was 0.1% (-4.6 to 4.3%). There was no significant difference between decreases in penicillin resistance in the first and fourth practice quartiles for sputum and ENT samples (0.04%, -6.1 to 6.1%).

Penicillin resistance was also examined alongside quartiles of change in BSP dispensing (Table 6.16(c)). For all tested isolates, both the first and fourth quartiles saw a non-significant reduction in penicillin resistance. The difference between decreases in penicillin resistance in the first and fourth practice quartiles was 1.4% (-3.6 to 6.4%). A similar difference was seen in sputum and ENT isolates (1.8%, -5.3 to 8.8%) (Appendix VII(c)).

Table 6.16 Changes (%) in resistance to erythromycin and penicillin over an 8-year period, in all *S. pneumoniae* isolates, by quartile of reductions in:

(a) Total antibiotic dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance					
1998, %	8.4	9.91	4.5	11.0	8.5
2005, %	11.7	12.30	9.6	9.3	10.7
Change, % (95% CI)	↑3.3 (-2.3 to 8.9)	↑2.4 (-2.9 to 8.1)	↑5.1 (0.6 to 9.5)	↓1.7 (-3.1 to 6.7)	↑2.1 (-0.4 to 4.6)
Penicillin (including amoxicillin) resistance					
1998, %	4.5	2.4	5.1	4.3	4.1
2005, %	3.2	4.4	3.8	3.1	3.6
Change, % (95% CI)	↓1.3 (-2.2 to 5.1)	↑2.0 (-1.2 to 5.2)	↓1.3 (-2.2 to 5.1)	↓1.2 (-1.8 to 4.3)	↓0.5 (-1.1 to 2.2)

(b) Macrolide dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance					
1998, %	10.8	6.8	10.0	5.6	8.5
2005, %	11.1	9.8	9.5	13.1	10.7
Change, % (95% CI)	↑0.2 (-5.4 to 5.8)	↑3.0 (-1.5 to 7.8)	↓0.5 (4.3 to 5.3)	↑7.5 (2.0 to 13.1)	↑2.1 (-0.4 to 4.7)

(c) BSP dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Penicillin resistance					
1998, %	5.4	2.4	3.4	5.6	4.1
2005, %	3.9	3.8	4.4	2.7	3.6
Change, % (95% CI)	↓1.5 (-2.5 to 5.9)	↑1.4 (-1.6 to 4.3)	↑1.0 (-2.4 to 4.5)	↓2.9 (-0.2 to 6.2)	↓0.5 (-1.1 to 2.2)

6.4.6.3 *S. pyogenes isolates*

Resistance data for 1998 and 2005 were available for 268 practices for all samples and 151 practices for the sputum and ENT samples, and were used in the analysis. Included practices had lower levels of antibiotic dispensing than excluded practices in both 1998 and 2005. Three practices did not have any dispensing data and therefore 265 practices were analysed for all isolates and 148 for sputum and ENT isolates. The same reductions in dispensing were seen in this sample of practices of all antibiotics except for flucloxacillin, trimethoprim and tetracyclines during the study period. Once again, quartiles were calculated based on change in total dispensing rates with equal number of practices in each quartile and defined according to the values shown in the final row of Table 6.17.

Table 6.17 Quartiles with 5th and 95th percentiles for decrease in dispensed antibiotics rates (per 1,000 practice population) between 1998 and 2005

	Percentile				
Antibiotics	**95th**	**75th**	**50th**	**25th**	**5th**
Penicillin	44.9	23.5	9.8	-1.9	-20.4
BSPs	235.5	109.8	59.0	13.6	-42.5
Flucloxacillin	16.5	-2.9	-12.7	-24.5	-43.5
Cephalosporins	111.3	49.1	18.1	-2.2	-32.7
Tetracyclines	36.4	12.7	2.2	-9.1	-24.3
Macrolides	92.7	45.0	16.5	0.9	-30.9
Quinolones	43.8	13.2	4.0	-3.0	-15.8
Trimethoprim	26.6	8.5	-3.7	-14.1	-30.5
Beta-lactams	294.5	144.9	81.1	29.4	-54.7
Total antibiotics	383.9	191.4	97.8	38.7	-59.7

For all isolates, erythromycin resistance fell in both the second and fourth practice quartiles (based on total dispensing) over time but these changes were not significant (Table 6.18(a)). The difference between quartiles (fourth minus first practice quartiles) was 3.0% (95% CI=-0.5 to 6.5%). In sputum and ENT isolates, an increase was seen across all quarters except for quartile 4 where a significant reduction in resistance rates was observed (3.7%, 0.4% to 6.8%) (Appendix VIII(a)). The change in erythromycin resistance between the first and fourth practice quartiles (fourth minus first practice quartiles) was significantly different (6.1%, 0.8 to 11.3%).

Erythromycin resistance was also examined alongside quartiles of change in macrolide dispensing (Table 6.18(b)). Again no significant reductions were seen and the difference between changes in erythromycin resistance in the first and fourth practice quartiles was -0.8% (-4.3 to 2.7%). For sputum and ENT samples, only the fourth quartile reduced their erythromycin resistance over the period and the differences between quartiles (fourth minus first practice quartiles) were non-significant (1.9% (-3.1 to 7.0%)) (Appendix VIII (b)).

Table 6.18 Changes (%) in resistance to erythromycin over an 8-year period, by quartile of reductions in total antibiotic dispensing in *S. pyogenes* isolates

(a) Total antibiotic dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance					
1998, %	3.7	4.6	2.9	4.2	3.8
2005, %	4.4	3.2	4.2	1.9	3.4
Change[i], % (95% CI)	↑0.8 (-2.2 to 3.6)	↓1.4 (-1.7 to 4.4)	↑1.3 (-1.6 to 4.0)	↓2.3 (-0.1 to 4.5)	↓0.4 (-0.9 to 1.7)

(b) Macrolide dispensing

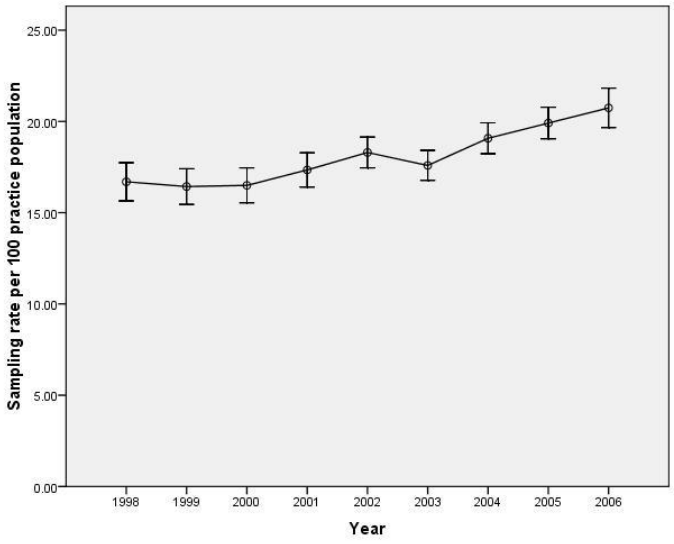
	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance`					
1998, %	5.1	2.7	4.2	3.2	3.8
2005, %	3.2	4.2	4.0	2.1	3.4
Change, % (95% CI)	↓1.9 (-0.9 to 4.7)	↑1.5 (-1.4 to 4.1)	↓0.2 (-2.7 to 2.9)	↓1.1 (-1.4 to 3.6)	↓0.4 (-0.9 to 1.7)

[i] *Resistance in 1998 minus 2005*

6.4.7 Sampling data

To examine the extent of the sampling bias in the dataset, an annual sampling rate was calculated for each practice based on specimens from all sites (sputum, wound, urine etc). As there is limited evidence on general practices' rates of submissions of samples no prior hypothesis is offered. It is therefore unclear whether practices with low or high sampling rates have higher resistance rates. For the 363 UTS practices that submitted *H. influenzae* isolates, sampling rates (number of samples submitted per 100 practice population per annum) ranged from 0.01 to 76.01 per 100 practice population (mean rate =18.08 (SD=8.80)). On average, in these practices sampling rates increased over the study period from 16.69 in 1998 to 20.74 in 2006 per 100 practice population (Figure 6.3).

Figure 6.3 Trends in sampling rates for practices submitting *H. influenzae* isolates between 1998 and 2006 (average rate and 95% confidence interval)



In section 6.4.4.1 we identified that practice level annual sampling rates were not significantly associated with resistance in any of the isolates examined. What practice characteristics are associated with high sampling? At the univariate level, multi-handed practices (β=2.661, (SE=1.164)), younger GPs (β=-0.382 (SE=0.060)), fewer male GPs per practice (β=-0.058 (SE=0.018) were associated with higher sampling. The sampling rate increased over the study period (β=0.560 (SE=0.034)). When these significant explanatory variables were entered into a multivariate model only year (β=0.547 (SE=0.034), p<0.001) and average age of the GPs (β=-0.380

(SE=0.060), p<0.001) independently predicted the sampling rate per 100 practice population. There was significant unexplained variation in resistance rates between practices (σ^2_{v0}=53.64 (SE=4.32)).

6.4.8 Duplicate isolates

6.4.8.1 *Trends in duplicates*

As described in Table 6.3, from 25,453 *H. influenzae* isolates from 363 UTS practices, 2,368 (9%) were flagged as duplicates (using the 91 day rule), in *S. pneumoniae* isolates 964 (8%) and in *S. pyogenes* isolates 973 (5%). These percentages were stable over time and no trends in duplicates were identified between 1998 and 2005.

6.4.8.2 *Association with resistance*

Table 6.19 shows the resistance rates for duplicate and non-duplicate isolates for each organism and the difference (with 95% CIs). *H. influenzae* isolates, amoxicillin resistance was significantly higher in non-duplicates than in duplicates but there was no significant difference in resistance to tetracyclines. In tested *S. pneumoniae* isolates, resistance was higher in non-duplicates although these differences were non-significant. In *S. pyogenes* isolates resistance to erythromycin was significantly higher in duplicates than non-duplicates.

Table 6.19 Resistance rates (%) (N isolates tested) for duplicate and non-duplicate isolates

Organism	Antibiotic	Duplicates	Non-duplicates	Difference (95% CI)
H. influenzae	Amoxicillin	15.4 (2,244)	19.3 (22,031)	-3.9 (-5.4 to -2.3)
	Tetracycline	1.7 (1,544)	1.6 (13,463)	0.1 (-0.5 to 0.9)
S. pneumoniae	Erythromycin	7.8 (874)	8.7 (10,454)	-0.9 (-2.6 to 1.1)
	Penicillin (inc. amoxicillin)	3.1 (928)	3.3 (1,1011)	-0.2 (-1.2 to 1.2)
S. pyogenes	Erythromycin	5.7 (944)	3.8 (16,678)	1.9 (0.5 to 3.6)

6.4.8.3 *Sample and practice characteristics of duplicate isolates*

In an attempt to further understand duplicates, a three-level regression model was fitted with the individual binary outcome (duplicate or not) as the outcome and individual patient, sample and practice characteristics as explanatory variables.

In *H. influenzae* isolates, the multivariate multilevel model showed that amoxicillin resistance, age group, and specimen site were all independently associated with duplicate status (Table 6.20). Duplicates were likely to have lower resistance to amoxicillin and there were significantly fewer of them in the age groups 5 to 44 years and the elderly when compared to the 0 to 4 age group. There were also significantly fewer duplicates in specimens sent from the genitalia area, when compared to sputum samples and significantly more sent from the high sampling practices. There was significant unexplained variation in duplicates between practices (σ^2_{u0}=0.169 (SE=0.029)) but none between laboratories.

Table 6.20 Multivariate model for duplicates in *H. influenzae* isolates

		Log_e parameter estimate	**SE**	**OR (95% CI)**
Amoxicillin resistance		-0.27	0.07	0.76 (0.66 to 0.88)
Age group	0-4	Ref	-	-
	5-15	-0.59	0.17	0.55 (0.39 to 0.78)
	16-24	-1.28	0.29	0.28 (0.16 to 0.50)
	25-44	-0.63	0.16	0.53 (0.39 to 0.73)
	45-64	-0.18	0.15	0.84 (0.62 to 1.13)
	65-84	-0.20	0.15	0.82 (0.61 to 1.11)
	85+	-0.70	0.23	0.50 (0.31 to 0.79)
Specimen	Sputa	Ref	-	-
	ENT	-0.24	0.15	0.79 (0.58 to 1.06)
	Eye	-0.21	0.15	0.81 (0.60 to 1.09)
	Genitalia	-1.15	0.30	0.32 (0.17 to 0.58)
	Other (inc. wound)	0.06	0.17	1.06 (0.76 to 1.49)

In *S. pneumoniae* isolates, age group and specimen site were both independently associated with duplicates. Duplicates were more likely to be observed in samples from 0-4 year olds and also in eye specimens (OR=1.40, 95 CI%=1.04 to 1.90) and

less likely to be seen in ENT samples (0.55, 0.39 to 0.77) relative to sputa. Again there was significant variation in duplicates by practice (σ^2_{u0}=0.117 (SE=0.039)) but not by laboratory.

In *S. pyogenes* isolates, erythromycin resistance and age group were both independently associated with duplicates. Duplicates were more likely to be resistant to erythromycin than non-duplicates (1.40, 1.02 to 1.93), less likely to occur in the younger age groups (5 to 24 years old) and more likely in the older age groups (25 years plus).

6.5 Discussion

6.5.1 Main findings

This study included 25,453 *H. influenzae* isolates, 12,256 *S. pneumoniae* isolates and 17,927 *S. pyogenes* isolates from samples submitted for resistance testing between 1998 and 2006 by around 360 general practices in Wales (covering at least 84% of the Welsh population). In all isolates, significant reductions over time were found in resistance to both amoxicillin and tetracycline in *H. influenzae* isolates, and a significant increase in resistance to erythromycin in *S. pneumoniae* isolates. Similar trends were observed for samples taken from sputum and ENT (linked to the respiratory tract). No such trends were found in resistance to penicillin in *S. pneumoniae* isolates or resistance to erythromycin in *S. pyogenes* isolates. Resistance rates also varied by age group and specimen site for most observed organism/ antibiotic resistance combinations. In particular sputum samples had the highest resistance to tetracyclines and erythromycin in *H. influenzae* isolates, and *S. pneumoniae* and *S. pyogenes* isolates respectively.

The relationship between lagged antibiotic dispensing in the community and resistance was assessed again in isolates from all sites and samples taken from sputum and ENT separately. This was to examine whether practices with higher resistance rates also had higher antibiotic dispensing rates (based on dispensing for the past year), after adjusting for other factors that could also affect resistance rates. In *H. influenzae* isolates, a positive association held between resistance to amoxicillin and the dispensing of BSP, in *S. pneumoniae* isolates between penicillin resistance and tetracycline dispensing, and in *S. pyogenes* isolates between erythromycin resistance and dispensing of macrolides and beta-lactams. For sputum and ENT samples, the same relationship held in *H. influenzae* isolates and also in *S. pyogenes* between resistance to erythromycin and macrolide dispensing. Adjusting for significant confounders such as age group and specimen site made little difference to the strength of the association. Inclusion of the year in which the sample was submitted diluted the association.

If high dispensing is associated with higher resistance, will reducing dispensing lead

to reduced resistance? The potential effectiveness of reducing antibiotic dispensing to contain antibiotic resistance has been questioned (Heinemann *et al*. 2000; Livermore D. 2004) but has been demonstrated in coliform isolates in tested urine samples submitted by GPs (Butler *et al*. 2007). For a subset of practices, the relationship between changes in antibiotic dispensing by general practices and changes in local levels of antibiotic resistance in all and respiratory isolates was examined. There was no clear pattern between changes in dispensing and changes in resistance. In particular, general practices with the greatest reduction in dispensed antibiotics did not show significantly different changes in resistance in any of the isolates and for any of the antibiotics tested, compared with practices that reduced dispensed antibiotics the least.

This study enabled a further exploration into duplicate samples and revealed that, contrary to expectation, duplicates do not have higher resistance to most antibiotics. In fact *H. influenzae* isolates duplicates were likely to have lower resistance to amoxicillin with significantly fewer of them in the 5 to 44 years and elderly age group when compared to those aged 0 to 4 years. However, duplicates in *S. pyogenes* isolates did have higher resistance to erythromycin. There were also significantly more duplicates sent from high sampling practices. This study also allowed the exploration of practices' annual sampling rates (the number of samples sent per practice population). No clear patterns existed between resistance rates and sampling rates and overall rates of sampling increased over the time period of the study.

6.5.2 Strengths and weaknesses of the study

This study has allowed an exploration of the trends in the proportion of submitted isolate samples tested for resistance and the proportion of these samples resistant to the antibiotics tested. We were also able to see how resistance varied by certain sample, patient and practice characteristics, by laboratory and general practice, and examine any associations between resistance and lagged dispensing rates. To our knowledge, this is the first observational study to examine the association between reductions in the rate of antibiotic dispensing at the level of general practice and change in antibiotic resistance in *H. influenzae*, *S. pneumoniae* and *S. pyogenes* isolates.

Resistance data could only be obtained from 11 of the 18 laboratories which serve Welsh general practices but the main analysis still included data from at most 363 practices, covering a population at risk of 84% of the official Welsh population. Whilst the included practices were not entirely representative of the whole of Wales (higher practice populations and less likely to be run single-handedly) and also geographically biased, they were broadly similar to the remaining Welsh practices with respect to their deprivation levels, in the pattern of their sampling, and dispensed antibiotics rate when these data were available for excluded practices.

An attempt has been made to address and quantify any possible bias present in the data to ensure that rates are as true a reflection as possible of resistance in the Welsh population. Routinely collected data using samples submitted by GPs may not necessarily be typical of all infections. Little is known about how representative reported levels of resistance are as the practice of submitting samples to microbiology by general practices vary widely. Systematic sampling of all patients with symptoms of an infection would be ideal but not feasible. A study in which resistance data was obtained from systematic sampling in patients with symptoms suggesting a urine tract infection showed similar resistance rates to a study using routinely collected data (Hillier *et al*. 2007; Butler *et al*. 2007). From this data there is no evidence to suggest that lower sampling rate (practices possibly with selective sampling) are associated with higher resistance rates. Selective testing at a laboratory level was also assessed and laboratories demonstrating selectivity in the samples that were tested were excluded from all analyses.

Whilst duplicates were excluded, as their inclusion may bias estimates of resistance rates, in most cases they were less likely to be resistant (e.g. in the case of amoxicillin resistance in *H. influenzae* isolates). Fewer duplicates were identified in this dataset in comparison with similar community isolates data from Wales (Magee *et al*. 2004). Duplicates however were more likely to be resistant to erythromycin in *S. pyogenes* duplicates although the difference between duplicates and non-duplicates was small (1.9%). When infections from the respiratory tract are examined, by looking at sputum samples and those taken from the ENT regions, there may be even more bias in resistance rates as it is thought that these samples are not submitted routinely unlike, for example, urine samples. The fact that duplicates

are not more resistant is surprising as practitioners are more likely to submit another sample after a non-response to initial antibiotic therapy. The 91 day threshold for identifying duplicates was an arbitrary cut off, adopted due to *"recommendation for distinction of continuing from repeat infection for infectious disease surveillance in Wales"* (Magee *et al*. 2004). Defining the cut-off is difficult as it is likely to vary within person and by organism. It may be that this period is too long; samples identified as duplicates could be isolates from a new period of infection of the same organism. If the cut-off was lower, a proportion of previously defined duplicates would be classed as initial isolates. This would increase the number of samples submitted but given that, for most organisms, duplicates are not more resistant, the resistance rate would decrease.

It would have been of use to have further information regarding the patients that had samples submitted to microbiology and an isolate identified. Whilst we knew their age, gender and the location where the sample was taken from (wound, sputum etc.), we did not have any information such as any co-morbidities or the diagnosis code that was subsequently recorded by the GP. This information would have been useful to further characterise these patients that had an identified isolate and also who were having duplicate samples taken.

As described in section 5.2.1, the amount of dispensed antibiotics at practice level is a proxy for antibiotic consumption in those patients from whom specimens were submitted. Although resistance data was at an individual level, dispensing data was only available at a practice level and data on individual usage were not available. Any effects found in this study between dispensing and resistance are likely to be underestimated as Donnan *et al.* (2004) showed.

Lagged dispensing data, defined here as dispensing summed over the four quarters up to and including the quarter in which the sample was submitted, was used. There is limited evidence to suggest what is an appropriate time lag between being dispensed an antibiotic and an increased risk of resistance to that antibiotic occurring; different (longer) lag periods could have been examined. Albrich *et al.* (2004) suggested that a period of one to two years seemed plausible but varying this period could affect the association between dispensing and resistance. The study of

Hillier *et al.* (2007) found that up to 6 months seemed the most important time period between dispensing of the antibiotic and resistance.

The relationship between antibiotic dispensing and resistance, after adjusting for practice, sample and patient characteristics, is not easy to interpret; there may be confounders that we have not been able to take into account. Adjusting for time allows for the possibility of a systematic change in resistance over time, not related to dispensing. Antibiotic dispensing is also correlated with time (collinearity), making the association harder to interpret. It is also possible that adjusting for year could have resulted in over-adjusting, masking any true associations.

The analysis looking at change in dispensing and resistance was restricted to a sub-sample of practices (N=275, around 65%) of practices in Wales with reliable data. Again these practices were not entirely representative of either the Welsh population or the set of general practices but this is unlikely to introduce much bias. Sensitivity analyses were run on these practices examining the relationship between lagged antibiotic dispensing and resistance and results were comparable for most organism/antibiotic combinations to using all practices with resistance data.

6.5.3 Comparisons with existing literature

6.5.3.1 *Prevalence and trends in resistance*

6.5.3.1.1 *H. influenzae*

From our data, resistance rates in 2006 for amoxicillin and tetracyclines in *H influenzae* isolates were 19.3% and 1.6% respectively and both decreased significantly over time. These rates were lower than the published all-Wales figures of 20.1% and 2.4% respectively (which included specimens sent from hospitals as well as the community) (Welsh Antimicrobial Resistance Programme Surveillance Unit 2007). Figures from a UK based surveillance programme showed similar trends in amoxicillin resistance in community-acquired lower RTIs, between 1999/2000 and 2003/04 at around 20%, before dropping to 16% in 2004/05 (Morrissey *et al*. 2008). They did however observe a higher increase in resistance of around 30% in 2006/07. In the same study, tetracycline resistance was higher (3.5% in 1999/2000) than our

figure but also decreased over time (1.2% in 2006/07). The Alexander Surveillance Project, a longitudinal study of antimicrobial resistance in participating European countries, found wide between country variations in beta-lactamase resistance in *H. influenzae* isolates e.g. from 2.9% in Italy to 35.6% in France in 2001(Felmingham *et al*. 2005). Increasing trends in resistance between 1992 and 2001 were seen in France, Belgium and the UK although it decreased in Poland, Switzerland, Germany, Spain and Italy (percentages not stated). In 2001, Wales and the UK had relatively high beta-lactamase resistance in comparison to other countries but high resistance was also seen in the US (24.5% in 2001), Hong Kong (22%) and Saudi Arabia (28.2%).

6.5.3.1.2 *S. pneumoniae*

Resistance rates in 2006 for erythromycin and penicillin in *S. pneumoniae* isolates were 11.7% and 3.8% respectively with resistance to erythromycin significantly increasing over time. These rates were comparable to the all-Wales figures published of 11.9% and 4.5% respectively (which included hospital specimens as well as the community) (Welsh Antimicrobial Resistance Programme Surveillance Unit 2007). Figures from the British Society for Antimicrobial Chemotherapy (BSAC) resistance website showed no real trend in erythromycin non-susceptibility (resistance and intermediate results) between 2001 and 2006 (14.1% and 14.3% respectively) (British Society for Antimicrobial Chemotherapy). Non-susceptibility to penicillin fell between 2001 and 2006 (from 8.8% to 4.8%) although here non-susceptibility consisted of intermediate results only.

Several studies have shown that the prevalence of resistance to penicillin and erythromycin in *S. pneumoniae* isolates varied widely. The Alexander Project showed that penicillin resistance was lowest in the UK and Germany with 1.1% and 1.4% respectively, and highest in Spain and France (30.2% and 35.8% respectively) (Felmingham *et al*. 2005). Another study examining resistance rates between eight European countries found that overall, 26.8% of *S. pneumoniae* isolates were non-susceptible to penicillin (including amoxicillin) between 2001 and 2003 but again rates varied between countries (Austria 4.4% to 70.9% in Spain) (Reinert *et al*. 2005). Data from the European Antimicrobial Resistance Surveillance System

(EARSS) suggested huge variation in non-susceptibility to penicillin across European countries in 2005 with Romania, Bulgaria and Israel having the highest (over 30%) and the UK, Sweden, Norway having less than 5% (SWEDRES 2005). The Alexander Project showed that erythromycin resistance in 2001 exceeded that of penicillin resistance in France, Germany, Italy, the UK and USA; Poland had the lowest resistance rates with 8.3% and France the highest 56.4% (Felmingham *et al*. 2005). Resistance to erythromycin (measured by clarithromycin resistance) varied within European countries, from 10% in Austria to 43.6% and 46.1% in Spain and France respectively (Reinert *et al*. 2005). Outside Europe, resistance to both antibiotics was also particularly high in the USA and Hong Kong (Felmingham *et al*. 2005).

Significant increases (between 1992 and 2001) have been shown worldwide in resistance to penicillin in *S. pneumoniae* isolates (Felmingham *et al*. 2005). In Europe there was an overall average increase in penicillin resistance of 8.1% over this 10 year period with the greatest increase seen in France, from 7.7% to 35.8%. Resistance rates also increased in the USA from 5.6% to 20.4%. Penicillin resistance decreased between 1996 and 2001 for Belgium and Poland. In Sweden, trends in penicillin resistance (or reduced susceptibility) decreased between 1997 and 2005 (from 10.1 to 7.3 per 100,000 population) (Cars *et al*. 2005). Between 1996 and 2001, increases were observed in erythromycin resistance in several countries with only Poland decreasing (Felmingham *et al*. 2005).

6.5.3.1.3 *S. pyogenes*

In 2006, erythromycin resistance in *S. pyogenes* isolates was 4.5%, comparable to the all-Wales figures published of 3.5% (Welsh Antimicrobial Resistance Programme Surveillance Unit 2007). Significant increases have been shown in resistance to macrolides in *S. pyogenes* isolates in many countries such as Italy, Poland and Belgium (Cornaglia *et al*. 1998; Szczypa *et al*. 2004; Malhotra-Kumar *et al*. 2005). For example in Poland, Szczypa *et al.* (2004) found that resistance to erythromycin increased from 1.8% in 1996/97 to 12% in 1998/99 and to 25.1% in 2000/02, and in Belgium, Malhotra-Kumar *et al.* (2005) demonstrated a 13% increase in macrolide resistance between 1999 and 2003. Although a general increase in Europe has been

observed, resistance rates to macrolides still varied between countries. Between 1994 and 2000, resistance rates to macrolide resistance varied, with northern European countries showing low levels (0 to 4%) and Greece, Italy and Spain demonstrating the highest levels (29% to 38%) (Albrich *et al*. 2004). The PROTEKT antimicrobial surveillance programme (with 25 participating countries worldwide), found that overall, almost 10% of all *S. pyogenes* isolates were resistant to erythromycin A (in 1999/2000) (Cantón *et al*. 2002). Similarly, northern European countries such as Austria, Belgium, the Netherlands and the UK showed little resistance and the highest rates of macrolide resistance were observed in Poland, Italy and Portugal (42%, 25% and 24% respectively).

6.5.3.2 *Risk factors*

A limited number of studies have examined factors associated with resistance. One study examined non-susceptibility to penicillin in *S. pneumoniae* isolates from invasive samples (from blood and cerebrospinal fluid) and found that rates were higher in the elderly and in young children (Buccholz *et al*. 2001). Additionally Bédos *et al.* (1996) found that resistance to penicillin in *S. pneumoniae* isolates was higher in samples taken from patients under 15 years of age and in samples from the upper respiratory tract or from the sinus and middle ear. These findings differ from our results where resistance to penicillin was significantly lower in 5-15 year olds (when compared to 0-4 year olds) and higher in the 85 plus age group. Resistance was also higher in sputum samples.

Resistance to penicillin in *H. influenzae* was more likely in younger (0-19 years) and older (70 and over) patients (Reynolds *et al*. 2002). Conversely in tetracyclines, susceptibility decreased with age indicating that non-susceptibility was higher in the elderly. Again, these findings differ from our results where resistance to amoxicillin was lower in the younger age groups and no association was found between tetracycline resistance and age.

6.5.3.3 *Associations between antibiotic dispensing and resistance*

The association between overall antibiotic use in the community and antibiotic resistance has been well described at European (Bronzwaer *et al*. 2002; Albrich *et al*. 2004; Goossens *et al*. 2005; van de Sande-Bruinsma *et al*. 2008), regional (Arason *et al*. 1996; Granizo *et al*. 2000; Boccia *et al*. 2002; Garcia-Rey *et al*. 2002), general practice (Priest *et al*. 2001) and individual levels (Melander *et al*. 1998; Nasrin *et al.* 2002; Chung *et al*. 2007; Malhotra-Kumar *et al*. 2007). Most of these studies have been in *S. pneumoniae* isolates, examining associations between penicillin and erythromycin resistance, and total antibiotic, beta-lactam, penicillin and macrolide use. The majority of these studies found a significant correlation between antibiotic use (or sales) and antibiotic resistance. One study found no clear relationship between penicillin and erythromycin resistance in *S. pneumoniae* isolates and prescribing of penicillin or beta-lactams (Priest *et al*. 2001).

For *H. influenzae* isolates, only one study has examined the effect of beta-lactam use and resistance (Chung *et al*. 2007). This study, performed at the individual level in children, found that prescribing amoxicillin to a child doubles the risk of isolation of beta-lactamase resistant *Haemophilus* species from that child's throat two weeks later. They concluded that there is a short term effect of resistance in children being prescribed amoxicillin which is sufficient to sustain a high level of antibiotic resistance in the population. In *S. pyogenes* isolates, macrolide resistance was significantly correlated with macrolide use between 1994 and 2000 at a country level, for 20 countries ($r=0.71$, $p= 0.004$) (Albrich *et al*. 2004). Another study carried out at country level also found a weaker significant correlation ($r=0.65$, $p=0.0015$) between erythromycin use and macrolides in 1999/2000 in 21 European countries (Goossens *et al*. 2005).

Few studies have demonstrated that reductions in antibiotic prescribing are associated with reduced levels of antibiotic resistance in the community especially in the organisms under examination in this study. In *S. pyogenes* isolates, two studies in Japan and Finland have shown that reductions in macrolide use were associated with reductions of resistance to erythromycin (Fujita *et al*. 1994; Seppälä *et al*. 1997). In *S. pneumoniae* isolates in Iceland the prevalence of penicillin-resistant pneumococci isolates fell after a campaign to reduce antibiotic prescribing for children (Arason *et al*. 1996). A controlled study in France showed that an education intervention

resulted in fewer antibiotics being prescribed in a community setting which led to significant reductions in rates of colonisation with penicillin G-nonsusceptible *S. pneumoniae* in children (Guillemot *et al*. 2005). A reduction in antibiotic prescribing was followed by a reduction in the percentage of penicillin-resistant pneumococci between 1997 and 2000 (Vardhan *et al*. 2003). More recently in *E. coli* isolates, a reduction in antibiotic dispensing between 1996 and 2003 at a general practice level was associated with reduced antibiotic resistance to ampicillin and trimethoprim (Butler *et al*. 2007).

6.5.4 Implications of findings for clinical practice and future research

Analysis of this individual level resistance data has been crucial to our understanding of antibiotic resistance for a large population of individuals in Wales; how they vary over time, by type of organism and antibiotic they are resistant to and also the variation in rates between general practices and laboratory. As previously discussed with antibiotic dispensing data, surveillance of trends is important, especially in identifying any problems or unexpected increases. Surveillance is required to track any such changes to see if these trends continue. In Wales, up to date information on antimicrobial resistance rates in primary and secondary care is monitored by the Welsh Antimicrobial Resistance Programme, established by Public Health Wales as a response to the increasing problems of antimicrobial resistance. Surveillance of resistance is essential when rates are fairly low, and is possible at a national level. This is harder at a local level due to the small number of isolates of organisms that are tested each year and so large studies are required, but the ability to examine local factors is then limited.

Although ecological level dispensing data was used to examine the association between antibiotic resistance and dispensing levels in general practices, sophisticated methodological techniques such as multilevel modelling as opposed to simple correlations were used. Multilevel modelling not only allowed variations in resistance at both general practice and laboratory levels to be examined, but confounders such as age, gender, the site of the specimen, and time trends could be adjusted for. As has been highlighted before, there are limitations to ecological analyses, as findings found at this level may hide associations at the individual level.

This study identified positive associations between resistance to several different organism/antibiotic combinations and antibiotic dispensing. Therefore, whilst these data cannot be used to make predictions about antibiotic use and resistance in individual patients, it would be worthwhile in future research to examine individual-patient records linking individual clinical, microbiology, and prescribing records on a large scale (such as the General Practice Research Database (GPRD) and the Secure Anonymised Information Linkage (SAIL)).

No associations were found between reductions in dispensing and reductions in resistance rates over the eight-year period. There may be a number of reasons for this. Firstly the number of isolates may be insufficient to warrant looking at reductions in resistance by quartiles of reductions in dispensing and categorising reductions in this way may hide important associations. Secondly antibiotic resistance may take longer to return to previous levels than the time it took for antibiotic resistance to increase after excessive use (Albrich *et al*. 2004). For example, if resistance decreased slowly, such situations may lead to different associations between use and resistance. Further analysis therefore may be required when more current data becomes available and more sophisticated methodology could be used, e.g. by using change in resistance as an outcome and looking at its association with change in dispensing whilst adjusting for practice, patient and sample characteristics. Future work would be beneficial in the area of exploring the impact of different lag periods of dispensing on resistance, and also defining duplicate isolates as the results are surprising in that resistance rates are not higher than the 'non-duplicates'. The cut-off of 91 days from the initial isolate is arbitrary and exploration is required to see if it varies by the organism under examination.

6.6 Introduction to hospital events for complications in Wales

In summary, this chapter uniquely used a large dataset at the individual patient level using robust methods, to examine up to date trends in antibiotic resistance in Wales and any associations between resistance and antibiotic dispensing. Chapter 7 will similarly examine the status of hospital admissions of complications arising from respiratory tract infections using Welsh hospital admissions data.

Chapter 7 Hospital events for acute RTIs and complications in Wales

7.1 Introduction

Chapters 5 and 6 identified that both overall antibiotic dispensing in Wales and amoxicillin and tetracycline resistance in *H. influenzae* isolates had significantly decreased over the study period whilst erythromycin resistance in *S. pneumoniae* isolates had significantly increased.

As a result of GPs reducing their antibiotic prescribing, concerns have been raised that instead of reducing *inappropriate* antibiotic prescribing, a 'blanket' reduction in prescribing has occurred indicating that prescribing that may benefit patients may also be decreasing. Patients most likely to benefit from antibiotics may therefore be harmed through unintended adverse events such as complications that can arise from untreated RTIs, such as pneumonia and rheumatic fever. It is hypothesised that a decrease in antibiotic dispensing might lead to an increase in hospital admissions from these complications.

Therefore, to complete the picture of the relationship between antibiotic dispensing, resistance and clinical outcomes in Wales, all-Wales trends in hospital admissions for acute RTIs, and complications that can arise from them, were investigated using routinely collected data. Annual and quarterly trends were examined retrospectively over the period 1996 to 2006 for all ages and for children aged 0-14 years. Where numbers allowed, the variation in trends of certain RTIs and complications by general practices and LHBs were examined, and possible factors that may be associated with these variations using practice demographic factors were determined.

The reason for examining acute RTIs alongside complications is that if a patient was admitted as an in-patient to hospital and subsequently diagnosed with an acute RTI, then the infection must be at the more severe end of the spectrum of infections.

7.2 Methods

7.2.1 Data source - Patient Episode Database for Wales (PEDW)

The function of the Patient Episode Database for Wales (PEDW) is to provide data on hospital admissions in Wales; it is the equivalent of the hospital episodes statistics database in England. Data are supplied by all NHS Trusts in Wales on completion of a patient's episode of care to the NHS Wales Informatics Service (NWIS), which collates, validates and stores the data on behalf of the Welsh Assembly Government and the NHS in Wales. Monthly submissions are received and added to PEDW, with over 800,000 records captured every year.

PEDW was implemented in April 1991 and contains all inpatient and day case activity (as well as regular attendees and maternity admissions) in NHS Wales (including non-Welsh treated in Wales), together with data for Welsh residents treated in English Trusts. It excludes patients treated in private hospitals and any patients admitted to beds that are not under the care of a consultant e.g. in a nurse-led or midwifery-led unit. PEDW records contain patient demographics such as age, sex, place of residence and ethnicity, administrative details such as key dates, hospital, specialty and consultant, and clinical details such as diagnoses and operative procedures. Diagnoses included in the patient's records use a coding system known as ICD10 (International Statistical Classification of Diseases and Related Health Problems, 10th revision) and procedure codes use the OPCS coding system (versions 4.2 to 4.5) (Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures).

7.2.2 PEDW records

Individual records are submitted to PEDW on the basis of a patient's consultant episode, that is the time an admitted patient spends in the continuous care of one consultant within one NHS trust. A new consultant episode record is generated if the patient is transferred to the care of another consultant. A new consultant episode record is also generated if the patient is discharged and re-admitted at a later date.

PEDW consultant episodes can be linked into larger hospital spells. According to the

PEDW definition of a hospital spell, any episodes that take place during the same continuous stay in one hospital (i.e. between admission and discharge) are said to be part of the same hospital spell. Where a patient is transferred from one hospital to another, a new hospital spell is generated. Compared to episodes, hospital spells provide more of an admissions-based view of the data, which more closely aligns with a patient event-based view of the world. However, it should be noted that hospital spells are still highly dependent on NHS organisational structures, and have been developed mainly with the requirements of finance or performance management in mind, where it may be reasonable to count activity in different hospitals separately. From the point of view of the actual patient, however, or indeed a researcher in public health, the entire continuous spell of care (independent of which hospitals are involved) is more likely to be of interest.

7.2.3 Identifying acute RTIs and complications

Episodes with acute RTIs or complications were identified according to whether their hospital diagnosis met any of the conditions listed in Appendix IX and Appendix X, looking only at the primary diagnosis. By examining the primary diagnosis we can attribute a single diagnosis to the admission i.e. it would be the main reason a patient came into hospital rather than any chronic or other condition they may have. Identifying a comprehensive list of ICD codes to capture all acute RTIs and complications was an extensive process. An academic GP searched all chapters of ICD10 to identify a list of the relevant acute RTIs and complications and this was double-checked by a further two GPs. An initial data request was put in to NWIS for overall patient numbers in Wales per annum for each ICD10 code, in order to identify which codes were feasible to analyse individually and which codes would require grouping with others.

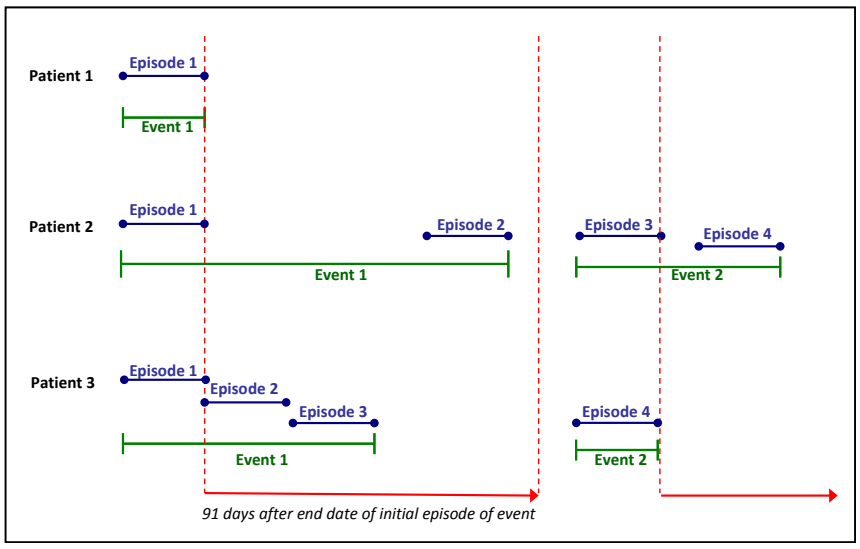
7.2.4 Linking episodes

The requirements for our analysis could not be met using traditional PEDW currencies such as spells or admissions, due to the NHS organisational dependence issues mentioned previously. Instead, an alternative definition of an event was developed, which took an initial episode (containing either an acute RTI or

complication) and linked with it all subsequent episodes of an acute RTI or complication starting within 91 days of its end date. The belief was that episodes within 91 days of each other were likely to arise from the same underlying infection (or organism) and therefore a single event represented a single infection (containing a number of episodes and diagnoses). The cut-off point of 91 days not only replicated that used in the antibiotic resistance data in Chapter 6 to identify duplicate samples, reflecting the likely maximum duration between two samples being part of the same infection, but also other papers that used a 3 month follow up to identify hospital admissions in patients (Winchester *et al*. 2009).

Patients may have had more than one event if their episodes were more than 91 days apart, assuming a new infection. If a patient was diagnosed with the same ICD10 code more than once within an event then it was only counted once, again to avoid double counting diagnoses within an event. Figure 7.1 shows the different scenarios that could arise in the dataset.

Figure 7.1 Scenarios of patients' events and consultant episodes in hospital



Patient 1 had one episode with no subsequent episodes in the 91 days after the end date of episode 1, thus the event contained the single event. Patient 2 had two events; both events contained two episodes (within 91 days of each other) but since episode 3 occurred more than 91 days after the end date of episode 1, a new event was generated. Thus although episode 3 was close to episode 2 it is the duration from

episode 1 that is important. Similarly patient 3 had three episodes within 91 days of each other but episode 4 started after 91 days, hence generating a new event.

7.2.5 Study population and period

Data were requested on hospital events for acute RTIs and complications for the whole population of Wales (Welsh residents treated anywhere). The dataset was constrained to cover events with an initial episode starting between January 1996 and December 2006. Therefore initial episodes of events starting in late 2006 may have had subsequent related episodes in early 2007. Events were excluded if their first episode started before 1996.

7.2.6 Dataset fields

For each event per patient the following information was obtained: event and patient identification number, episode number, episode start and end dates, diagnoses for each episode, (using ICD10 codes to 3 and 4 digits and descriptions), method of discharge (death, patient discharged him/herself, clinical discharge), age and gender of patient, deprivation score of the area in which the patient lived (based on Townsend scores) and the patient's encrypted general practice code. Prior to receipt of the data, patient details were fully anonymised so no identifiable information, such as date of birth or postcode, was included.

7.3 Statistical analysis

7.3.1 Counting acute RTIs and complications

An event contains episodes of either (a) acute RTIs only, (b) complications only or (c) both acute RTIs and complications. When counting the overall number of acute RTI events then all events falling into categories (a) and (c) will be included. Each event will be counted once irrespective of the number of distinct ICD10 codes within the event[1]. Similarly, the overall number of complication events will comprise of

[1] Where a group of ICD10 codes is used to define an acute RTI or complication, e.g. Pneumonia with the group of codes J13 to J18, then if more than one of these diagnoses codes appeared within an event, they would only be counted once.

events falling into categories (b) and (c). When counting events for individual RTI or complication diagnoses (using ICD10 codes) each distinct diagnosis will be counted. If a single event contained several different acute RTI episodes with distinct diagnoses e.g. two episodes within one event, one of acute serous otitis media and one of acute sinusitis, these would each be counted for each relevant acute RTI category (Sinusitis and OM).

7.3.2 Main analysis

For each event, the year and quarter at the first episode start date were extracted and used for all subsequent episodes within that event. Counts of all-Wales hospital events for acute RTIs and complications (overall and individual) were converted into rates (per 10,000 or 100,000 population) and examined between 1996-2006, using Wales mid-year estimates of population data from the Office for National Statistics (Stats Wales, Welsh Assembly Government). For acute RTIs and complications with more than 50 events over the period, a basic single-level linear regression analysis was undertaken to establish all-Wales trends in rates of events for the individual acute RTIs and complications listed in Appendix IX and Appendix X.

Counts of hospital events for acute RTIs and complications in Wales were aggregated at general practice level per annum to allow multilevel modelling (at the level of LHB (22 in Wales), Welsh general practices (426 UTS) and time (1996-2006)) . Due to the small numbers when data was aggregated at the general practice level, only events of overall acute RTIs, complications, pneumonia and septicaemia were examined for all ages. In children (aged 0-14 years), the numbers were even smaller and only overall acute RTIs and complications were studied.

7.3.2.1 *Poisson regression*

A three-level repeated measures Poisson regression model was fitted with independent counts of acute RTIs or complications as the outcome variable, to account and correct for variation at the level of LHB, practice and time. The model also included time and the following significant practice characteristics as explanatory variables:

- Percentages of the practice population aged 0-14 years, 15-64, and 65 and over
- Single-handed status of the practice (single or multi-handed)
- Practice deprivation quintile (based on Townsend 2001 scores)
- Average age of GPs in a practice
- Proportion of male GPs in a practice.

Poisson regression was used since the data are constrained to be non-negative. Fitting a normal model could produce negative predicted counts. Therefore a Poisson model is fitted to the hospital events data using a log link function. An offset variable was created as the $\log_e$ expected counts of complications per annum based on the practice's list size (calculated by multiplying the complication rate over all practices by the practice's list size). Including the offset allows comparison of the observed to expected counts taking account of the practice's list size.

Therefore, the Poisson regression model can be written in the following form:

$$log_e(obs\ counts) = log_e(exp\ counts) + \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots$$

$$log_e\left(\frac{obs}{exp}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots$$

$$\text{Standardised Incidence Ratio (SIR)} = \left(\frac{obs}{exp}\right) = exp^{(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots)}$$

For a one unit change in a predictor variable x, the log ratio of observed to expected counts would change by β, given the other predictor variables in the model were held constant. The ratio of observed to expected counts (or the Standardised Incidence Ratio (SIR)) would therefore change by exp(β). The aim was therefore to examine the distribution of this ratio over time and by practice characteristics.

A characteristic of the Poisson distribution is that its mean is equal to its variance. For some sets of count data, when a Poisson model is a candidate, overdispersion occurs in which the observed variance is greater than the mean (usually in datasets with long-tailed distributions). An over-dispersed Poisson model can be assessed by allowing the level-1 error to be estimated. In these circumstances the Poisson model

is not appropriate. If the count in a practice has a Poisson distribution, but the mean varies between practices as a Gamma distribution, then the overall distribution is negative binomial which allows for this type of over-dispersion. The consequence of not taking overdispersion into account is that the standard errors are underestimated and so the null hypothesis may be rejected when it should not be. Therefore estimates from the negative binomial (NB) regression model were used as a comparison; these estimates are more conservative and standard errors are larger when dispersion is allowed for.

In the case of the Poisson models, parameters were estimated using Monte Carlo Markov Chains (MCMC) methods to give less biased estimates, with initial estimates obtained by using the restricted iterative generalized least squares (RIGLS) estimation procedure (1^{st} order PQL). MCMC methods were used also to derive confidence intervals for non-symmetrical distributions. The Deviance Information Criterion (DIC) diagnostic was used to assess goodness of fit. MCMC in MLwiN often produces highly correlated chains (in part due to the fact that the parameters of the model are highly correlated; variance=mean) and therefore requires a substantial number of simulations, typically much larger than for Normal or for Binomial. MCMC methods cannot currently be used in NB models and estimates were obtained using the RIGLS procedure (1^{st} order PQL).

All multilevel modelling was performed using MLwiN version 2.16 and all other analyses using SPSS version 16.0.

7.4 Results

7.4.1 All-Wales events of hospital infections for acute RTIs and complications arising from RTIs

A total of 320,752 events of infections (containing an acute RTI, a complication or both) were identified from 253,081 individual patients residing in Wales. These patients had a range of one to 28 events over the study period. A total of 162,950 (50.8%) events were in males, 89,868 (28.0%) were in 0-14 year olds, 82,406 (25.7%) in 15-64 year olds and 148,442 (46.3%) in the 65 and over age group. The majority of events (91.8%, 294,210 events) came from patients registered in 585 unique Welsh practices, with 0.5% (1,751 events) from patients registered in 401 non-welsh practices and 7.7% (24,791 events) where the practice was not recorded (but most likely to be Welsh). This section will examine the All-Wales data, based on 320,752 events.

Within the 320,752 events were a total of 341,459 episodes (with distinct ICD10 codes to 4 digits). The majority of events (301,236 (93.9%)) contained only one episode (no subsequent episodes within 91 days) and 19,516 (6.1%) events contained more than one episode (18,371 with 2 distinct episodes, 1,101 with 3 episodes, 42 with 4 episodes and 2 with 5 episodes).

Table 7.1 shows a breakdown of the number of episodes within an event by acute RTI or complication. Although for the first episode within an event there were roughly equal numbers of acute RTIs and complications, subsequent episodes were more likely to be complications.

Table 7.1 Breakdown of acute RTI and complication episodes within an event

	Episodes within an event N(%)					
	1st	**2nd**	**3rd**	**4th**	**5th**	**Total**
Complications	166,260	14,995	929	34	2	182,220
	(51.8)	(76.8)	(81.1)	(77.3)	(100)	(53.4)
Acute RTIs	154,492	4,521	216	10	0	159,239
	(48.2)	(23.2)	(18.9)	(22.7)	(0)	(46.6)
Total	320,752	19,516	1145	44	2	341,459
	(100)	(100)	(100)	(100)	(100)	(100)

If an event has only one episode, this can either be an acute RTI or a complication. For events with more than one episode, these can either be all distinct diagnoses of an acute RTI (e.g. a first episode of 'Acute tonsillitis' followed by an episode of 'Other diseases of upper respiratory tract' within 91 days) or a complication, or a combination of both (the above scenario followed by 'Other abscess of pharynx'). Of the 320,752 events 150,441 (47%) contained only an RTI episode, 163,399 (51%) a complication episode and 6,912 (2%) contained at least one acute RTI and at least one complication episode. Thus, there was a total of 157,353 (150,441+6,912) events that contained an RTI episode and 170,311 that contained a complication (163,399+6,912).

7.4.1.1 *Trends in events of hospital infections*

The number of events (320,752) with a respiratory tract related infection (containing episodes of acute RTIs and/or complications arising from RTIs) per 10,000 population increased by 32.4% between 1996 and 2006 (from 85.60 to 113.33 per 10,000 population respectively) (Figure 7.2). After fitting a single-level linear regression, the trend indicated an increase of 2.19 events per 10,000 population per annum (95% confidence interval (CI) =1.38 to 3.00, $p<0.001$).

Figure 7.2 Annual overall incidence of hospital events (for both acute RTIs and complications) (per 10,000 population) in Wales

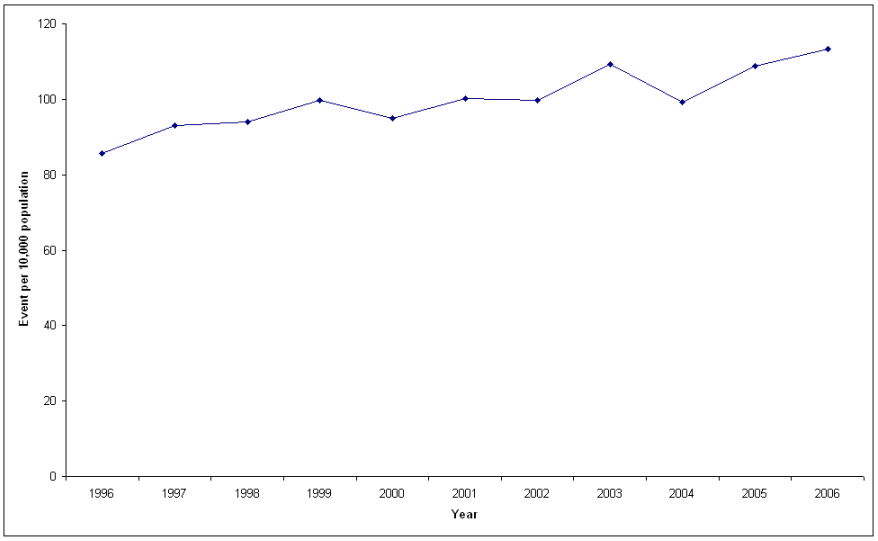
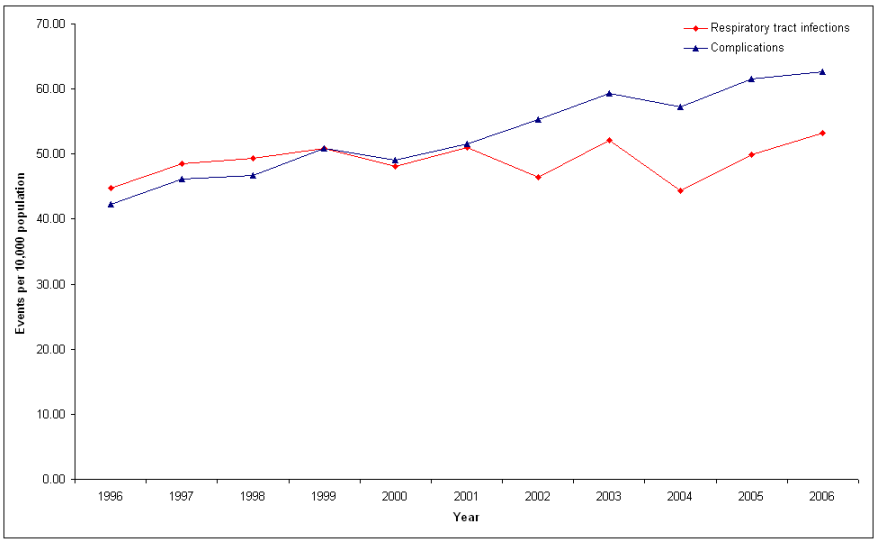


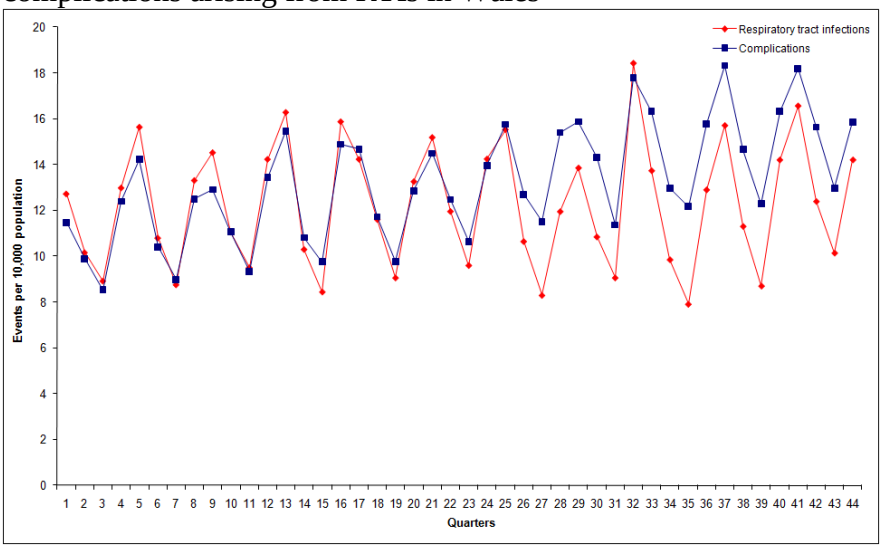
Table 7.2 shows the rates and trends in acute RTIs and complications by age-group and gender. The number of events comprising of at least one RTI (157,353) per 10,000 population increased by 13.6% between 1996 and 1999 (from 44.79 to 50.88 per 10,000 population respectively) but thereafter the trend was more sporadic, finally rising to 53.29 per 10,000 population in 2006 (Figure 7.3). No significant increase over time was indicated by the single-level regression model (β=0.31, 95% CI=-0.30 to 0.92, p=0.280). The number of events comprising of at least one complication (170,311) per 10,000 population increased by 48.2% between 1996 and 2006 (from 42.27 to 62.65 per 10,000 population) respectively and this trend was significant (an increase of 1.99 events per 10,000 population per annum, 95% CI=1.66 to 2.31, p<0.001) (Figure 7.3).

Figure 7.3 Annual incidence of events (per 10,000 population) by acute RTIs and complications in Wales



A smoother pattern of hospital events for complications over time is apparent compared to the more sporadic pattern of events for acute RTIs. The quarterly rates show the seasonal variation with higher rates in quarter 1 (January to March) and lower in quarter 3 (July to September) (Figure 7.4).

Figure 7.4 Quarterly incidence of events (per 10,000 population) by acute RTIs and complications arising from RTIs in Wales



Time=1 (January-March 1996) to 44 (October-December 2006)

Trends of event rates of acute RTIs by gender were stable. The 0-14 year age group had higher rates of acute RTIs than the 15-64 and 65 and over age groups but again all trends were stable over time (Figure 7.5).

Figure 7.5 Quarterly incidence of acute RTIs events (per 10,000 population) by age group, in Wales

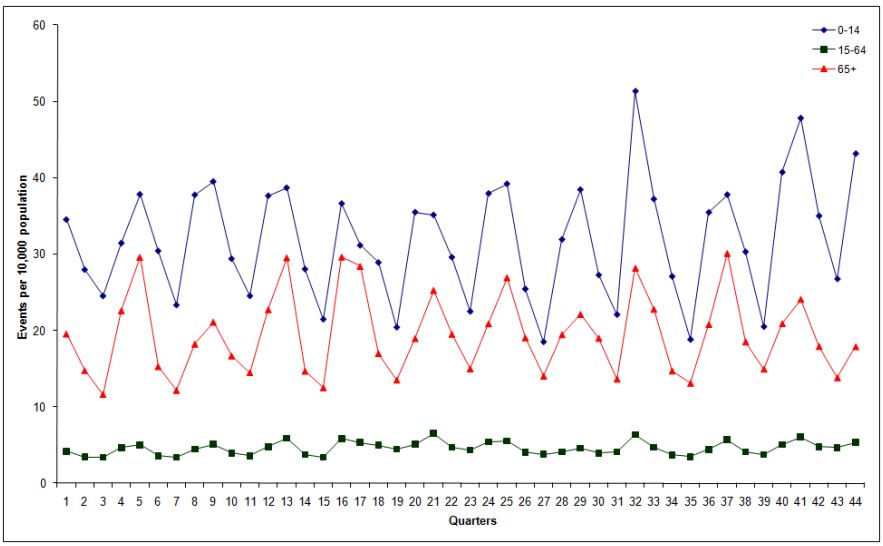
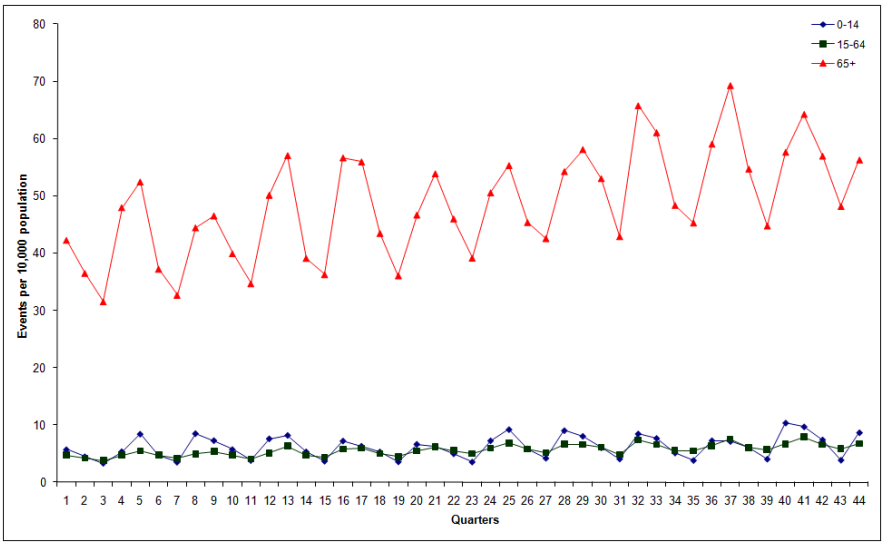


Table 7.2 Annual incidence of events (per 10,000 population) of acute RTIs and complications by age group and gender in Wales, 1996-2006

		1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% change 96-06
All Events		85.60	93.04	94.07	99.68	95.02	100.20	99.62	109.24	99.31	108.74	113.33	32.4
Acute RTI events													
Total acute RTIs		44.79	48.50	49.31	50.88	48.15	50.98	46.42	52.17	44.40	49.91	53.29	19.0
Age group	**0-14**	118.38	129.27	131.00	124.74	115.89	125.10	115.00	139.07	118.51	129.25	152.66	29.0
	15-64	15.67	16.42	17.38	18.84	19.83	20.98	17.50	18.97	16.26	18.58	20.75	32.4
	65+	68.51	75.23	74.96	86.32	77.82	80.63	79.40	82.90	71.37	84.44	73.69	7.6
Gender	**Male**	46.93	50.76	52.63	51.66	48.53	52.01	47.83	52.66	44.20	49.39	54.65	16.5
	Female	42.75	46.29	46.13	50.13	47.77	49.99	45.07	51.70	44.58	50.41	51.98	21.6
Complication events													
Total complications		42.27	46.09	46.73	50.89	49.01	51.56	55.34	59.34	57.23	61.59	62.65	48.2
Age group	**0-14**	18.83	25.19	24.42	24.42	21.83	22.07	28.29	26.61	23.87	27.68	29.63	57.4
	15-64	17.46	19.28	19.26	21.13	20.86	22.62	24.37	24.87	23.89	25.93	27.03	54.8
	65+	158.38	166.90	171.36	189.15	182.25	189.65	197.58	219.84	213.82	226.40	225.71	42.5
Gender	**Male**	46.60	51.09	50.58	54.52	52.69	55.43	59.52	62.02	60.99	64.01	65.63	40.8
	Female	38.17	41.31	43.05	47.42	45.52	47.90	51.40	56.81	53.66	59.28	59.82	56.7

For complications, event rates were higher in males than females and both increased over time. Adults aged 65 and over had a higher rate of events and also saw a significant increase over time (β=7.08 per 10,000 population aged 65 years and over per annum, 95% CI=5.82 to 8.34, p<0.001) (Figure 7.6). There was also a significant increase in the 15-64 age group (β=0.90 per 10,000 population aged 15-64 years per annum, 95% CI=0.75 to 1.06, p<0.001). Rates for children (0-14 age group) were more stable over the period (β=0.67 per 10,000 population aged 0-14 years per annum, 95% CI=0.15 to 1.18, p=0.017).

Figure 7.6 Quarterly incidence of complication events (per 10,000 population) by age group, in Wales



Time=1 (January-March 1996) to 44 (October-December 2006)

7.4.2 Events of hospital infection by type of acute RTI

In Wales between 1996 and 2006, there were 158,948 episodes of acute respiratory tract related hospital infection of which 77,576 (49%) were in children aged 0-14 years. There were fewer episodes of acute RTIs than reported in table 7.1 (159,239) since within an event there may be more than one acute RTI episode with a distinct 4 digit ICD10 code but since in these analyses, codes are combined (such as J20/J22) then they would only be counted once (Table 7.3). Therefore some events may have more than one J20/J22 episode but these are only counted once i.e. one event had a code of either J20 or J22.

Table 7.3 Example of two events containing several episodes

Event ID	Episode 1	Episode 2	Episode 3	Note
1	J202	J22X	-	Event counted once in J20/J22 acute RTI
2	J209	J208	J157	Event counted once in J20/J22 and once in J15

Table 7.4 and Table 7.5 show these events classified by type of acute RTIs, for all ages and children respectively. The most common acute RTI for all ages was acute bronchitis and unspecified acute lower respiratory infections (ICD10 codes J20 and J22 respectively) with a total of 68,958 (21.5%) events over the 11 year period, and a mean rate per annum of 214.65 (per 100,000 Welsh mid-year population). Only 9,224 (13.4%) of these events were attributable to children (0-14 age group) with 40,580 (58.8%) attributable to adults in the 65 and over age group. The next most common across all ages were acute nasopharyngitis and acute upper respiratory infections of multiple and unspecified sites (J00 and J06 respectively) with a total of 44,474 events over the 11 year period and a mean rate per annum of 138.47 (per 100,000 population). Acute nasopharyngitis and acute upper respiratory infections of multiple and unspecified sites were the most common in children with 39,448 events (89% of events for all ages). The second most common acute RTI in children were acute pharyngitis and tonsillitis (J02 and J03 respectively) which appeared in 19,831 events (62.4% of all events for all ages). Events of otitis media were also common in children 0-14 years of age, constituting over 72% of OM events for all ages.

Table 7.4 Hospital events of infections in Wales by diagnosis of acute RTIs between 1996 and 2006-all ages[i]

			Rate per 100,000 population				
ICD10 codes	**Description**	**Total events**	**Mean rate per annum**	**1996**	**2006**	**% change**	**β[ii] (se), p-value**
J20/J22	Acute bronchitis (exc. viruses) and unspecified acute lower respiratory infections	68,958	214.65	182.93	220.10	20.3	2.304 (1.459) p=0.149
J00/J06	Acute nasopharyngitis and acute upper respiratory infections of multiple and unspecified sites	44,474	138.47	130.74	141.04	7.9	-0.139 (1.167) p=0.908
J02/J03	Acute pharyngitis and acute tonsillitis	31,761	98.77	87.75	145.18	65.5	3.649 (1.259) p=0.018
H659 H664 H669	Unspecified otitis media (non-suppurative and suppurative)	10,900	33.99	41.02	26.16	-36.2	-2.142 (0.237) p<0.001
H650 H651 H660	Acute otitis media (serous, non-suppurative and suppurative)	1,016	3.17	3.77	2.50	-33.8	-0.187 (0.069) p=0.024
J04	Acute laryngitis and tracheitis	937	2.92	2.49	1.99	-20.1	-0.078 (0.045) p=0.115
J01	Acute sinusitis	902	2.81	2.80	2.29	-18.2	-0.064 (0.030) p=0.057
H67	Otitis media in diseases classified elsewhere	0	-	-	-	-	-

[i] *Table sorted by total events*

[ii] *Coefficient for trend using single-level linear regression model with rates as the outcome variable*

Table 7.5 Hospital events of infections in Wales by diagnosis of acute RTIs between 1996 and 2006-children aged 0-14 years[i]

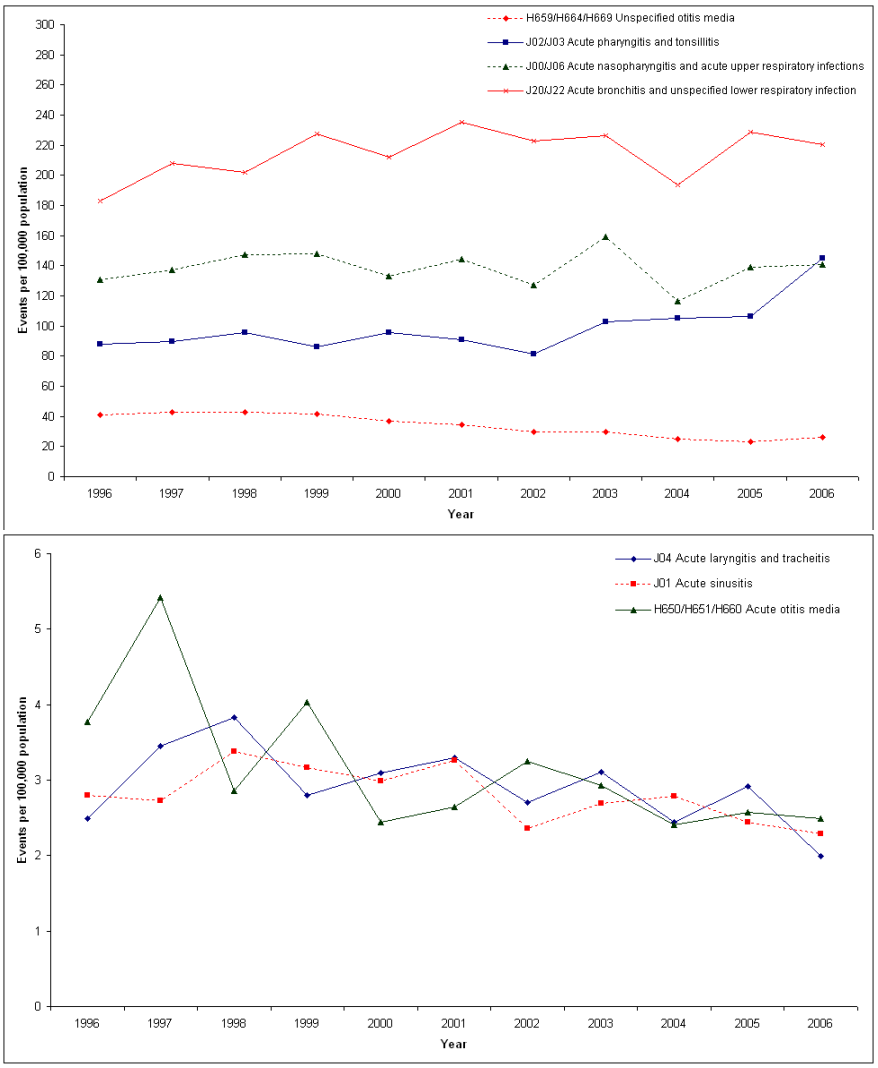
			Rate per 100,000 children population				
ICD10 codes	**Description**	**Total events (% of all ages)**	**Mean rate per annum**	**1996**	**2006**	**% change**	**β[ii] (se), p-value**
J20/J22	Acute bronchitis (exc. viruses) and unspecified acute lower respiratory infections	9,224 (13.4)	153.81	121.81	197.79	62.4	4.760 (1.870) p=0.031
J00/J06	Acute nasopharyngitis and acute upper respiratory infections of multiple and unspecified sites	39,448 (88.7)	657.78	608.86	720.68	18.4	5.225 (5.559) p=0.372
J02/J03	Acute pharyngitis and acute tonsillitis	19,831 (62.4)	330.67	289.45	511.18	76.6	1.469 (0.470) p=0.012
H659 H664 H669	Unspecified otitis media (non-suppurative and suppurative)	7,920 (72.7)	132.06	161.76	115.22	-28.8	-7.837 (1.429) p<0.001
H650 H651 H660	Acute otitis media (serous, non-suppurative and suppurative)	726 (71.5)	12.11	13.73	9.60	-30.1	-0.540 (0.320) p=0.126
J04	Acute laryngitis and tracheitis	281 (30.0)	4.69	3.39	2.30	-32.0	-0.262 (0.123) p=0.063
J01	Acute sinusitis	146 (16.2)	2.43	1.78	2.50	40.0	-0.027 (0.067) p=0.694
H67	Otitis media in diseases classified elsewhere	0	-	-	-	-	-

[i] *Table sorted by total events for all ages*
[ii] *Coefficient for trend using single-level linear regression model with rates as the outcome variable*

7.4.2.1 *Trends in acute RTIs*

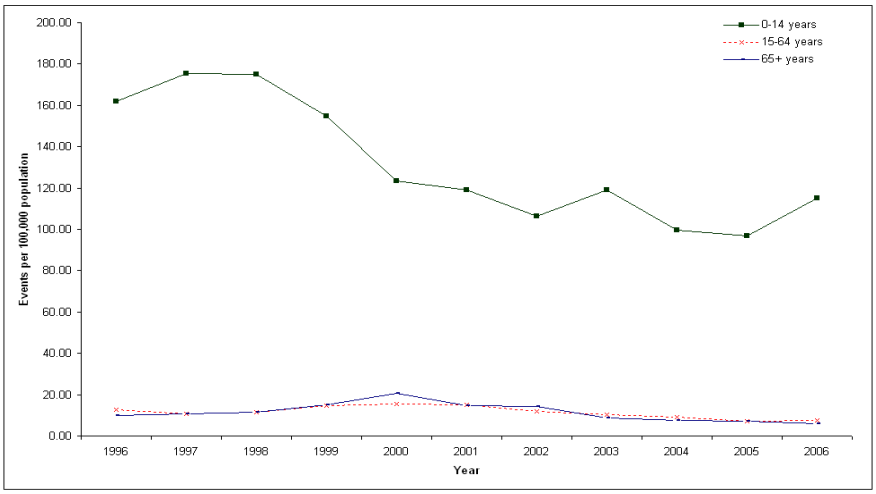
Trends over all ages by type of acute RTI are shown in Figure 7.7 and results from a single-level linear regression model used to estimate the trend in acute RTI rates are shown in the last column of table 7.4 and 7.5. Significant decreases were found in event rates of otitis media (OM), which fell by 36.0% between 1996 and 2006 (from 44.65 to 28.56 per 100,000 population respectively). This decrease was seen in both acute OM (H650/H65/H660) and unspecified OM (non-suppurative and suppurative) (H659/H664/H669) with rates significantly falling by 0.187 (95% CI= 0.031 to 0.343, p=0.024) and 2.142 (95% CI=1.607 to 2.677, p<0.001) per annum per 100,000 population respectively (an absolute decrease of 33.8% and 36.2% between 1996 and 2006).

Figure 7.7 Annual incidence of events (per 100,000 population) by acute RTI type, in Wales



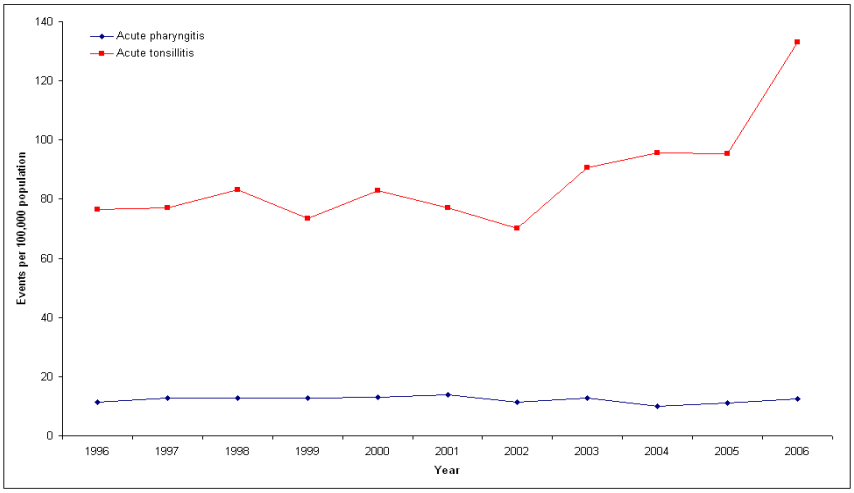
Unspecified OM was most common in children, whose rates decreased 28.8% between 1996 and 2006 (from 161.76 to 115.22 per 100,000 children population respectively) (Figure 7.8). For the 15-64 and 65 plus age groups, rates of unspecified OM were much lower, peaking in 2000 but thereafter decreasing.

Figure 7.8 Annual incidence of unspecified otitis media events (per 100,000 population) by age group, in Wales



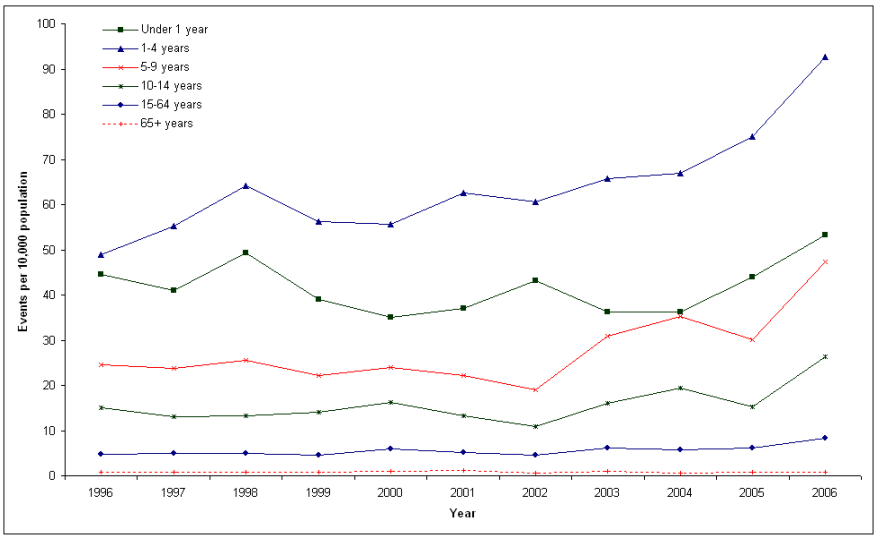
Event rates for acute pharyngitis and tonsillitis significantly increased over the period by 65.5% between 1996 and 2006 (from 87.75 to 145.18 per 100,000 respectively). Trends in acute pharyngitis and tonsillitis examined separately showed that this trend was mainly due to acute tonsillitis; rates for acute pharyngitis were stable (Figure 7.9).

Figure 7.9 Annual incidence of acute pharyngitis and tonsillitis events (per 100,000 population) in Wales



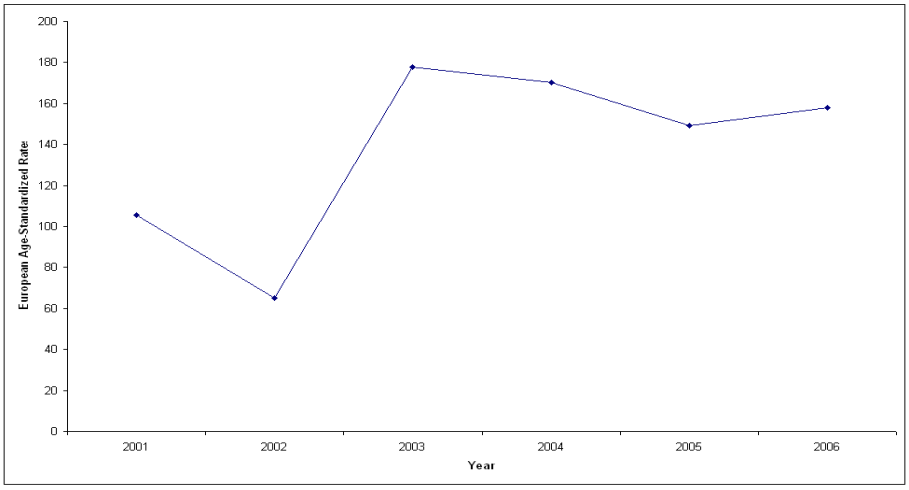
Broken down by age group, events for acute pharyngitis and tonsillitis were more common in children although there was still an upward trend in the 15-64 age groups (rate of increase of 1.469 per annum per 100,000 population (96% CI=0.405 to 2.532) p=0.012) (Figure 7.10). More specifically in children, acute pharyngitis and tonsillitis events were more common in the 1-4 year olds and the 5-9 year olds with an 89.4% and 92.4% increase respectively between 1996 and 2006. Significantly increasing trends were found in these age groups (β=3.003, 95% CI=1.546 to 4.459, p=0.001 and β=1.638, 95% CI=0.305 to 2.971, p=0.021 respectively).

Figure 7.10 Annual incidence of acute pharyngitis and tonsillitis events (per 10,000 population) by age group, in Wales



The increase in tonsillitis may be accounted for by the decision to stop tonsillectomies in September 2002, with only emergency tonsillectomies being performed until February/March 2003 when tonsillectomies were restarted. Figure 7.11 shows the European age standardised rates (EASRs) for Wales for tonsillectomy admissions (Heath Solutions Wales, Health Maps Wales). Tonsillectomy rates dropped in 2002 (taken as financial year 2002/03) in Wales and rose again in 2003.

Figure 7.11 Hospital admissions for tonsillectomies (European age standardised rates (EASRs)) in Wales, 2001 and 2006



7.4.3 Events of hospital infection by type of complication

Tables 7.6 and 7.7 show the overall number of events of complications, the average rate per annum as well as the rates in 1996 and 2006, the percentage change in rates between these years and the coefficient for trend from a single-level linear regression model for all ages and children.

The most common complications seen in hospital were for pneumonia (ICD10 codes J13 to J18) with 71,823 events over the study period and a mean rate per annum of 223.35 per 100,000 population, and COPD with acute lower respiratory infections (J440) and COPD with acute exacerbation unspecified (J441) which had 28,608 and 37,223 events respectively (mean rates per annum of 88.88 and 115.85 per 100,000 population respectively) (Table 7.6).

Pneumonia was also the most common complication in children aged between 0-14 years with 13% of total pneumonia events and a mean rate of 159.08 per annum (Table 7.7). Second most common in children was meningococcal infection (A39) making up 78% of total meningococcal events (mean rate per annum of 27.79). Children made up 97% of all scarlet fever events (A38) and acute lymphadenitis of face, head and neck, other sites and unspecified (L040/L048/L049) were also more common in children with 72% of all events.

Table 7.6 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-all ages[i]

ICD10 codes	Description	Total events	Rate per 100,000 population			% change	β[ii] (se), p-value
			Mean rate per annum	1996	2006		
J13 to J18	Pneumonia	71,823	223.35	189.95	277.86	46.3	9.361 (1.297) p<0.001
J18	Pneumonia, organism unspecified	67,686	210.48	177.26	262.05	47.8	9.040 (1.215) p<0.001
J441	COPD with acute exacerbation, unspecified	37,223	115.85	94.63	116.66	23.3	1.781 (0.788) p=0.05
J440	COPD with acute lower respiratory infections (excludes with influenza)	28,608	88.88	43.23	120.10	177.8	7.531 (0.681) p<0.001
A40/A41	Septicaemia	10,860	33.73	22.07	51.52	133.5	2.815 (0.257) p<0.001
A41	Other septicaemia	9,935	30.93	19.78	47.64	140.8	2.648 (0.245) p<0.001
J90/J91	Pleural effusion	9,336	29.02	20.96	38.98	86.0	1.697 (0.150) p<0.001
J36/ J390/ J391	Peritonsillar, retropharyngeal, parapharyngeal and other pharynx abscesses	5,059	15.74	12.94	16.86	30.3	0.365 (0.103) p=0.006
J36	Peritonsillar abscess (quinsy)	4,946	15.39	12.66	16.39	29.4	0.348 (0.102) p=0.008
J47	Bronchiectasis	3,252	10.11	8.34	12.21	46.4	0.417 (0.044) p<0.001
J15	Bacterial pneumonia, not elsewhere classified	2,702	8.40	6.61	11.50	74.0	0.452 (0.088) p=0.001
A39	Meningococcal infection	2,154	6.72	7.26	4.38	-39.7	-0.523 (0.136) p=0.004

Table 7.6 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-all ages[i]

ICD10 codes	Description	Total events	Rate per 100,000 population			% change	β[ii] (se), p-value
			Mean rate per annum	1996	2006		
J40	Bronchitis, not specified as acute or chronic	2,093	6.52	7.30	7.22	-1.1	-0.007 (0.076) p=0.927
M001/M002/ M008/M009	Pyogenic arthritis	1,872	5.83	5.29	6.10	15.3	0.053 (0.048) p=0.298
I00/I01/I02/ I301/I33/I38	Rheumatic fever	1435	4.47	4.18	4.45	6.3	-0.040 (0.035) p=0.286
J13	Pneumonia due to Streptococcus pneumoniae	1,233	3.84	4.63	4.69	1.1	0.042 (0.064) p=0.529
A40	Streptococcal septicaemia	954	2.97	2.32	3.98	71.7	0.173 (0.029) p<0.001
J86	Pyothorax (includes empyema, abscess of pleura, thorax, pyopneumothorax)	942	2.93	2.28	4.18	83.2	0.177 (0.042) p=0.002
J398/J399	Other specific and unspecific diseases of upper respiratory tract	850	2.66	3.15	0.71	-77.5	-0.264 (0.210) p=0.240
H70/H75	Mastoiditis and related conditions and other disorders of middle ear and mastoid	840	2.62	2.80	1.82	-35.0	-0.179 (0.052) p=0.007
G00/G01/G042 /G048/G050	Bacterial meningitis, encephalitis, myelitis, encephalomyelitis.	820	2.55	2.94	2.83	-3.7	-0.049 (0.038) p=0.232
L040/L048/ L049	Acute lymphadenitis of face, head and neck, other sites and unspecified	758	2.36	1.49	2.36	58.7	0.062 (0.039) p=0.148

Table 7.6 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-all ages[i]

ICD10 codes	Description	Total events	Rate per 100,000 population			% change	β[ii] (se), p-value
			Mean rate per annum	1996	2006		
G00	Bacterial meningitis	718	2.24	2.84	2.60	-8.5	-0.052 (0.039) p=0.215
J14	Pneumonia due to Haemophilus influenzae	500	1.56	1.87	1.75	-6.1	-0.025 (0.020) p=0.239
J340	Abscess, furuncle and carbuncle of nose	338	1.05	1.04	0.98	-5.8	0.029 (0.018) p=0.141
G06	Intracranial and intraspinal abscess and granuloma	281	0.87	0.62	1.05	67.9	0.043 (0.014) p=0.015
J85	Abscess of lung and mediastinum	262	0.82	0.80	0.57	-27.9	0.006 (0.014) p=0.707
J051	Acute epiglottitis	259	0.80	0.52	1.11	114.5	0.062 (0.020) p=0.013
A491/A492/ A493	Bacterial infection of unspecified site (Streptococcal, Haemophilus influenzae, Mycoplasma)	239	0.74	0.38	0.81	112.7	0.023 (0.015) p=0.165
M028/M029	Reactive arthropathies	216	0.67	0.55	0.78	40.1	0.025 (0.019) p=0.226
N00/N01	Acute and rapidly progressive nephritic syndrome	200	0.62	1.18	0.30	-74.2	-0.041 (0.022) p=0.092
A481	Legionnaires' disease	145	0.45	0.35	0.94	173.0	0.037 (0.014) p=0.028
A38	Scarlet fever	122	0.38	0.38	0.37	-2.5	0.004 (0.013) p=0.780
G08	Intracranial and intraspinal	110	0.34	0.38	0.44	15.2	0.016 (0.016)

Table 7.6 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-all ages[i]

ICD10 codes	Description	Total events	Rate per 100,000 population Mean rate per annum	1996	2006	% change	β[ii] (se), p-value
	phlebitis and thrombophlebitis						p=0.342
The following codes had <50 events in total and could not be analysed for trends:							
J16	*Pneumonia due to other infectious organisms (not elsewhere classified)*		*B961*	*Klebsiella pneumoniae as the cause of disease classified to other chapters*			
A70	*Chlamydia psittaci infection*		*A36*	*Diptheria*			
B960	*Mycoplasma pneumoniae as the cause of disease classified to other chapters*		*M010/M013*	*Meningococcal arthritis and arthritis in other bacterial diseases classified elsewhere*			
J170/J178	*Pneumonia in bacterial and other diseases classified elsewhere*		*L540*	*Erythema marginatum in acute rheumatic fever*			
			M03	*Postinfective and reactive arthropathies in disease classified elsewhere*			

[i] *Table sorted by total events*
[ii] *Coefficient for trend using single-level linear regression model with rates as the outcome variable*

Table 7.7 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-children aged 0-14 years[i]

ICD10 codes	Description	Total events (% of all ages)	Rate per 100,000 children population			% change	β[ii] (se), p-value
			Mean rate per annum	1996	2006		
J13 to J18	Pneumonia	9,506 (13)	159.08	109.68	204.13	86.1	0.032 (0.047) p=0.517
J18	Pneumonia, organism unspecified	8,901 (13)	148.95	103.26	190.11	84.1	0.113 (0.063) p=0.107
A39	Meningococcal infection	1,676 (78)	27.79	26.57	19.97	-24.8	-1.820 (0.638) p=0.019
A40/A41	Septicaemia	630 (6)	10.55	8.20	14.21	73.2	0.546 (0.146) p=0.005
L040/L048/ L049	Acute lymphadenitis of face, head and neck, other sites and unspecified	544 (72)	9.11	4.28	11.14	160.2	0.550 (0.173) p=0.011
J15	Bacterial pneumonia, not elsewhere classified	508 (19)	8.51	4.46	12.87	188.6	0.457 (0.069) p<0.001
A41	Other septicaemia	472 (5)	7.92	6.24	11.71	87.7	0.531 (0.112) p=0.001
J36/ J390/ J391	Peritonsillar, retropharyngeal, parapharyngeal and other pharynx abscesses	417 (8)	6.96	3.92	6.14	56.6	0.052 (0.074) p=0.501
J36	Peritonsillar abscess (quinsy)	396 (8)	6.61	3.92	5.38	37.0	-0.057 (0.111) p=0.622
G00/G01/ G042/G048/ G050	Bacterial meningitis, encephalitis, myelitis, encephalomyelitis.	357 (44)	5.96	4.99	7.11	42.3	0.127 (0.111) p=0.281

Table 7.7 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-children aged 0-14 years[i]

ICD10 codes	Description	Total events (% of all ages)	Rate per 100,000 children population			% change	β^{ii} (se), p-value
			Mean rate per annum	1996	2006		
G00	Bacterial meningitis	334 (47)	5.57	4.99	6.91	38.4	0.070 (0.119) p=0.571
H70/H75	Mastoiditis and related conditions and other disorders of middle ear and mastoid	311 (37)	5.18	3.92	4.99	27.3	-0.010 (0.090) p=0.916
M001/M002/ M008/M009	Pyogenic arthritis	250 (13)	4.17	4.10	4.61	12.4	-0.057 (0.111) p=0.622
J40	Bronchitis, not specified as acute or chronic	203 (10)	3.32	6.96	0.19	-97.2	-0.815 (0.142) p<0.001
J86	Pyothorax (includes empyema, abscess of pleura, thorax, pyopneumothorax)	160 (17)	2.71	1.96	5.76	193.7	0.457 (0.069) p<0.001
A40	Streptococcal septicaemia	159 (17)	2.65	1.96	2.50	27.3	0.020 (0.056) p=0.723
A38	Scarlet fever	118 (97)	1.97	1.96	2.11	7.7	0.062 (0.071) p=0.410
A491/A492/ A493	Bacterial infection of unspecified site (Streptococcal, Haemophilus influenzae, Mycoplasma)	110 (46)	1.84	0.36	1.92	438.4	0.123 (0.074) p=0.133
J441	COPD with acute exacerbation unspecified	107 (0.3)	1.84	0.00	9.03	-	0.618 (0.176) p=0.007
J90/J91	Pleural effusion	105 (1)	1.76	1.96	2.69	37.0	0.113 (0.063) p=0.107
J13	Pneumonia due to	101 (8)	1.69	1.25	2.11	69.2	0.076 (0.046)

Table 7.7 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-children aged 0-14 years[i]

ICD10 codes	Description	Total events (% of all ages)	Rate per 100,000 children population			% change	β[ii] (se), p-value
			Mean rate per annum	1996	2006		
	Streptococcus pneumoniae						p=0.134
M028/M029	Reactive arthropathies	96 (44)	1.60	1.25	1.15	-7.7	0.052 (0.074) p=0.501
N00/N01	Acute and rapidly progressive nephritic syndrome	81 (41)	1.34	4.46	0.96	-78.5	-0.152 (0.100) p=0.165
J398/J399	Other specific and unspecific diseases of upper respiratory tract	81 (10)	1.34	2.68	0.96	-64.1	-0.152 (0.100) p=0.165
J47	Bronchiectasis	77 (2)	1.29	0.54	1.15	115.3	0.032 (0.047) p=0.517
I00/I01/I02/ I301/I33/I38	Rheumatic fever	62 (4)	1.04	1.07	1.92	79.5	0.061 (0.048) p=0.241

The following codes had <50 events in total and could not be analysed for trends:

A36	*Diptheria*	*J16*	*Pneumonia due to other infectious organisms (not elsewhere classified)*
A481	*Legionnaires' disease*	*J170/J178*	*Pneumonia in bacterial and other diseases classified elsewhere*
A70	*Chlamydia psittaci infection*	*J340*	*Abscess, furuncle and carbuncle of nose*
B960	*Mycoplasma pneumoniae as the cause of disease classified to other chapters*	*J440*	*COPD with acute lower respiratory infections (excludes with influenza)*
B961	*Klebsiella pneumoniae as the cause of disease classified to other chapters*	*J85*	*Abscess of lung and mediastinum*
G06	*Intracranial and intraspinal abscess and granuloma*	*L540*	*Erythema marginatum in acute rheumatic fever*
G08	*Intracranial and intraspinal phlebitis and*	*M03*	*Postinfective and reactive arthropathies in*

Table 7.7 Hospital events of infections in Wales by complications arising from RTIs between 1996 and 2006-children aged 0-14 years[i]

ICD10 codes	Description	Total events (% of all ages)	Rate per 100,000 children population			% change	β^{ii} (se), p-value
			Mean rate per annum	1996	2006		
	thrombophlebitis				*disease classified elsewhere-*		
J051	*Acute epiglottitis*		*M010/M013*		*Meningococcal arthritis and arthritis in other bacterial diseases classified elsewhere*		
J14	*Pneumonia due to Haemophilus influenzae*						

[i] *Table sorted by total events;*
[ii] *Coefficient for trend using single-level linear regression model with rates as the outcome variable*

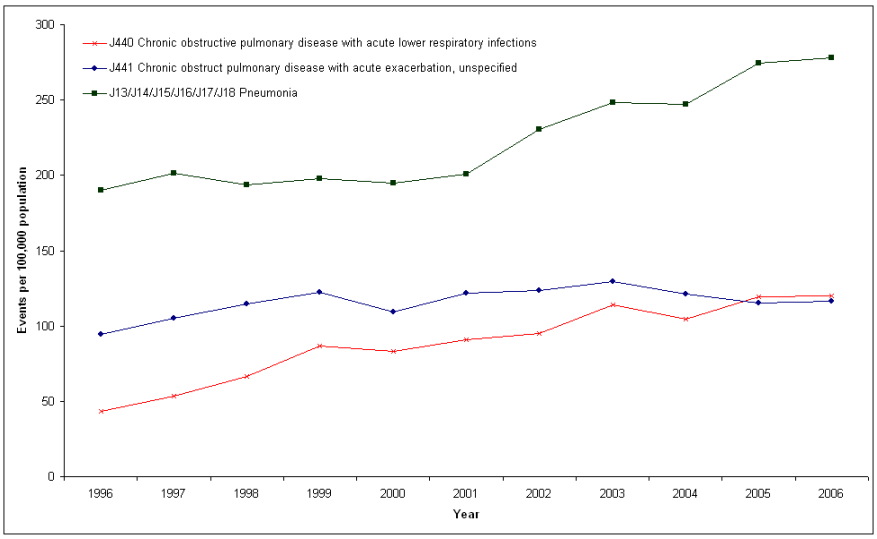
7.4.3.1 *Trends in complications*

7.4.3.1.1 *COPD and pneumonia*

Over all ages, the most common complications were pneumonia and COPD; they showed significant increases in rates and changes over time are shown in Figure 7.12. For COPD with acute lower respiratory infections (excludes with influenza) (J440), the rate of infection significantly increased over the 11 year period by 7.531 per 100,00 population per annum (95% CI=5.992 to 9.071, p<0.001). For COPD with acute exacerbation, unspecified (J441), the trend was not significant (β=1.781, 95% CI=-0.001 to 3.563, p=0.05).

For pneumonia, the rate of infection significantly increased over the 11 year period by 9.361 events per 100,000 population per annum (95% CI=6.426 to 12.296, p<0.001) (Figure 7.12).

Figure 7.12 Annual incidence of pneumonia and COPD events (per 100,000 population) in Wales



The increase in overall pneumonia rates was mainly from two ICD10 codes: bacterial pneumonia, not elsewhere classified (J15) and pneumonia, organism unspecified (J18) which increased by 0.452 (95% CI=0.253 to 0.650) and 9.040 (95% CI=6.290 to 11.789) events per 100,000 population per annum, respectively (Figure 7.13). For both codes, the increases were seen in the predominantly elderly age group (65 year and over) (J15: β=1.529, 95% CI=0.813 to 2.246, p<0.001 and J18: β=29.442, 95% CI=18.115 to 40.770, p<0.001) (Figure 7.14 and Figure 7.15). A significant increase was also seen for children (0-14 years of age) in bacterial pneumonia (β=0.457, 95% CI=0.301 to 0.613, p<0.001).

Figure 7.13 Annual incidence of pneumonia events by type (per 100,000 population) in Wales

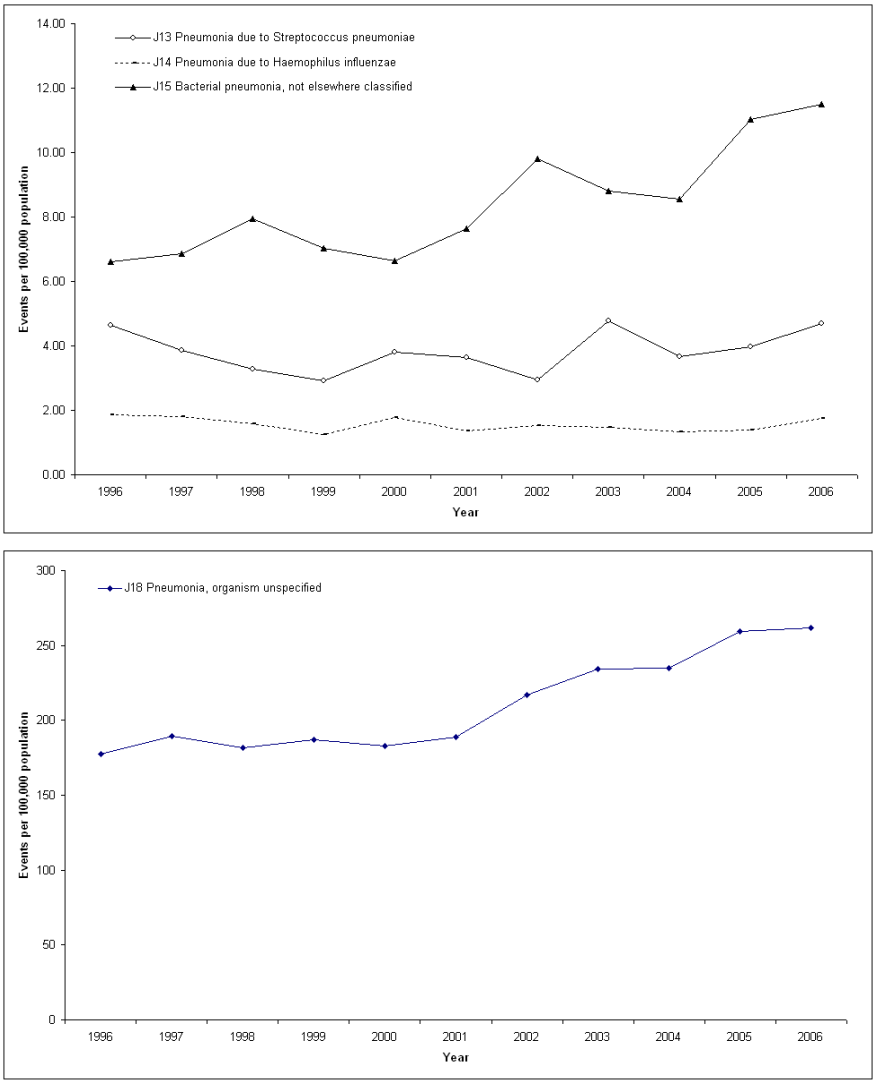


Figure 7.14 Annual incidence of bacterial pneumonia, not elsewhere classified (J15) events by type (per 100,000 population), by age group

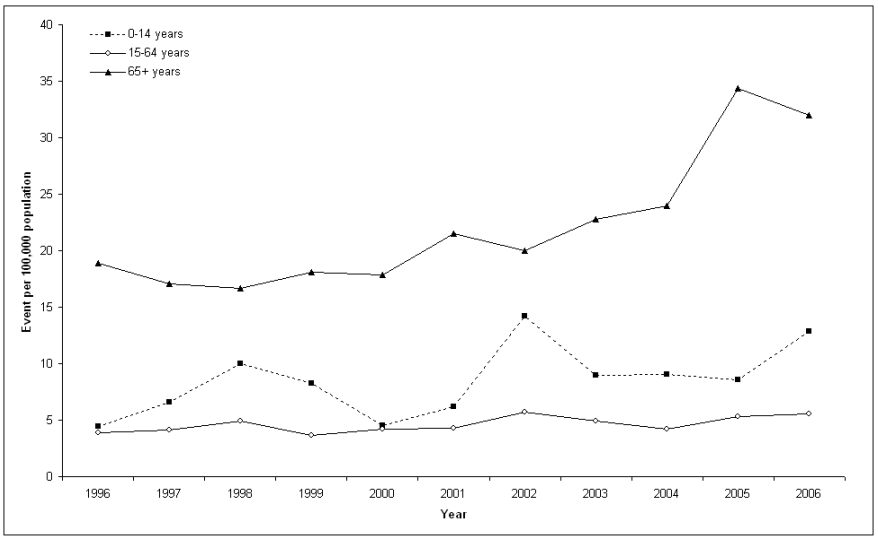
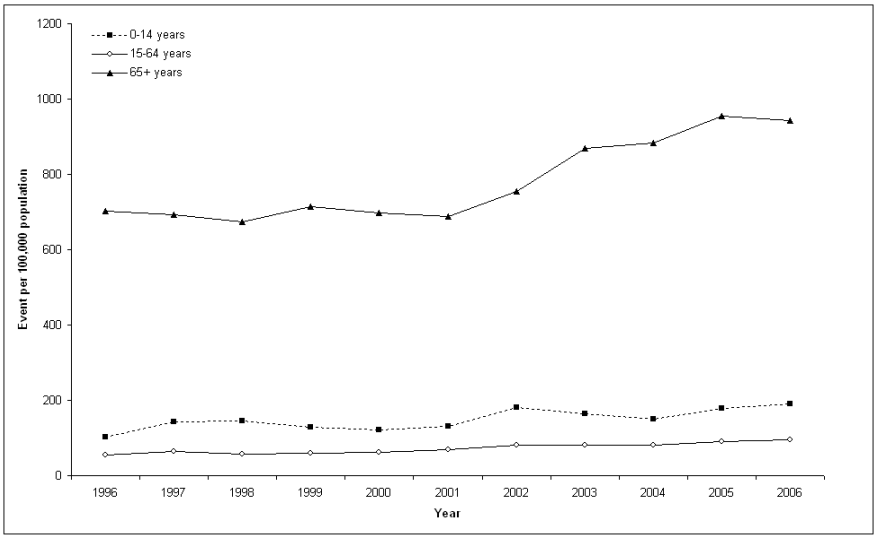


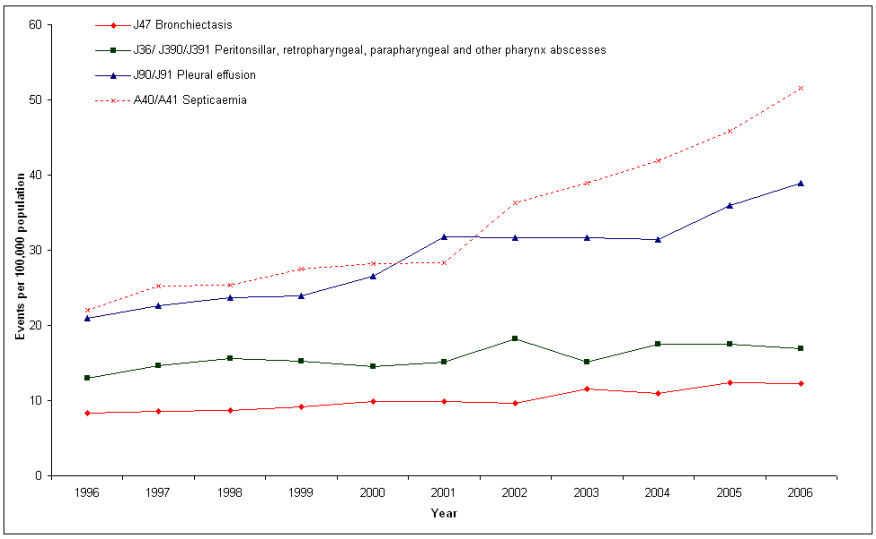
Figure 7.15 Annual incidence of pneumonia, organism unspecified (J18) events by type (per 100,000 population), by age group



7.4.3.1.2 *Septicaemia, pleural effusion, peritonsillar abscess and bronchiectasis*

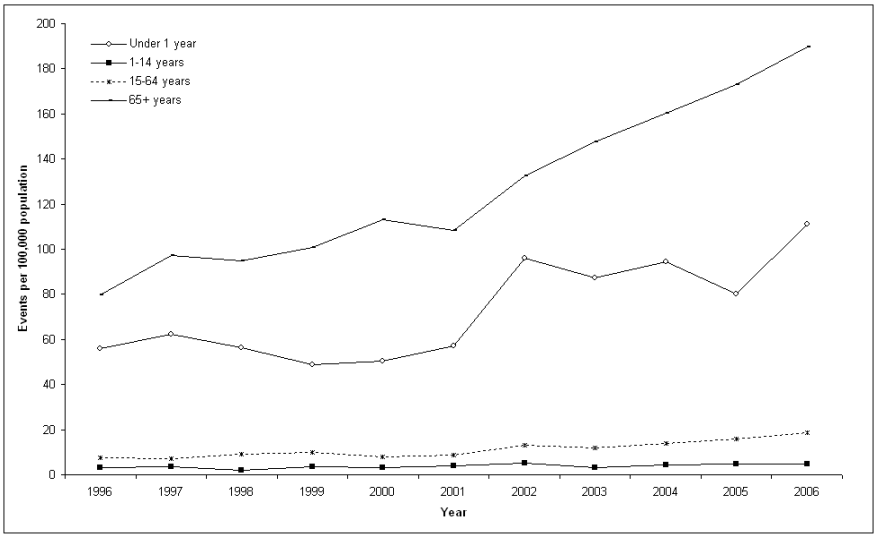
Events of septicaemia, pleural effusion, peritonsillar abscess (quinsy), and bronchiectasis also showed increases in rates over time (Figure 7.16). The increase in the rate of septicaemia infections (A40 and A41) was highly significant over time (β=2.815, 95% CI=2.233 to 3.397, $p<0.001$) with a 133.5% increase over time (from 22.07 events per 100,000 population in 1996 to 51.52 events per 100,000 population in 2006). This result was again replicated in children with a 73.2% increase over time (from 8.20 to 14.21 events per 100,000 children population respectively). Although most of the cases of septicaemia were classified as "other septicaemia" (A41), positive trends were also observed in "streptococcal septicaemia" (A40), although the latter was not replicated in children.

Figure 7.16 Annual incidence of bronchiectasis, peritonsillar abscess, pleural effusion and septicaemia events (per 100,000 population) in Wales



The increase in streptococcal septicaemia (A40) was seen in both the 15-64 and the 65 and over age group (β=0.103, 95% CI=0.066 to 0.14, p<0.001 and β=0.590, 95% CI=0.288 to 0.892, p=0.002 respectively). For events coded as other septicaemia (A41), rates were higher in the under 1 and 65+ age groups where significant increases were observed (β=5.302, 95% CI=2.387 to 8.217, p=0.003 and β=10.566, 95% CI=8.637 to 12.494, p<0.001 respectively) (Figure 7.17).

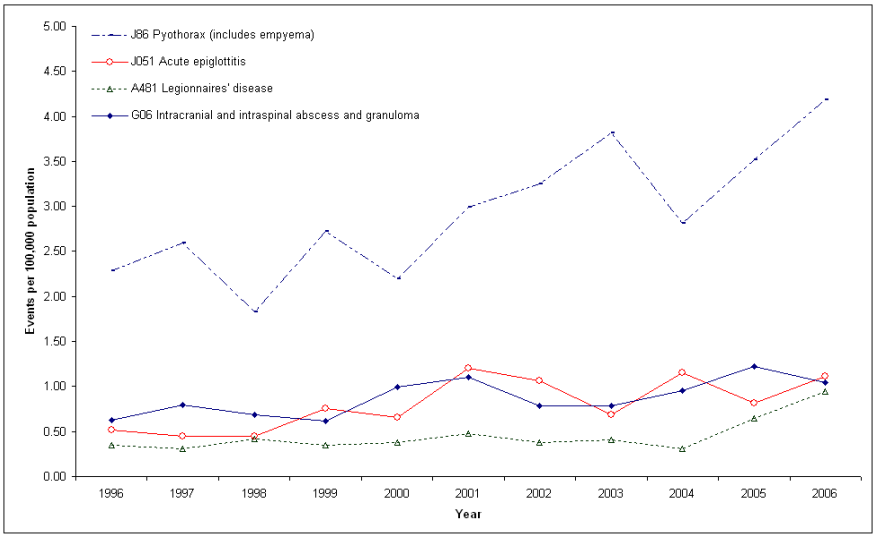
Figure 7.17 Annual incidence of other septicaemia (A41) events (per 100,000 population) by age group, in Wales



7.4.3.1.3 *Other complications*

Figure 7.18 shows the change over time of some less common complications such as for pyothorax (including empyema), epiglottitis, intracranial and intraspinal abscess and granuloma, and legionnaire's disease. These results should be interpreted with caution as the numbers of events per annum were small (on average <25 events per annum), with the exception of pyothorax (on average 85 events per annum).

Figure 7.18 Annual incidence of pyothorax, acute epiglottitis, legionnaire's disease and intracranial and intraspinal abscess events (per 100,000 population), in Wales

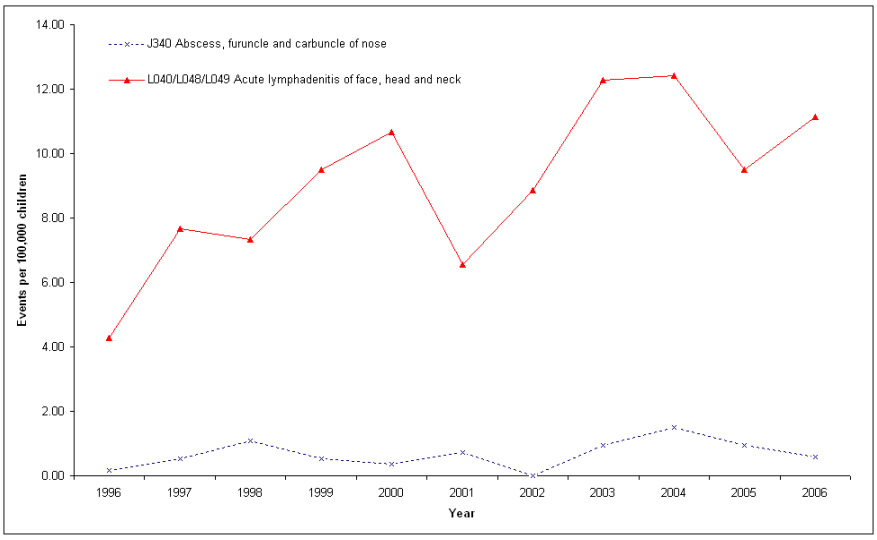


Events of infection for both pyothorax (includes empyema) (J86) and intracranial and intraspinal abscess and granuloma (G06) significantly increased over time. In pyothorax, these significant increases were mainly seen in the 15-64 and 65 and over age group. The trend in intracranial and intraspinal abscess and granuloma was also seen in children aged 0-14 years. The significant increases over the time period in events of acute epiglottitis (J051), and legionnaire's disease (A481) were not seen in children 0-14 years of age.

Complications that significantly increased over time for all ages but were not seen in children were pleural effusion (J90 and J91), peritonsillar abscess (including quinsy) (J36/ J390/J391) and bronchiectasis (J47). For pleural effusion, an 86.0% increase was seen between 1996 and 2006 (from 20.96 to 38.98 per 100,000 population

respectively) (β=1.697, 95% CI=1.357 to 2.037). Increases were mainly seen in pleural effusion and bronchiectasis in the 65 and over age group (β=6.640, 95% CI=5.178 to 8.103, p<0.001) and (β=2.217, 95% CI=1.587 to 2.846, p<0.001 respectively) and in the 15-64 age group for peritonsillar abscess (β=0.498, 95% CI=0.176 to 0.820, p=0.007). Acute lymphadenitis of face, head and neck (L040/L048/L049), abscess, furuncle and carbuncle of nose (J340) were both seen to increase in children only (Figure 7.19) although the numbers of events for abscess, furuncle and carbuncle of nose were very small.

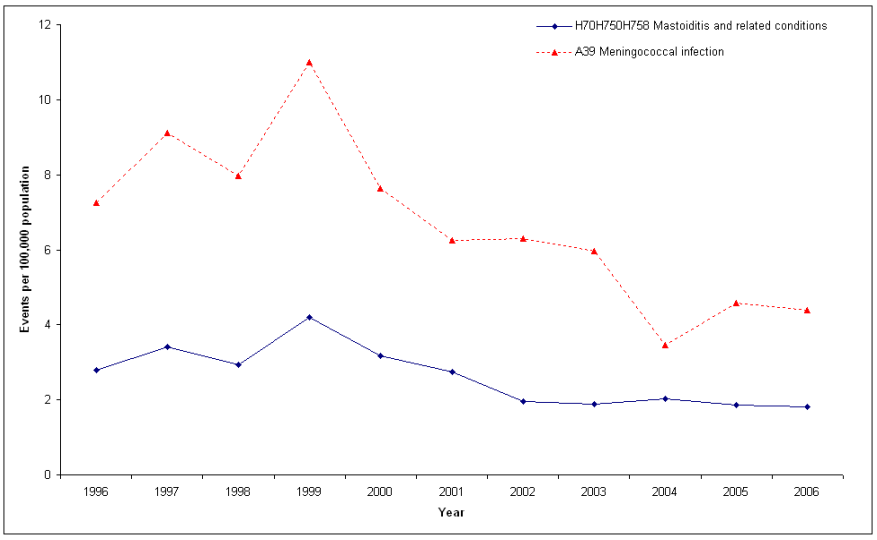
Figure 7.19 Annual incidence of abscess, furuncle and carbuncle of nose and acute lymphadenitis of face, head and neck events (per 100,000 children population) in children, in Wales



7.4.3.1.4 *Complications decreasing over the study period*

For all ages, the rate of meningococcal infection and mastoiditis significantly decreased over the period by 39.7% and 35.0% respectively (Figure 7.20). In meningococcal infection, a significant decrease was seen over all age groups. In mastoiditis, the decrease was seen in all age groups apart from in the 0-4 year olds, where rates increased from 3.34 to 8.74 events per 100,000 population (β =0.525, p=0.05, 95% CI=0.001 to 1.049). The rate of bronchitis also decreased significantly over time in children (β=-0.815, 95% CI=-1.137 to -0.493).

Figure 7.20 Annual incidence of mastoiditis and meningococcal infection events (per 100,000 population), in Wales

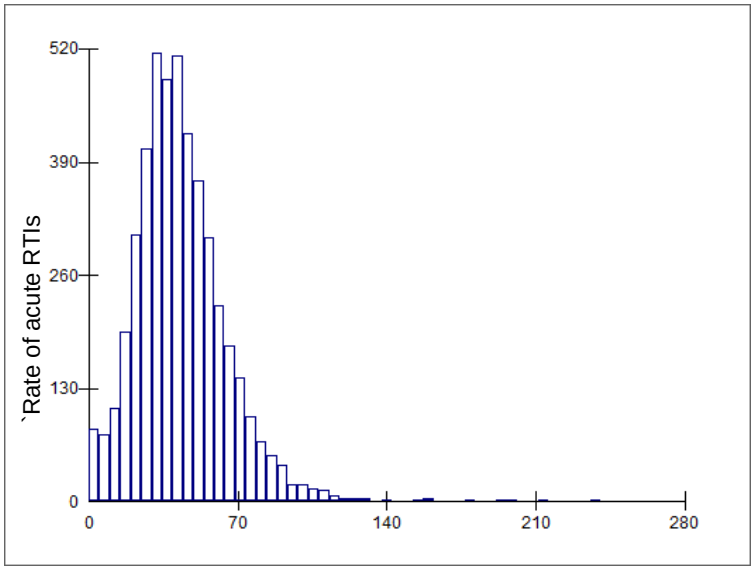


7.4.4 Multilevel modelling of hospital events

7.4.4.1 *Acute RTIs*

To examine how hospital events varied by general practice this section of the analysis was restricted to the 426 UTS practices in Wales and covered 2,802,319 (94.5%) of the Welsh population. In total 127,306 events of hospital based RTIs were identified from these practices during the study period (1996 to 2006). The number of hospital events for acute RTIs per practice per annum ranged from 0 to 152 with a median of 23 (25^{th} to 75^{th} percentile =14 to 37) (Figure 7.21). The median acute RTI rate was 41.02 per 10,000 practice population (25^{th} to 75^{th} percentile =29.47 to 54.55) and ranged from 0 to 240.66 per annum.

Figure 7.21 Histogram of the rate of acute RTIs (per 10,000 practice population) practice per annum



For acute RTIs over all ages, a Poisson model which incorporated time, deprivation quintile, average age of the GP and percentages of the practice population that were children (aged 0-14) and aged 65 and over was found to be the best fit (DIC =32922.04 when compared to model with time only DIC =33536.11) (Table 7.8). For all ages, time and deprivation quintile were treated as continuous terms rather than categorical since a linear association was found with respect to acute RTIs. For children, time was treated as a categorical variable as no linear association was found with event of acute RTIs. There was some indication of over-dispersion with a level

1 variance of 2.27. A negative binomial (NB) model was therefore run for comparison purposes although resulted in small differences in the parameter estimates. Therefore estimates from the Poisson model were used.

The Poisson (MCMC) model found that the SIR (i.e. observed / expected count of all acute RTIs) increased over time by a factor of 1.034 (95% CI=1.015 to 1.052) per annum. That is, the risk of an acute RTI hospitalisation increased by 3.4% each year. This result differed from that found in the single level model where the trend was not significant.

Table 7.8 Multilevel model for standardised incidence rates (SIRs) for acute RTI hospital events-all ages and children

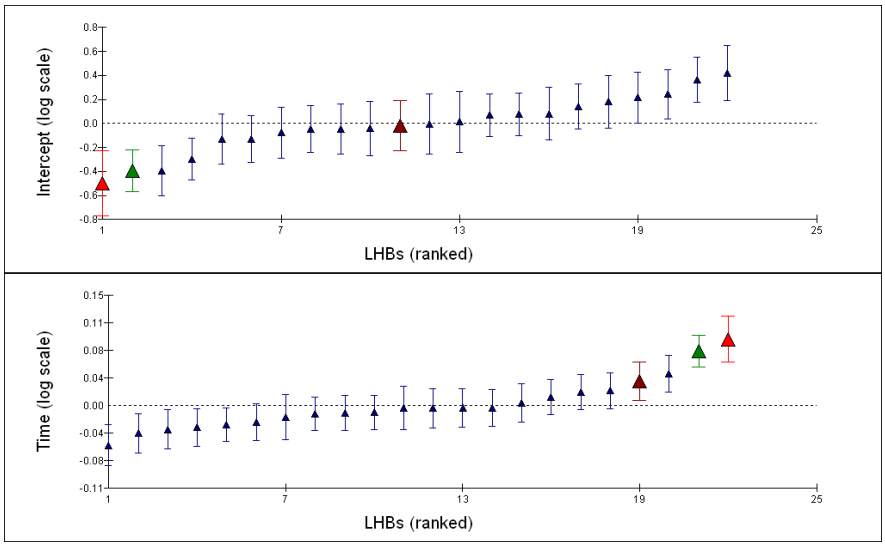
	Log_e parameter estimate (SE)		**SIR[i] (95% CI)**
Parameters	**Negative binomial**	**Poisson (MCMC)**	**Poisson (MCMC)**
All ages			
Year (1996 to 2006)	0.032 (0.008)	0.033 (0.009)	1.034 (1.015 to 1.052)
Deprivation quintile[ii]	0.070 (0.011)	0.068 (0.010)	1.070 (1.050 to 1.092)
% practice pop aged 0-14	0.052 (0.004)	0.056 (0.004)	1.058 (1.049 to 1.066)
% practice pop aged 65 and over	0.021 (0.004)	0.021 (0.003)	1.021 (1.015 to 1.027)
Average age of GPs (years)	0.006 (0.002)	0.004 (0.002)	1.004 (1.000 to 1.008)
Children			
1996	Ref	Ref	1.000
1997	0.109 (0.031)	0.101 (0.022)	1.106 (1.060 to 1.155)
1998	0.316 (0.030)	0.322 (0.021)	1.380 (1.324 to 1.438)
1999	0.338 (0.030)	0.342 (0.021)	1.408 (1.351 to 1.467)
2000	0.267 (0.030)	0.274 (0.021)	1.315 (1.262 to 1.370)
2001	0.344 (0.030)	0.355 (0.021)	1.426 (1.369 to 1.486)
2002	0.261 (0.031)	0.275 (0.021)	1.317 (1.263 to 1.372)
2003	0.449 (0.030)	0.459 (0.020)	1.582 (1.522 to 1.646)
2004	0.281 (0.030)	0.293 (0.021)	1.340 (1.286 to 1.397)
2005	0.368 (0.030)	0.376 (0.021)	1.456 (1.398 to 1.518)
2006	0.539 (0.030)	0.539 (0.020)	1.714 (1.648 to 1.783)
Deprivation quintile	0.093 (0.013)	0.090 (0.013)	1.094 (1.067 to 1.122)

[i] *Observed over expected counts*
[ii] *1 =least deprived to 5 =most deprived*

A positive association also existed between the rate of acute RTIs and deprivation quintile, indicating that more deprived practices (based on the average deprivation score of the practice population) were more likely to have patients presenting in hospital with an acute RTI. Acute RTIs were also more likely to have been seen in practices with a higher proportion of children aged 0-14 and also of patients aged 65 and over. That is, the risk of an acute RTI hospitalisation increased by 58% with every 10% increase of 0-14 year olds in the practice population and by 21% with every 10% increase of 65 year olds and over in the practice population. There was also some indication that the risk of acute RTIs in hospital was higher in practices with older GPs.

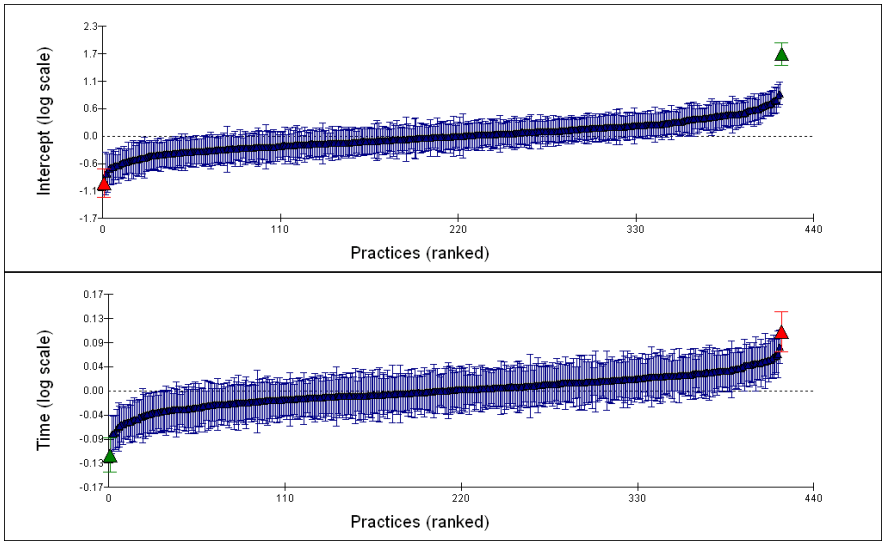
There was nearly twice as much variability in log SIRs between practices (σ^2_{u0}=0.121 (SE=0.010)) than between local health boards (LHBs) (σ^2_{v0}=0.075 (SE=0.028)). There was still however significant variation in the LHBs' departure from the average intercept (β_0) and slope (β_1) as shown in the caterpillar plots below (Figure 7.22).

Figure 7.22 Caterpillar plots: LHB-level residuals (± 1.96SD) vs. rank



At the practice level, one practice in particular had a greater positive departure from the overall intercept but this practice initially had a high number of hospital events for acute RTIs which reduced over time (Figure 7.23).

Figure 7.23 Caterpillar plots: Practice-level residuals (± 1.96SD) vs. rank

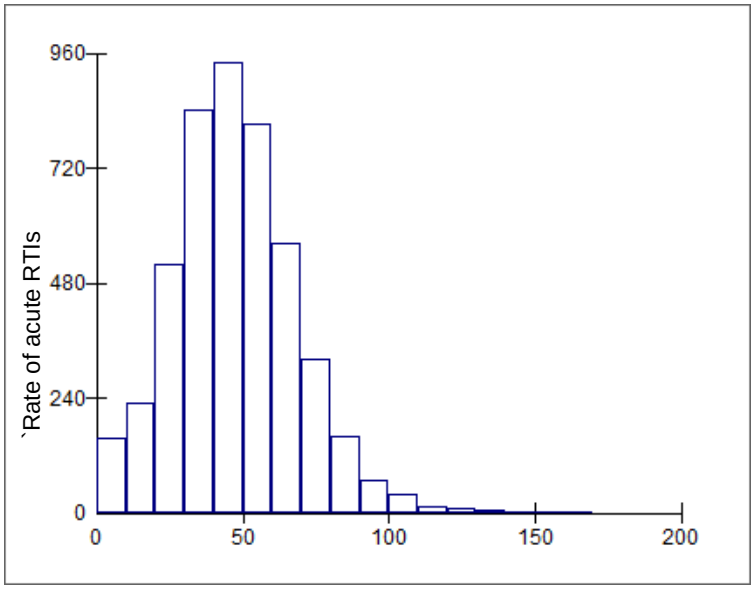


A similar relationship held for acute RTI hospitalisations in children; rates in all acute RTIs significantly increased over time and the same positive association with deprivation was shown. There was still significant variation at both LHB and general practice level.

7.4.4.2 *Complications*

In total 130,023 events of complications arising from acute RTIs were identified from the 426 UTS practices during the study years (April 1996 to March 2006). The number of hospital events for complications per practice per annum ranged from 0 to 157 with a median of 27 (25^{th} to 75^{th} percentile =15 to 40) (Figure 7.24). The median complication rate (per 10,000 practice population) was 46.16 (25^{th} to 75^{th} percentile =33.48 to 60.23) and practice rates ranged from 0 to 166.32.

Figure 7.24 Histogram of complication rates (per 10,000 practice population) per practice per year



A model which incorporated time, deprivation quintile, average age of the GP and percentages of the practice population that were aged 15 to 64 and 65 plus was found to be the best fit (DIC 32210.53 when compared to the null model=DIC 38021.73) (Table 7.9). Time and deprivation were treated as continuous variables rather than categorical since a linear association was found with respect to complications. Again there was some indication of over-dispersion with a level 1 variance of 1.89 and a negative binomial (NB) model was also run for comparison purpose. The NB model showed little differences in the parameter estimates and results from the Poisson model were used. The Poisson model confirmed that the SIR increased over time by a factor of 1.068 per annum, a stronger effect than in RTIs. A positive association also existed between complications and deprivation quintile, indicating that practices

with a lower deprivation quintile (based on the average deprivation score of the practices population) were more likely to have patients presenting in hospital with a complication.

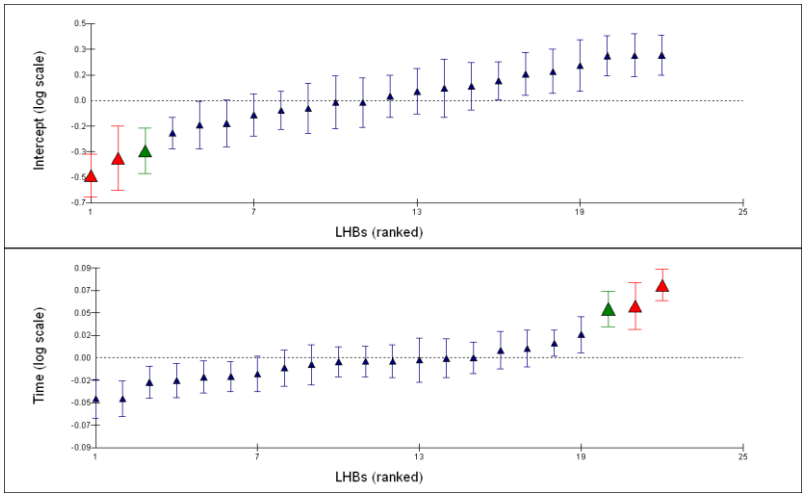
Table 7.9 Multilevel model for standardised incidence rates (SIRs) for hospital events for complications-all ages and children

	Log_e parameter estimate (SE)		**SIR[i] (95% CI)**
Parameters	**Negative binomial**	**Poisson (MCMC)**	**Poisson (MCMC)**
All ages			
Year (1996 to 2006)	0.060 (0.007)	0.066 (0.006)	1.068 (1.056 to 1.081)
Deprivation quintile[ii]	0.094 (0.008)	0.093 (0.008)	1.097 (1.080 to 1.115)
% practice pop aged 0-14	0.031 (0.003)	0.035 (0.003)	1.036 (1.030 to 1.042)
% practice pop aged 65 and over	0.039 (0.003)	0.040 (0.003)	1.041 (1.035 to 1.047)
Average age of GPs	0.004 (0.002)	0.004 (0.001)	1.004 (1.002 to 1.006)
Children			
Year	0.039 (0.011)	0.039 (0.010)	1.040 (1.020 to 1.060)
Deprivation quintile	0.043 (0.012)	0.043 (0.011)	1.044 (1.022 to 1.067)

[i] *Observed over expected counts*
[ii] *1 =least deprived to 5 =most deprived*

Complications were also more likely to have been seen in practices with a higher proportion of elderly patients aged under 15 and 65 and over. There was also some indication that the risk of complications was higher from practices with older GPs. Variability between practices (σ^2_{u0}=0.075 (SE=0.007)) and between LHBs (σ^2_{v0}=0.065 (SE=0.023) were similar. There was significant variation in the LHBs' departures from the average intercept (β_0) and slope (β_1) and those with the steepest positive slopes were LHBs from the more deprived areas in Wales (Figure 7.25). Similarly, hospital events of complications in children increased significantly linearly over time and the same positive association with deprivation was shown.

Figure 7.25 Caterpillar plots: LHB-level residuals (± 1.96SD) vs. rank



7.4.4.3 *Pneumonia*

The number of hospital events for pneumonia over all ages per practice per annum ranged from 0 to 65 with a mean of 12.57 (SD=8.95) events. Practice rates in 2006 varied greatly, from 0 to 4019.67 per 100,000. For pneumonia a very similar pattern to overall complications existed albeit a weaker association; an upward trend over time and a positive association with deprivation quintile and percentage of the practice population aged under 15 and 65 and over (Table 7.10). The level 1 variance was 1.51 and a negative binomial (NB) model was again run for comparison purposes. From the Poisson model, there was more variation between practices (σ^2_{u0}=0.083 (SE=0.010)) than LHBs (σ^2_{v0}=0.056 (SE=0.021)).

Table 7.10 Multilevel model for standardised incidence rates (SIRs) for pneumonia hospital events-all ages

	Log$_e$ parameter estimate (SE)		**SIR[i] (95% CI)**
Parameters	**Negative binomial**	**Poisson (MCMC)**	**Poisson (MCMC)**
All ages			
Year (1996 to 2006)	0.065 (0.006)	0.063 (0.005)	1.065 (1.055 to 1.076)
Deprivation quintile[ii]	0.057 (0.008)	0.053 (0.008)	1.054 (1.038 to 1.071)
% practice pop aged 0-14	0.026 (0.004)	0.025 (0.003)	1.025 (1.019 to 1.031)
% practice pop aged 65 and over	0.041 (0.003)	0.038 (0.002)	1.039 (1.035 to 1.043)

[i] *Observed over expected counts;* [ii] *1 =least deprived to 5 =most deprived*

7.4.4.4 *Septicaemia*

The number of hospital events for septicaemia per practice per annum ranged from 0 to 20 with a mean of 1.95 (SD=2.12). Practice rates in 2006 varied greatly between 0 to 284.81 per 100,000 population in 2006. For septicaemia a very similar pattern to that for pneumonia existed, with an upward trend over time and a positive association with the practice's deprivation quintile where septicaemia rates were significantly higher in deprivation quintile 5 (most deprived) when compared to quintile 1 (least deprived). Septicaemia was also more likely to have been seen in practices with a higher proportion of patients aged under 15 and 65 and over (Table 7.11). The level 1 variance was 1.092. There was more variation between LHBs (σ^2_{v0}=0.078 (SE=0.028) than practices (σ^2_{u0}=0.021 (SE=0.005)).

Table 7.11 Multilevel model for standardised incidence rates (SIRs) for septicaemia hospital events-all ages

	Log$_e$ parameter estimate (SE)		**SIR[i] (95% CI)**
Parameters	**Negative binomial**	**Poisson (MCMC)**	**Poisson (MCMC)**
All ages			
Year (1996 to 2006)	0.099 (0.004)	0.100 (0.004)	1.105 (1.097 to 1.114)
Deprivation quintile			
1 (least deprived)	Ref	Ref	1
2	0.050 (0.043)	0.049 (0.044)	1.050 (0.963 to 1.145)
3	0.016 (0.046)	0.024 (0.047)	1.024 (0.934 to 1.123)
4	0.059 (0.047)	0.062 (0.048)	1.064 (0.968 to 1.251)
5 (most deprived)	0.128 (0.050)	0.124 (0.051)	1.132 (1.024 to 1.257)
% practice pop aged 0-14	0.015 (0.006)	0.015 (0.005)	1.015 (1.005 to 1.025)
% practice pop aged 65 and over	0.048 (0.004)	0.047 (0.005)	1.048 (1.038 to 1.058)

[i] *Observed over expected counts*

7.4.5 Comparison of results from single- and multi-level modelling

Table 7.12 shows the estimates for the parameter year (1996 to 2006) from the single- and multi-level models for each diagnosis over all ages. The actual estimates here are not comparable; only the direction and significance of the trend indicated by the confidence intervals. For most diagnoses (complications, pneumonia, septicaemia) the estimates demonstrate a significant trend in events but in acute RTIs, the single level showed no significant trend but a weak trend was shown using multilevel modelling.

Table 7.12 Comparison of estimates for year from the single- and multilevel modelling - parameter estimate (confidence interval)

Diagnosis	**Single-level linear regression**	**Multi-level poisson regression**
Acute RTIs	0.31 (-0.30 to 0.92)[i]	1.034 (1.015 to 1.052)
Complications	1.99 (1.66 to 2.31)[i]	1.068 (1.056 to 1.081)
Pneumonia	0.94 (0.64 to 1.23)[ii]	1.065 (1.055 to 1.076)
Septicaemia	0.28 (0.22 to 0.34)[ii]	1.105 (1.097 to 1.114)

[i] *rate per 10,000 population*
[ii] *rate per 100,000 population*
[iii] *Standardised incidence rates (observed over expected counts)*

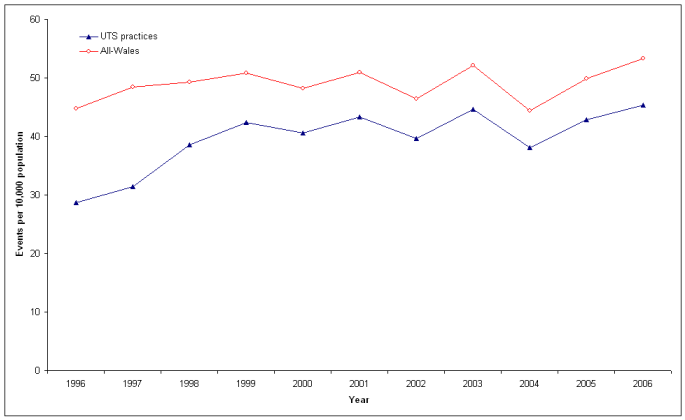
In acute RTIs, the difference in results of the trend in rates obtained from the single and multilevel models can perhaps be partly explained by the different number of practices used in both analyses. The single-level model used all-Wales rates per annum based on Wales mid-year population estimates. The multilevel model used practice level rates for the 426 "Up-to-Standard" (UTS) Welsh practices only.

Figure 7.26 a and b show the impact of restricting the analysis to UTS practices, on annual acute RTI and complication rates. From 1999 onwards, rates from UTS practices, although lower, reflect the same pattern seen in the all-Wales data. However, some discrepancies are highlighted in the early period, particularly between 1996 and 1998, when rates appear to have been consistently much lower in the UTS practices. The only explanation that could be given for this is that there were a high proportion of patients (24,791, 7.7% of the total population with an

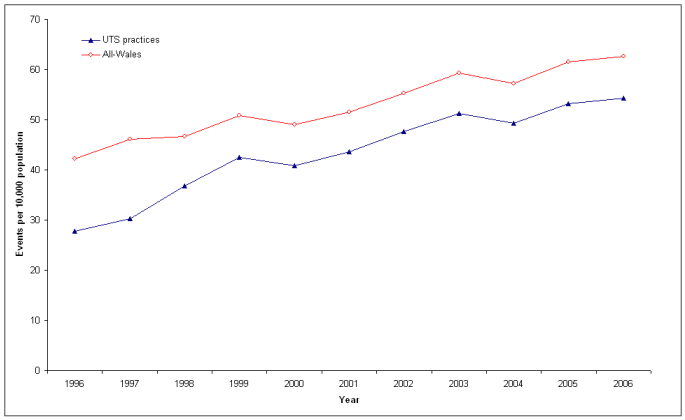
event) not allocated to a genuine practice code (as it was unknown); when the dataset was restricted to the UTS practices these patients would have been excluded. The explanation in the inconsistency over time may come from improvements in data quality; as improvements were made, the proportion of patients allocated to a genuine practice code would increase. Therefore the number of patients excluded as a result of restricting the analysis to UTS practices would decrease over time. For example, 25% of the unallocated patients were in 1996, which reduced to 4% in 2006 (6,210 unallocated patients to 1,002 respectively).

Figure 7.26 Comparison of acute RTI and complication event rates (per 10,000 population) from all-Wales and 'Up to Standard' (UTS) practices

(a) Acute RTI event rates



(b) Complication event rates



7.5 Discussion

7.5.1 Main findings

This study sought to examine trends in hospital admissions of acute respiratory tract infections (RTIs) and complications for the population of Wales over a 10 year period. Between 1996 and 2006, hospital events (comparable to admission rates) of acute RTIs had increased by 19% and after adjusting for practice characteristics, significant increases in trends remained. There was great variation in the rate of acute RTIs by Local Health Board (LHB) and general practices in Wales, both in the number of events and trends. Not all practices saw an increase in acute RTIs over time with some observing a reduction which is not surprising given that the trend was barely significant. A positive association existed between events and deprivation quintile (practices with a more deprived practice population were more likely to have patients presenting in hospital with an acute RTI), and were also more likely to have been seen in practices with a higher proportion of children aged 0-14 and also of patients aged 65 and over. There was also some indication that the risk of acute RTIs was higher in practices with on average older practising GPs. Similarly, hospital events of acute RTIs in children increased significantly over time.

Events of acute bronchitis were the most common hospitalisation over all ages and in children significantly increased over time (using single-level regression). Events of acute nasopharyngitis and acute upper respiratory infections were most common in children aged 0-14 years. Rates of acute pharyngitis and acute tonsillitis significantly increased over the study period, mainly due to increases in acute tonsillitis in children, but an increase was also observed in the 15-64 age group. Rates of otitis media (OM) significantly decreased over the study period for all ages.

Between 1996 and 2006, events of complications increased by 48% and again significant increases were identified after adjusting for practice characteristics. Events of complications were also more likely to have been seen in practices with a higher proportion of elderly patients aged under 15 and 65 and over, and from practices with older GPs. A similar pattern was found specifically in hospital events of complications in children, which significantly increased over time. Again there

was variability in rates of complications both between LHBs and practices.

Other significant increases detected in all ages, and in children, over the study period were for chronic obstructive pulmonary disease (COPD) (with acute exacerbation, unspecified, septicaemia and pyothorax (pleural empyema)). Additionally, pleural effusion and bronchiectasis were found to have significantly increased over time, mainly in the elderly age group, whilst peritonsillar abscesses significantly increased in the 15-64 age group. Mastoiditis and meningococcal infection were the only complications which had significantly decreasing rates over the time period. Events of meningococcal infection decreased over all age groups, but there was a significant increase in mastoiditis events in children aged 0-4 years of age.

7.5.2 Strengths and weaknesses of the study

This study is the first to examine trends in a wide array of hospital admissions for outcomes of acute RTIs and their complications, on a national level over a long time period, for all ages and for the paediatric population. It is also the first to examine the variation in these outcomes at a general practice level. As a result of this study we have identified increases in certain acute RTIs and complications that warrant future monitoring and further investigation into the cause of the increase.

Quality and using events of infections

The Patient Episode Database for Wales (PEDW) database is based on routinely collected administrative data using Welsh Hospital Episode Statistics (HES) and covers all 3 million residents in Wales. The data quality of PEDW is of a high standard and is monitored by the Welsh Assembly Government.

PEDW data is based on episodes of consultant care which are usually combined to create hospital admissions (or spells) to ensure that double counting of diagnoses is kept to a minimum. The use of a 91 day cut-off (linking episodes within 91 days of the initial infection) to create an *event* of infection may mean that we have under-estimated the number of complications. It is arguable that the cut-off is quite long and that episodes of infection over two months apart may be separate complications. Our measure of infection is therefore likely to be conservative but is unlikely to

change over time and trends should be unaffected. Reassuringly, examination of trends in admission rates (European age standardised rates (EASRs) per 100,000) for pneumonia (ICD10 codes J12 to J18), showed an increase of 30% between 2001 and 2006 (from 158.62 to 206.55 respectively) (Health Solutions Wales, Health Maps Wales), compared to a 38% increase for pneumonia using the codes J13-J18 (J12 is for viral pneumonia) demonstrated by this study.

True incidence rate of acute RTIs and complications

The study was limited to the available evidence in the database. Data arising from the PEDW database does not capture the true incidence rate of complications in the population; it contains data only on those patients whose condition is severe enough to be admitted as an inpatient to hospital. These are of course of importance since it is these serious complications that might cause concern if there were suggestions that they could arise from not being prescribed antibiotics. A proportion of patients will have been treated in the community solely by their GP or treated in accident and emergency and then discharged. When comparing primary care diagnosed complications in Chapter 4 (albeit from a small sample of practices between 1996 and 2000), an increase in mastoiditis and a decrease in pneumonia and empyema were found. This contrasts the findings from the Welsh hospital admissions data where a decrease was seen in mastoiditis and an increase in pneumonia. These data highlight the need to examine complications diagnosed in both settings but it also may be showing the locations where patients present with their complications are changing. For example, patients with mastoiditis may be more likely to be diagnosed and treated by their GP rather than in secondary care.

Explanation for a change in events over time

Although the data showed an increase in rates of certain complications, we are not able to identify the reasons for these increases. We were only able to adjust for the characteristics and population structure of a practice, available through administrative datasets. These included the age structure of GPs, single-handed status and practice deprivation, some of which are known to be associated with higher risk of complications. We also examined rates of hospital events, divided into age groups, to take into account a changing and ageing population in Wales.

Other reasons for these changes over time could be coding changes or changes to organisation of health services. Diagnoses are coded by clinical coders within each trust and therefore, whilst there is undoubtedly some variability in diagnoses codes between NHS trusts, this variability mainly affects secondary diagnoses and not primary diagnoses. Also if clinicians changed the way they coded certain diseases (e.g. from a general pneumonia code to a bacterial pneumonia code, perhaps to justify prescribing) then this would have been revealed by looking at the codes in pairs to try to detect a decrease in one code and an increase in another. For this reason we grouped codes from the same sub chapter such as ICD10 codes J13-J18 for pneumonia. Overall, pneumonia events increased over time but within these codes trends varied. In 2003 the GP contract changed and GPs were allowed to opt out of out-of-hours care from April 2004. New arrangements were put in place to ensure coverage of care, such as with Accident and Emergency (A&E) Units. Therefore patients may be more likely to put themselves in a position where they could be admitted to hospital instead of waiting to see their GP. The largest increases seen in our study happened before 2004 and so it is unlikely that this is the main reason behind the increase.

There is evidence to suggest that consultation rates for acute RTIs decreased in the community over this ten-year period, especially for upper RTIs (Smith *et al*. 2006; Gulliford *et al*. 2009). Acute RTIs have either become less common, or people are less likely to present to their GP with a minor infection. If the latter is true then patients may be more likely to present to A&E, especially if the infection develops into a complication.

We have already demonstrated that for most practices in Wales, overall antibiotic dispensing decreased between 1996 and 2006. This decrease also applies to antibiotic prescribing for patients specifically presenting with an RTI, as shown by Gulliford *et al*. (2009). It is therefore plausible that reduced usage of antibiotics in primary care for acute RTIs may have contributed to an increase in hospitalisations for RTIs and complication, especially if a blanket reduction was employed. Resistance may also be playing a part as resistance rates to certain antibiotics have been shown to be increasing in Wales (Chapter 6) and in certain countries (Felmingham *et al*. 2005). Patients with a resistance to an antibiotic could be less likely to respond to treatment

and therefore be more likely to develop a complication.

7.5.3 Comparisons with existing literature

The findings in this study raise the questions of whether these trends in acute RTIs and complications are a true reflection of what is happening in the population and, if so, what has caused them. Few studies have examined hospitalisations for acute RTIs and their complications. One study using official hospital episode statistics (HES) in England, examined trends in episodes with a primary diagnosis of pneumonia (ICD10 code J12-J18) (Trotter *et al.* (2008)). Numbers were based on persons admitted at least once a year, as opposed to the number of admissions. They found that, between April 1997 and March 2005, rates increased by 34% (from 1.48 to 1.98 per 1,000 population). This increase was noted in all age groups, but was most marked in older adults, and rates were higher in males than females. They observed that most of the increase over the study period was observed after 2000/01 in lobar pneumonia (J181) and pneumonia unspecified (J189). Although they included an extra ICD10 code-J12 (viral pneumonia), they found a slightly lower increase in rates over the study period than the 46% in our study (J13-J18)). This may be related to the fact that they counted patients, as opposed to linked episodes or admissions. However, other results between the studies were consistent in that pneumonia, organism unspecified (J18) made up the majority of cases in both (94% of all our pneumonia events) and that rates increased most in the elderly. A study by Koshy *et al.* (2010) examined hospital admissions for bacterial pneumonia and empyema between 1997 and 2008 in children (<15 years) in England using HES data. They found an increase of 31% in bacterial pneumonia admissions and that empyema admissions nearly tripled over the study period.

A review of peritonsillar abscess cases in three hospitals in Northern Ireland during 2001/02 found 128 inpatient cases (equivalent to 1 in 10,000 per population per annum) which again were comparable figures to ours (1.54 per 10,000) (Hanna *et al.* 2005). In another study carried out in England using hospital admissions data, standardised admissions ratios for RTIs increased over the time period (1996-2002) and varied four-fold between PCTs (Majeed *et al.* 2004). More recently, a study by Koshy *et al.* (2012) observed trends between 1999 and 2010 in acute throat

infections (ATI) (pharyngitis and tonsillitis) and peritonsillar abscess in children using emergency admissions data from HES in England. They found a comparable increase in ATI of 76% over the decade and similarly found no such trend in emergency admissions of peritonsillar abscesses. The study found a decline in tonsillectomies over the period.

Several studies have reported trends in complications in children. Sharland *et al.* (2005) reported an increase of 19% in mastoiditis admissions in children (aged 15 and under) between 1993 and 2002 (from 6.9 to 8.2 per 100,000 children) based on HES data for England. This increase was mainly seen in children aged 4 years of age or less (from 5.2 to 8.6 per 100,000). We similarly observed an increase in event rates of mastoiditis in children between 1996 and 2003 (from 3.92 to 5.77 per 100,000 population) but this trend was not significant, mainly due to the small numbers (in children aged 4 or less the trend was weakly significant from 3.34 to 6.88 per 100,000). They also found no trends in peritonsillar abscesses or rheumatic fever in children.

Ho *et al.* (2008) found no evidence of a trend in mastoiditis in children between 1996 and 2005 using data collected from one hospital in Australia (although numbers were small with fewer than 20 cases per annum). In Scotland hospital admissions of pneumonia (ICD10 codes J12-J18) increased between 1980 and 2005, by an average of 50 per million children per annum in the 1-4 year age group (Roxburgh *et al.* (2008)). We found a larger increase of 213.0 per million children per annum, in rates of pneumonia in children aged 1-4 years between 1996 and 2006. Conversely, data from SWEDRES showed that hospital admissions in pneumonia, acute mastoiditis, quinsy and rhinosinusitis in children were stable or decreased between 1987 and 2003 (Cars *et al.* 2005).

Roxburgh *et al*. (2008) also found a significant positive trend in empyema admissions between 1998 and 2005 with the highest rates seen in 1-4 year olds (8.3 admissions per million per annum). This significant trend in 1-4 year olds was also replicated in an English study by Gupta and Crowley (2006) where rates (per million) increased from 14 in 1995/6 to 46 in 2002/3. We found similar results with children aged 0-4 years having the highest pyothorax (including empyema) rates,

which had also significantly increased.

7.5.4 Implications of findings for clinical practice and future research

We have found that event rates of a number of acute RTIs and complications increased over the study period. We can be reasonably confident that our findings are reliable and generalisable as they are based on an entire population and results are in agreement with the majority of population based published evidence. Whilst the numbers involved for some of the complications are small, these increases are of concern and warrant further investigation. There is a need for these trends to be monitored, which is not currently routinely done. For surveillance of infections to be worthwhile, monitoring needs to be timely and use standardised high quality data that is comparable within and between countries. In Wales, data from the Patient Episode Database for Wales (PEDW) would be the obvious and best choice although surveillance would be limited to hospitalisations of infections and complications arising from them, highlighting the more severe end of the spectrum of infections (i.e. the infection was severe enough to be admitted to hospital).

7.6 Introduction to antibiotic dispensing and complications at an All-Wales level

Until now we have examined trends in dispensing, resistance and clinical outcomes on an all-Wales basis but using practice-level models. Future research is required to identify causes of these increases in rates so that their implications can be understood. One way of proceeding would be to link PEDW data to other routinely collected and, in most cases, administrative datasets such as antibiotic dispensing by GPs and resistance data. Results from these linked datasets could then start to inform clinical decisions to try and reduce complications, either by examining and possibly changing GPs' prescribing behaviour or by regularly submitting samples to test the resistance status of patients. This is the basis of the next chapter in which we wish to explore these associations. This chapter will investigate how these are related by examining associations between the three datasets at a general practice level.

Chapter 8 Antibiotic dispensing and complications arising from RTIs: an All-Wales study

8.1 Introduction

The aim of this chapter is to examine in greater depth the relationship explored in Chapter 4 using the data described in Chapters 5 to 7. These three datasets will be linked together at the general practice level for each year. The hypothesis is that at the level of general practice in Wales, reduced overall levels of community antibiotic dispensing may be associated with increases in hospital admissions in complications arising from common respiratory tract infections (RTIs). In addition the effects that practice characteristics and resistance have on the relationship will be investigated.

8.2 Methods

8.2.1 Linking antibiotic dispensing to hospital events of infections

Antibiotic dispensing items using Prescribing Analyses and Cost (PACT) data and hospital infection events using Patient Episode Database for Wales (PEDW) were aggregated at a general practice level and study year as described in chapters 5 and 7 respectively. These two datasets were linked using the general practice code and study year common to each dataset. Data were available for the period April 1996 to March 2006 and study years were created (e.g. 1996=April 1996 to March 1997) leaving ten years of data to analyse (1996 to 2005).

8.2.2 Linking to antibiotic resistance

The number of resistant isolates and the number of samples sent for resistance testing by GPs (with the *H. influenzae, S. pneumoniae* and *S. pyogenes* organisms) (using Datastore data) were aggregated at a general practice level. When resistance data was included in any model the study period was defined as from April 1998 to March 2006 creating eight years of data. Again these datasets were linked using the general practice encrypted practice code and study year common to each dataset. Annual practice populations (pp) and characteristics were obtained as before from the Welsh

Demographic Service (WDS).

8.2.3 General practices

The 426 "Up-To-Standard" (UTS) general practices in Wales with stable list sizes, described in Chapter 5, were used in this analysis. Hospital events for complications, dispensing and practice population data were available for all 426 practices. Resistance data was only available for a sample of these practices, numbers varying by type of organism. For example 341 practices had data on resistance to *H. influenzae* isolates. The dataset analysed was therefore reduced when resistance was included in any of the models.

8.3 Statistical analysis

8.3.1 Main analysis

Hospital infection events for total acute RTIs, total complications and a sub-group of pneumonia were examined over all ages, as were dispensing for total antibiotics, broad spectrum penicillins (BSPs), macrolides, cephalosporins, quinolones (used in the treatment of upper respiratory tract infections), and tetracyclines. Apart from pneumonia, individual categories of acute RTIs and complications (including septicaemia) were not examined due to the small numbers per practice. Dispensing items and hospital events for children were not linked and analysed due to the possible imprecise nature of liquid oral antibiotics as a proxy for antibiotic dispensing in children.

For each practice and study year, hospital infection event rates were calculated for total acute RTIs, total complications and pneumonia per 100,000 practice population (pp) per study year. Antibiotic dispensing rates were also calculated per 1,000 pp per study year. The percentage of resistant isolates was calculated for each practice and study year for the following organism/antibiotic combinations (excluding duplicate samples and certain laboratory selectivity as defined in section 6.2.4):

- Amoxicillin resistance in *H. influenzae* isolates;
- Erythromycin and penicillin resistance in *S. pneumoniae* isolates;
- Erythromycin resistance in *S. pyogenes* isolates.

Resistance to tetracyclines in *H. influenzae* isolates was not examined due to the small numbers of both hospital events and tested isolates when examined at practice/study year level. All samples were used, regardless of the source, rather than just sputum and ENT samples, again due to the small numbers involved.

8.3.1.1 *Negative Binomial regression*

As described in section 7.3.2.1, both a Poisson and negative binomial (NB) model were used to account for the overdispersion with independent counts of hospital admissions as the outcome variable, to account and correct for variation at the level of LHB, Welsh general practices and time. The NB model resulted in more conservative parameter estimates although the standard errors were similar and thus a three-level repeated measures negative binomial (NB) regression model was used. Estimates were obtained by using the restricted iterative generalized least squares (RIGLS) estimation (1st order penalised quasi-likelihood (PQL)) procedure; Monte Carlo Markov Chains (MCMC) estimation cannot be used at present with the NB method.

The results are summarised using the standardised incidence ratio (SIR) and 95% confidence intervals (CIs), which compares the ratio of the observed to expected counts at the 75th percentile to that at the 25th percentile (measured over all practices between 1996 and 2005) for each antibiotic. A value >1 means the rate of hospital infections was higher at the higher level of dispensing and a value <1 means the rate was lower at the higher level of dispensing. For example, the 25th and 75th percentiles for the BSP dispensing rate were 249.7 and 410.7 per 1,000 pp respectively (interquartile range (IQR) =161.0 per 1,000 pp).

8.3.2 Adjusting for confounders

Using NB regression analysis, the relationship between hospital events and antibiotic dispensing was adjusted for the following practice characteristics:

- Percentages of the practice population aged 0-14 years, 15-64, and 65 and over;
- Single-handed status of the practice (single or multi-handed);

- Practice deprivation quintile (based on the Townsend 2001 score of the practice population);
- Average age of GPs in a practice;
- Proportion of male GPs in a practice.

8.3.3 Comparisons of antibiotics, infections and resistance

Pragmatic comparisons were used to examine the association between hospital events for infections, antibiotic dispensing and resistance. The following comparisons were examined:

- Hospital admissions for all acute RTIs, all complications and pneumonia and:
    - antibiotic dispensing rates per 1,000 pp for total antibiotics, BSPs, quinolones, and tetracyclines and:
        - resistance to amoxicillin in *H. influenzae* isolates;
        - resistance to penicillin in *S. pneumoniae* isolates;
        - resistance to erythromycin in both *S. pneumoniae* and *S. pyogenes* isolates.

- Hospital admissions for all acute RTIs, all complications and pneumonia and:
    - antibiotic dispensing rates per 1,000 pp of macrolides and:
        - resistance to erythromycin in *S. pneumoniae* isolates;
        - resistance to erythromycin in *S. pyogenes* isolates.

- Hospital admissions for all acute RTIs, all complications and pneumonia and:
    - antibiotic dispensing rates per 1,000 pp of cephalosporins (beta lactams) and:
        - resistance to amoxicillin in *H. influenzae* isolates;
        - resistance to penicillin in *S. pneumoniae* isolates.

8.3.4 Sensitivity analyses

The analysis was re-run for the data period 1998 to 2005 to determine whether excluding the period between 1996 and 1998, where the greatest decline in antibiotic dispensing, made an impact on the relationship between hospital events and antibiotic dispensing.

8.3.5 Changes in antibiotic dispensing and complications

Change in dispensing rates per 1,000 pp and complications for individual practices were analysed between 1998 (April 1998 to March 1999) and 2005 (April 2005 to March 2006). Practices with data on dispensing in both 1998 and 2005 were included in this analysis to explore the relationship between practice level reductions in total antibiotic dispensing and changes in overall complications over the same period. Practices were grouped into quartiles based on their reduction of total antibiotic dispensing between 1998 and 2005. Complication rates for 1998, 2005, and the actual change in rates (with 95% CIs) were compared between these quartiles.

All multilevel modelling was performed using MLwiN version 2.16 and all other analyses using SPSS version 16.0.

8.4 Results

This analysis uses hospital events and community antibiotic dispensing data from 426 'Up-to-Standard' (UTS) practices covering 94.5% (2,802,319 population) of the official Welsh population. These two datasets have previously been summarised in Chapters 5 and 7.

A three-level Poisson multilevel model was fitted with the observed number of hospital events per annum at a general practice level as the outcome variable and in the first instance included antibiotic dispensing rates (per 1,000 pp) as an explanatory variable. The association was then adjusted for significant practice characteristics. Finally the same analysis was repeated on a subset of practices with reliable resistance data to examine the impact of adding resistance rates to the models.

Three separate models for hospital events were examined: total number of hospital events for complications, acute RTIs and pneumonia events.

8.4.1 The relationship between hospital events for complications arising from acute RTIs and antibiotic dispensing at a general practice level

Table 8.1 shows the parameter estimates from the univariate NB multilevel model examining the association between hospital events for overall complications and antibiotic dispensing. It also shows the ratio of the complication rates at the 75th percentile of the dispensing distribution (over all practices and years) to the 25th percentile for each antibiotic (SIR (IQR)). The 25th and 75th percentiles for each antibiotic dispensing rate are displayed for this reason. There were significant negative associations between hospital events for all complications arising from an acute RTI and antibiotic dispensing (by type and total). This indicates that practices with higher levels of dispensing per annum were associated with lower levels of complications. For BSPs, the rate of complications were 22% lower (SIR=0.78, 95% CI=0.71 to 0.86) in practices with a dispensing rate at the 75th percentile (410.7 dispensed items per 1,000 pp per study year) compared to practices with dispensing rate at the 25th percentile (249.7 dispensed items per 1,000 pp per study year). For

other antibiotics, the rate of complications ranged from 22% (SIR=0.78, 0.68 to 0.89) lower in cephalosporins to 4% (SIR=0.96, 0.93 to 0.99) lower in tetracyclines.

Table 8.1 Unadjusted multilevel models for hospital events for complications and antibiotic dispensing per 1,000 pp: 1996 to 2005

Antibiotic	**Log_e parameter estimate (SE) x 10^3**[i]	**Dispensing rate 25^{th} to 75^{th} percentile**	**SIR (IQR)**[ii]	**95% CI Lower limit**	**Upper limit**
BSPs	-1.53 (0.31)	249.7 to 410.7	0.78	0.71	0.86
Macrolides	-2.54 (0.65)	66.1 to 119.8	0.87	0.81	0.93
Cephalosporins	-3.89 (1.04)	37.2 to 102.2	0.78	0.68	0.89
Quinolones	-4.23 (1.52)	15.4 to 35.7	0.92	0.86	0.98
Tetracyclines	-1.47 (0.61)	39.6 to 66.4	0.96	0.93	0.99
Total antibiotics	-0.84 (0.17)	626.0 to 905.9	0.79	0.72	0.87

[i] *For total antibiotics the parameter estimate would be -0.000838 (0.000174)*
[ii] *SIR (IQR) = SIR of complications at 75^{th} percentile of dispensing distribution compared to the 25^{th} percentile*

Significant variation can be observed in complications at the LHB and practice levels (σ^2_{v0} =0.430 (SE=0.146) and σ^2_{u0} =0.455 (0.059) respectively) and thus a three-level model was retained. Significant variations were also seen in the association between total dispensing rates and complications (σ^2_{v1} =0.773 (0.258) and σ^2_{u1} =0.608 (0.087) respectively) with greater variation at the LHB level. Figure 8.1 shows the NB model with total antibiotic dispensing rate (*totr*) as an explanatory variable.

Figure 8.1 MLwiN output for three-level repeated measures NB model for hospital events for complications

$$N\_comps_{ijk} \sim \text{-ve Binomial}(\pi_{ijk})$$
$$\log(\pi_{ijk}) = offs_{ijk} + \beta_{0jk}cons + \beta_{1jk}totr_{ijk}$$
$$\beta_{0jk} = 0.738(0.148) + v_{0k} + u_{0jk}$$
$$\beta_{1jk} = -0.972(0.197) + v_{1k} + u_{1jk}$$

$$\begin{bmatrix} v_{0k} \\ v_{1k} \end{bmatrix} \sim N(0,\ \Omega_v) \ :\ \Omega_v = \begin{bmatrix} 0.430(0.146) & \\ -0.555(0.190) & 0.773(0.258) \end{bmatrix}$$

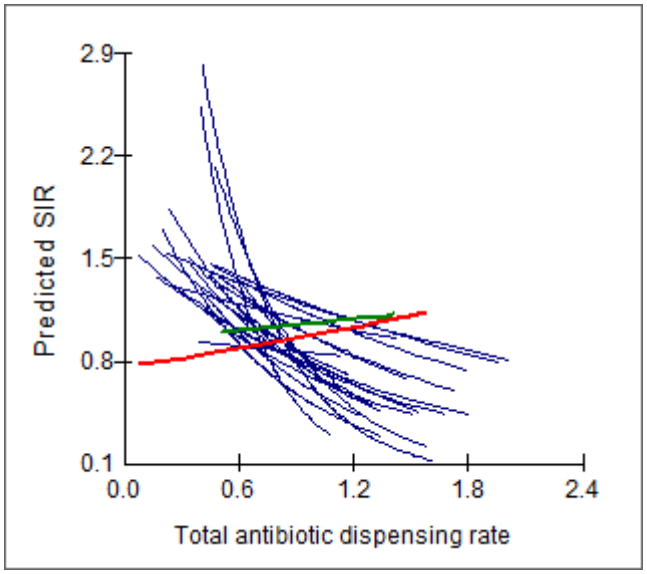
$$\begin{bmatrix} u_{0jk} \\ u_{1jk} \end{bmatrix} \sim N(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} 0.455(0.059) & \\ -0.450(0.069) & 0.608(0.087) \end{bmatrix}$$

$$\text{var}(N\_comps_{ijk} | \pi_{ijk}) = \pi_{ijk} + \pi_{ijk}^2 / v$$

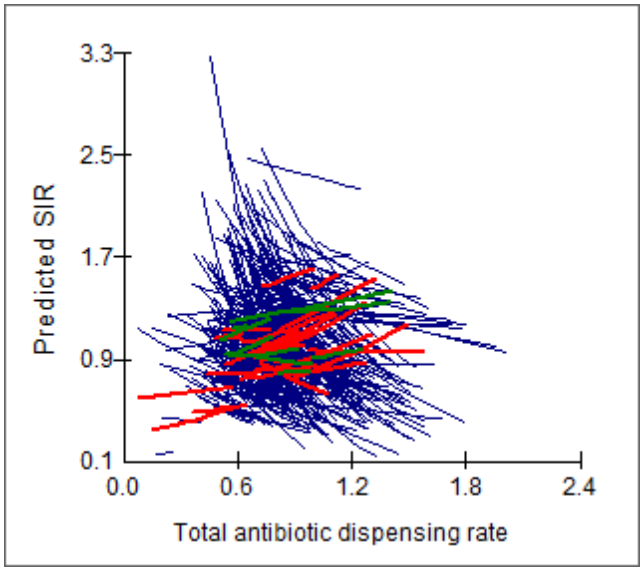
All groups of antibiotics except for tetracyclines used a three-level model. For tetracylines, the variations at both the practice and LHB level were small and including it as a random term improved the goodness of fit of the model by an insignificant amount. In this case the antibiotic dispensing term was fixed at both levels. Figure 8.2 shows the predicted values from the fitted models (a) for each of the 22 LHBs and (b) of the 426 UTS general practices in the case of total antibiotic dispensing. Almost all LHBs and practices show a negative association between complications and total antibiotic dispensing rates. Two LHBs were identified as having a positive association. This demonstrates that conclusions based on the whole dataset did not necessarily hold at an individual LHB or practice level.

Figure 8.2 Fitted association between hospital events for complications (predicted SIR) and total antibiotic dispensing rate

(a) by Local Health Boards (N=22)



b) by UTS practices (N=426)



8.4.1.1 *Addition of practice characteristics*

Unadjusted NB regression was performed to determine any significant explanatory variables that could be added to attempt to explain variation in complications. Complications were more likely to be found in practices with older GPs (SIR=1.007, 95% CI=1.003 to 1.011) and with an older practice population (aged 65 plus) (SIR=1.019, 95% CI=1.013 to 1.025). This indicates that an increase in one year in GP average age and an increase in one percentage of the practice population that is aged 65 plus would increase the complication rate by 0.7% and 1.9% respectively. The proportion of the practice aged 0-14 years was negatively associated with complications (SIR=0.943, 95% CI=0.935 to 0.950). Deprivation quintile (entered as a continuous term due to its linear association with complications) was also associated with complications, with the more deprived quintile having an increased probability of hospital events for complications (SIR=1.088, 95% CI=1.069 to 1.107).

When these variables were included in the multivariate model, all variables remained independently associated with complications. How these characteristics modified the relationships between complications and antibiotic dispensing rates are shown in Table 8.2 (alongside the unadjusted estimates from Table 8.1). After adjusting for significant practice characteristics, the relationship between antibiotics and hospital events of complications were weaker but remained for all type of antibiotics under examination. As already demonstrated in Chapter 7, a significant positive association held between year and complications (SIR=1.062, 95% CI=1.058 to 1.066). When study year was included in the antibiotics model, the associations between complications and dispensing disappeared for all antibiotic type (Table 8.2). This suggests that study year is a confounder in this model and an unknown factor caused dispensing to fall and another factor caused complications to rise.

Table 8.2 Unadjusted and adjusted models for hospital events for complications and dispensing rate per 1,000 pp by type of antibiotic, 1996 to 2005 (Parameter estimates (standard error) shown for dispensing rate only)

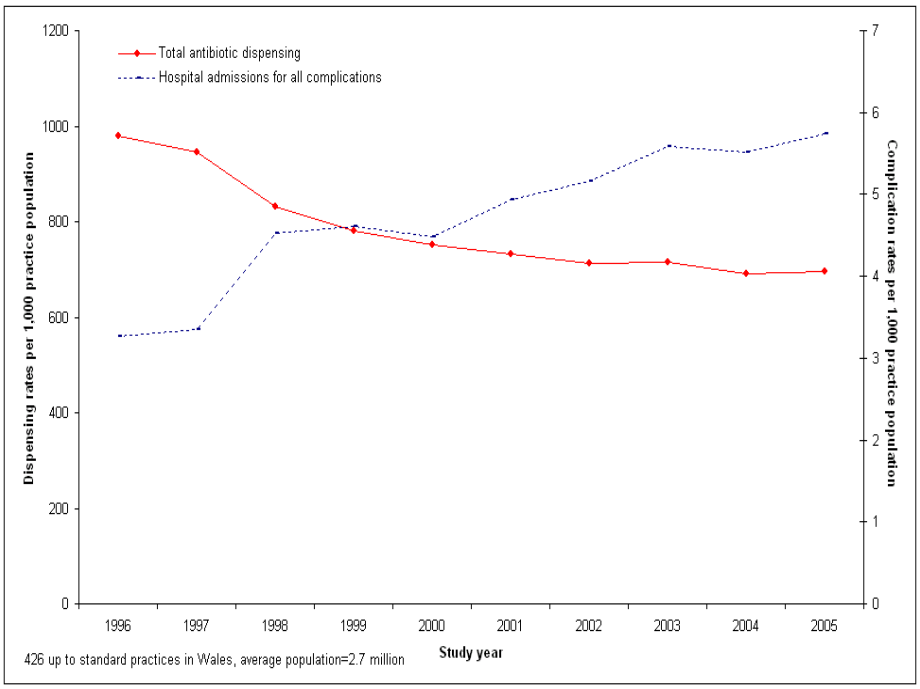
	Log_e parameter estimate (SE) x 10^3			**95% CI**		
Antibiotic	**Unadjusted**	**Adjusted for practice chars.**[i]	**Adjusted for practice chars and time**[ii]	**SIR (IQR)**[iii]	**Lower limit**	**Upper limit**
BSPs	-1.53 (0.31)	-1.72 (0.34)	-0.11 (0.27)	0.98	0.90	1.07
Macrolides	-2.54 (0.65)	-1.96 (0.64)	0.43 (0.48)	1.02	0.97	1.08
Cephalosporins	-3.89 (1.04)	-3.27 (0.96)	-0.44 (0.58)	0.97	0.90	1.05
Quinolones	-4.23 (1.52)	-3.52 (1.59)	-0.06 (1.05)	1.00	0.96	1.04
Tetracyclines	-1.47 (0.61)	-1.31 (0.62)	0.48 (0.47)	1.01	0.99	1.04
Total antibiotics	-0.84 (0.17)	-0.86 (0.19)	-0.01 (0.16)	1.00	0.91	1.09

[i] *Adjusted for deprivation quintile, average age of GP, percentage of practice population aged 0-14 and 65 plus*
[ii] *Adjusted for deprivation quintile, average age of GP, percentage of practice population aged 0-14, 65 plus and time (study year)*
[iii] *Standardised Incidence Ratio (SIR)(IQR) = rate of complications at 75th percentile of dispensing distribution compared to the 25th percentile*

8.4.1.2 *Excluding data from 1996 and 1997*

The greatest reduction in total antibiotic dispensing, and the largest increase in hospital admissions of complications, both occurred between 1997 and 1998. For example, total dispensing rates fell from 946.54 per 1,000 pp in 1997 to 830.65 in 1998, and hospital admissions of overall complications rose from 3.36 events per 1,000 pp in 1997 to 4.52 in 1998 (Figure 8.3).

Figure 8.3 Trends in total antibiotic dispensing and complication rates, 1996 to 2005



After excluding data for 1996 and 1997, the associations (unadjusted and adjusted for practice characteristics) between complications and antibiotic dispensing rates were re-examined and compared to the estimates for the whole period (1996 to 2005) alongside the reduction in dispensing rates between 1996 and 1998 (Table 8.3). After the exclusion of the first two years of data the unadjusted estimates for dispensing were diluted and became non-significant, with the exception of cephalosporins and quinolones. The dispensing of quinolones only reduced by 2.3% from 1996 which may explain why excluding data from 1996 and 1997 made little impact on the on the result. These associations did not hold after adjusting for significant practice characteristics mainly due to the addition of time (year) to the model.

Table 8.3 NB models for hospital events for complications and dispensing per 1,000 pp by type of antibiotic: 1996 to 2005 and 1998 to 2005 (Parameter estimates (standard error) shown for dispensing rate only)

		Log_e parameter estimate (SE) x 10^3			
	Reduction[i]	**1996 to 2005**		**1998 to 2005**	
Antibiotic	**(% change)**	**Unadjusted**	**Adjusted[ii]**	**Unadjusted**	**Adjusted[ii]**
BSPs	92.0 (20.4)	-1.87 (0.36)	-0.11 (0.27)	-0.28 (0.17)	0.43 (0.14)
Macrolides	13.3 (10.8)	-2.54 (0.65)	0.43 (0.48)	-0.33 (0.41)	0.73 (0.29)
Cephalosporins	22.0 (19.8)	-3.89 (1.04)	-0.44 (0.58)	-0.92 (0.30)	0.24 (0.23)
Quinolones	0.7 (2.3)	-4.23 (1.52)	-0.06 (1.05)	-1.89 (0.75)	0.07 (0.64)
Tetracyclines	7.1 (10.8)	-1.47 (0.61)	0.48 (0.47)	0.55 (0.50)	0.62 (0.41)
Total antibiotics	148.8 (15.2)	-0.97 (0.20)	-0.01 (0.16)	-0.14 (0.11)	0.26 (0.08)

[i] *Reduction in dispensing rates between 1996 and 1998 per 1,000 practice population and as a % of 1996 rate*
[ii] *Adjusted for deprivation quintile, average age of GP, percentage of practice population aged 0-14, 65 plus and time (study year)*

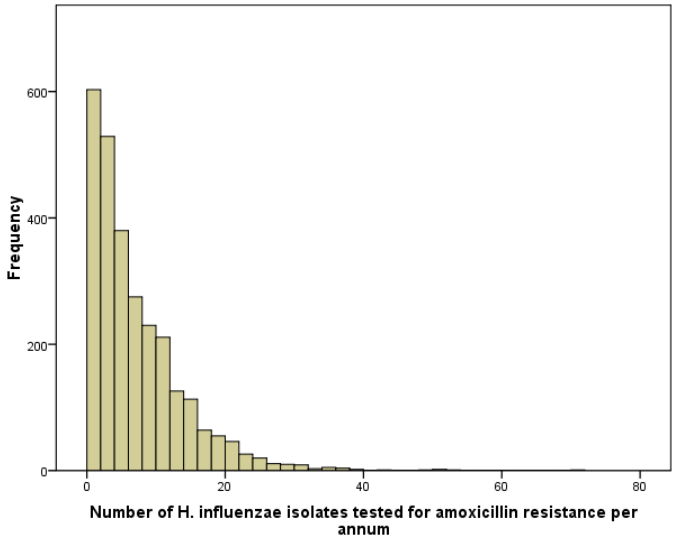
8.4.2 General practice level resistance data

Resistance data was only available for a sample of practices and covered the years 1998 to 2006 inclusive. For example, in *S. pneumoniae* isolates 337 practices had at least one isolate tested for resistance (Table 8.4). This number is slightly different from the 358 practices quoted in section 6.4.1 due to the restricted period used in this analysis (spanning March 1998 to April 2006 instead of January 1998 to December 2006). In Chapter 6, resistance data was examined at an individual level but since complications are only available at practice level, analysis must also be carried out at this level. The median number of *H. influenzae* isolates that were submitted for amoxicillin resistance testing was 6 isolates per practice (pp) per annum (range 0 to 70). The pattern of the number of isolates submitted pp per annum is shown in Figure 8.4.

Table 8.4 Summary of isolates and resistance per practice (pp) per annum

Organism	**Antibiotic resistance**	**Practices with data**	**Isolates tested pp per annum**	**% resistant pppa**
		N	**Median (25th to 75th quartile)**	
H. influenzae	Amoxicillin	341	5 (2 to 10)	15.8 (0 to 30)
S. pyogenes	Erythromycin	339	4 (2 to 7)	0 (0 to 0)
S. pneumoniae	Erythromycin	337	2 (1 to 5)	0 (0 to 10.8)
	Penicillin	337	2 (1 to 5)	0 (0 to 0)

Figure 8.4 Histogram of the number of *H. influenzae* isolates tested for amoxicillin resistance per practice per annum, 1998 to 2005



Of the isolates that were tested, a median of 15.8% were resistant. *S. pyogenes* and *S. pneumoniae* isolates were tested less frequently for resistance per annum and for all organisms, the distributions of the number of the number tested per practice were positively skewed.

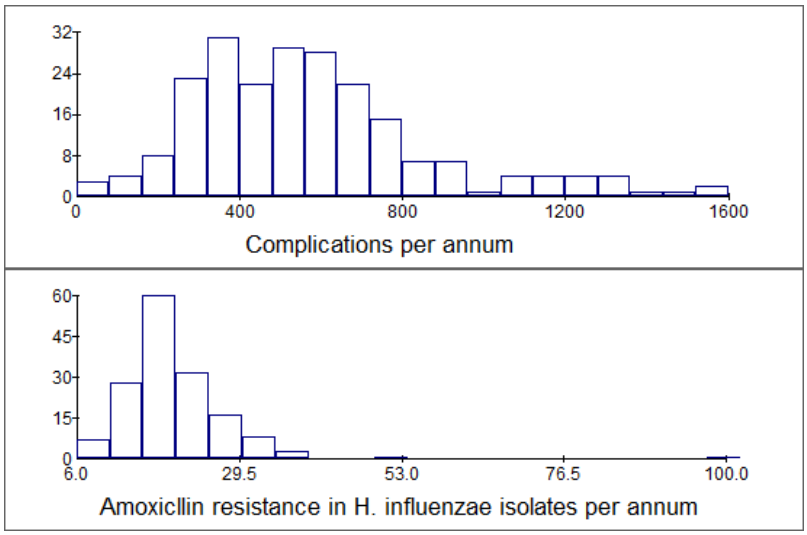
Since 35% of practices had no resistant isolates per annum it seems prudent to restrict any future analyses using resistance data to practices that had at least five isolates tested per annum. This was only possible in *H. influenzae* isolates where the restriction resulted in 88 possible practices to analyse the impact of resistance on the relationship between antibiotic dispensing and complications. For *S. pneumoniae* and *S. pyogenes* isolates only four and 24 practices respectively remained after the restriction. Although these 88 practices covered 21% (833,232 population) of the Welsh population, they were not a representative sample of the 426 Welsh practices. On average, these practices had significantly more complications presenting in hospital ($p<0.001$), were prescribed significantly fewer antibiotics ($p<0.001$), had a greater proportion of female and younger GPs ($p<0.001$), a smaller proportion of younger ($p=0.002$) and older practice population (0.041), and were more likely to be multi-handed ($p<0.001$).

The association between complications and total antibiotic dispensing was compared using the two samples: (1) from the 426 practices and (2) from the sub sample of 88 practices for the period 1998 to 2005. The unadjusted association seen between hospital events for complications and total antibiotic dispensing rates at a practice level for the UTS practices ($\beta=-0.97$ (SE=0.20)) was not observed for the sample of 88 practices ($\beta=-0.09$ (SE=0.20), thus confirming that the sample of 88 practices were not a representative sample of the 426 practices. Amoxicillin resistance in *H. influenzae* isolates was negatively associated with hospital events of complications at a GP level based on the 88 practices ($\beta=-0.002$ (SE=0.001). After adjusting for resistance, the association between complications and total antibiotic dispensing did not change ($\beta=-0.06$ (SE=0.20)).

8.4.3 The relationship at the Local Health Board level

As the impact of antibiotic resistance could not be fully explored at a general practice level, complications, dispensing and resistance data were aggregated for the 426 practices to the Local Health Board (LHB) level. At this level, the counts per annum (1998 to 2005) were greater and thus analyses were more robust (Figure 8.5).

Figure 8.5 Histogram of number of hospital events for complications and resistance by LHB per annum



The initial results from the univariate two-level (LHB and time) NB regression model examining the association between resistance from all specimens and complications show a significant negative association between hospital events of complications and amoxicillin resistance in *H. influenzae* isolates (β= -0.0032 (SE=0.0014)). This indicated that LHBs with higher complication rates per annum had lower resistance in the same year. No associations held between complications and erythromycin resistance in *S. pneumoniae* (β=0.00343 (SE=0.00264)) and *S. pyogenes* isolates (β=-0.00402 (SE=0.00516)) or penicillin resistance in *S. pneumoniae* (β=0.00092 (SE=0.00434)).

The relationship between complications and antibiotic dispensing was examined at a LHB level and where appropriate adjusted for amoxicillin resistance in *H. influenzae* isolates and also year (Table 8.5). Negative associations were observed between antibiotic dispensing rates and hospital events for complications for all type of

antibiotics. These associations remained after adjusting for resistance rates except for tetracyclines. In conclusion, LHB level resistance rates do not seem to modify the relationship between complications and dispensing although the resistance data are too few in number for analyses to be robust. After adjusting for secular trends, none of the negative associations held and significant positive associations were seen between complications and BSP, macrolide and total antibiotic dispensing.

Table 8.5 NB models for hospital events for complications and dispensing per 1,000 pp by type of antibiotic at LHB level, 1998 to 2005 (Parameter estimates (standard error) shown for dispensing rate only)

	Log_e parameter estimates (SE) x 10^3					
	1998 to 2005				**95% CI**	
Antibiotic	**Unadjusted**	**Adjusted**[i]	**Adjusted**[ii]	**SIR (IQR)**[iii]	**Lower limit**	**Upper limit**
BSPs	-3.11 (0.65)	-2.05 (0.56)	2.42 (0.56)	1.48	1.24	1.76
Macrolides	-10.55 (2.21)	-5.52 (1.27)	3.72 (1.71)	1.22	1.02	1.46
Cephalosporins	-11.08 (2.27)	-7.56 (1.35)	-0.91 (1.33)	0.94	0.80	1.12
Quinolones	-39.29 (8.42)	-19.82 (4.16)	-2.95 (3.87)	0.94	0.81	1.10
Tetracyclines	-11.33 (3.83)	-3.11 (4.55)	2.49 (3.25)	1.07	0.90	1.27
Total antibiotics	-1.81 (0.41)	-1.25 (0.56)	1.21 (0.35)	1.40	1.16	1.70

[i] *Adjusted for amoxicillin resistance in H. influenzae isolates*
[ii] *Adjusted for amoxicillin resistance in H. influenzae isolates and time (study year)*
[iii] *SIR (IQR) = SIR of complications at 75th percentile of dispensing distribution compared to the 25th percentile*

8.4.4 The relationship between hospital infections for acute RTIs and antibiotic dispensing at a general practice level

The models in the previous sections modelled the rate of complications in terms of antibiotic dispensing over time but adjusting for temporal trends and certain practice characteristics. This section models the rate of hospital events for acute RTIs and pneumonia using the same methods.

The negative binomial (NB) regression model found a significant negative association between hospital events for acute RTIs and the dispensing of tetracyclines (Table 8.6). Again the percentage of variation in hospital events for acute RTIs attributable to practice differences was greater than those due to LHB differences. After adjusting for significant practice characteristics (deprivation quintile, average age of GP and percentage of practice population aged 0-14 and 65 plus) and year, the relationship between acute RTI hospital events and antibiotic dispensing disappeared.

Excluding 1996 and 1997 changed the relationship between hospital events for acute RTIs and antibiotic dispensing in that most associations reversed and became significantly positive. The exception was for tetracycline dispensing which remained negatively associated but non-significant.

Table 8.6 Multivariate model for hospital events for acute RTIs and dispensing per 1,000 pp by type of antibiotic, 1996 to 2005 and 1998 to 2005 (Parameter estimate (standard error) shown for dispensing rate only)

		Log_e parameter estimate (SE) x 10^3			
	Reduction[i]	**1996 to 2005**		**1998 to 2005**	
Antibiotic	**(% change)**	**Unadjusted**	**Adjusted**[ii]	**Unadjusted**	**Adjusted**[ii]
BSPs	92.0 (20.4)	-0.61 (0.35)	-0.07 (0.33)	0.85 (0.16)	0.84 (0.14)
Macrolides	13.3 (10.8)	-0.50 (0.72)	0.63 (0.66)	1.48 (0.48)	1.22 (0.44)
Cephalosporins	22.0 (19.8)	-1.95 (1.10)	-0.69 (0.90)	0.90 (0.33)	0.79 (0.29)
Quinolones	0.7 (2.3)	-0.86 (1.56)	0.78 (1.34)	1.79 (0.95)	1.24 (0.81)
Tetracyclines	7.1 (10.8)	-1.43 (0.58)	-0.30 (0.56)	-0.77 (0.64)	-0.40 (0.61)
Total antibiotics	148.8 (15.2)	-0.33 (0.20)	0.02 (0.19)	0.57 (0.08)	0.42 (0.10)

[i] *Reduction in dispensing rates between 1996 and 1998 per 1,000 practice population and as a % of 1996 rate*

[ii] *Adjusted for deprivation quintile, average age of GP per practice, and percentage of practice population aged 0-14, 65 plus and time (study year).*

8.4.5 The relationship between hospital infections for pneumonia and antibiotic dispensing at a general practice level

The NB model found that for all hospital infections for pneumonia, there were significant negative associations with dispensing of all types of antibiotics at a general practice level, except for tetracycline dispensing (Table 8.7). After adjusting for significant explanatory variables (deprivation quintile, average age, the age distribution of the practice and year), these associations disappeared.

Excluding 1996 and 1997 weakened the unadjusted relationship between hospital events for pneumonia and antibiotic dispensing and the estimates decreased. However, significant associations still remained for all antibiotics apart for macrolide and total antibiotic dispensing. Again these negative associations disappeared when adjusted for practice characteristics and time.

Table 8.7 Multivariate model for hospital events for pneumonia and dispensing per 1,000 pp by type of antibiotic, 1996 to 2005 and 1998 to 2005 (Parameter estimate (standard error) shown for dispensing rate only)

		Log_e parameter estimate (SE) x 10^3			
	Reduction[i]	**1996 to 2005**		**1998 to 2005**	
Antibiotic	**(% change)**	**Unadjusted**	**Adjusted**[ii]	**Unadjusted**	**Adjusted**[ii]
BSPs	92.0 (20.4)	-1.37 (0.29)	0.14 (0.26)	-0.42 (0.20)	0.27 (0.15)
Macrolides	13.3 (10.8)	-1.80 (0.53)	0.62 (0.46)	-0.41 (0.45)	0.55 (0.33)
Cephalosporins	22.0 (19.8)	-2.10 (0.66)	0.12 (0.52)	-0.81 (0.34)	0.27 (0.29)
Quinolones	0.7 (2.3)	-3.13 (1.22)	-0.10 (0.98)	-2.23 (0.93)	-0.24 (0.80)
Tetracyclines	7.1 (10.8)	-0.91 (0.56)	0.79 (0.50)	0.57 (0.61)	0.56 (0.50)
Total antibiotics	148.8 (15.2)	-0.71 (0.16)	0.13 (0.14)	-0.21 (0.11)	0.17 (0.08)

[i] *Reduction in dispensing rates between 1996 and 1998 per 1,000 practice population and as a % of 1996 rate*

[ii] *Adjusted for deprivation quintile, average age of GP per practice, and percentage of practice population aged 0-14, 65 plus and time (study year)*

8.4.6 Changes in antibiotic dispensing and complications

The models in previous sections modelled the rate of complications and RTIs in terms of dispensing over time but adjusting for temporal trends by including the study year. Here the changes in complication rates are explicitly modelled in terms of changes in dispensing rates over the study period.

Reductions were seen in the mean dispensing of all antibiotics between 1998 and 2005 in the set of 426 UTS practices (Table 8.8). Quartiles were calculated based on change in total dispensing rates with equal number of practices in each quartile and defined according to the values shown in the final row of Table 8.9. Quartile 1 (75^{th} to 100^{th} percentile) refers to practices that reduced their dispensing the most and quartile 4 (0 to 25^{th} percentile) refers to the practices that reduced it least, or increased their dispensing. For total antibiotics, quartile 1 reduced dispensing by at least 237 items per 1,000 practice population per annum; quartile 2 by between 114 and 237; quartile 3 by between 39 and 114; and quartile 4 by less than 39.

Table 8.8 Median dispensed antibiotic items (per 1,000 practice population) in 1998 and 2005 in 426 Welsh practices

Antibiotics	**1998**	**2005**	**Reduction (% decrease)**
BSPs	346.2	271.8	74.4 (21)
Cephalosporins	71.9	49.0	22.9 (32)
Tetracyclines	51.8	50.8	1.0 (2)
Macrolides	100.1	77.2	22.9 (23)
Quinolones	26.5	21.6	4.9 (18)
Total antibiotics	820.4	675.3	145.1 (18)

Table 8.9 Quartiles with 5^{th} and 95^{th} percentiles, for reductions in dispensed antibiotic rates (per 1,000 practice population) between 1998 and 2005

	Percentile				
Antibiotics	**95%**	**75^{th}**	**50th**	**25th**	**5%**
BSPs	299.2	128.8	61.8	21.0	-47.9
Cephalosporins	125.1	49.6	18.3	-3.1	-34.6
Tetracyclines	43.1	14.2	1.7	-9.1	-27.9
Macrolides	109.0	46.8	17.3	0.6	-33.4
Quinolones	44.8	14.5	3.9	-3.0	-15.1
Total antibiotics	551.7	236.7	114.4	39.9	-67.2

Table 8.10 shows the changes in overall complications and in pneumonia by quartile of change in total antibiotic dispensing. A significant increase was observed in rates of overall complications between 1998 and 2005 in each dispensing quartile. Practices in the first quartile (that reduced their dispensing the most) saw an increase in hospital event for complications arising from acute RTIs by 117.0 per 100,000 population (95% CI=69.16 to 164.5) and the fourth quartile (practices that reduced their dispensing the least or increased it) saw an increase of 140.3 events per 100,000 population (106.1 to 174.5). Practices in the first quartile had the highest rate of complications in 1998 (520.0 events per 100,000 population); the other quartiles had similar rates of complication events.

For pneumonia there was a significant increase in rates between 1998 and 2005 in each dispensing quartile. Practices in the first quartile (that reduced their dispensing the most) saw an increase in hospital events for pneumonia by 94.2 per 100,000 population (95% CI=67.9 to 120.6) and the fourth quartile (practices that reduced their dispensing the least or increased it) saw an increase of 83.2 (63.9 to 102.5). The second quartile saw the highest increase in rates over the period of 96.1 pneumonia events per 100,000.

These analyses suggest that there is no association between changes in total antibiotic dispensing and changes in hospital event rates of complication and pneumonia when examined at an aggregate level. If there is an association between complications and antibiotic dispensing, it is not apparent by using aggregated levels of dispensing.

Table 8.10 Change (mean (sd)) in all complications and pneumonia (per 100,000 population) over an 8-year period, by quartile of reductions in total antibiotic dispensing per 1,000 population

	Reduced dispensing most		Reduced dispensing least		
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
	N=106	107	106	107	426
All complications					
1998, mean (sd)	520.0 (212.1)	427.9 (159.0)	428.7 (174.4)	420.0 (156.0)	449.0 (180.8)
2005, mean (sd)	637.1 (230.4)	549.7 (232.9)	558.1 (172.4)	560.3 (177.9)	576.2 (207.7)
Change, mean	117.0	121.8	129.4	140.3	127.2
(95% CI)	↑(69.2 to 164.5)	↑(82.1 to 161.4)	↑(95.1 to 163.7)	↑(106.4 to 174.2)	↑(107.78 to 146.5)
Pneumonia					
1998, mean (sd)	179.6 (88.8)	154.0 (84.2)	170.4 (72.9)	166.7 (72.9)	167.6 (81.7)
2005, mean (sd)	273.8 (115.7)	250.1 (116.1)	248.5 (90.7)	249.8 (99.3)	255.5 (106.2)
Change, mean	94.2	96.1	78.1	83.2	87.9
(95% CI)	↑(67.9 to 120.6)	↑(72.7 to 119.5)	↑(58.7 to 97.5)	↑(63.9 to 102.5)	↑(76.9 to 98.9)

8.5 Discussion

8.5.1 Main findings

Association between hospital events and antibiotic dispensing

Initial results from this all-Wales ecological level study suggested an apparent negative relationship between hospitalised complications and antibiotic dispensing in the community even after adjusting for practice characteristics (average age of GP, deprivation, % of patients aged 0-14 and 65 plus). Practices with a higher rate of these hospitalisations had a lower rate of antibiotic dispensing per annum. However, this relationship largely disappeared when the first two years (1996 and 1997) of data are excluded or when adjustments for study year were made. High hospital rates of acute RTIs were associated with lower dispensing of tetracyclines but again excluding 1996 and 1997 or adding year removed the association. Similarly, the associations found between hospital events of pneumonia and the dispensing of all types of antibiotics (apart from tetracyclines) disappeared after excluding 1996 and 1997 and/or year.

It is plausible that low rates of dispensing may be associated with high rates of complications, suggesting that reducing dispensing might lead to an increase in complications. Therefore, to further examine whether antibiotic dispensing was the main driver of complications, the relationship between changes in dispensing by general practices and changes in hospital events of complications and pneumonia were examined. All quartiles of change in total antibiotic dispensing demonstrated a significant increase in the rate of overall complications admitted to hospital between 1998 and 2005. In particular, general practices that reduced their total dispensing the most showed the smallest increase in complication rates. Conversely, practices that reduced their antibiotic dispensing the least (or increased) showed the largest increase in complication rates. This suggests that there is no association between changes in dispensing and changes in complication rates. This adds to the evidence that the apparent associations found between dispensing and complications are spurious and that study year is a confounder in this model.

Impact of resistance on the relationship

Using resistance data aggregated at the local heath board (LHB) level, the associations between antibiotic dispensing and complications did weaken after adjusting for amoxicillin resistance in *H. influenzae* but remained significant, with the exception of tetracycline dispensing.

8.5.2 Strengths and weaknesses of the study

Many of the strengths and weaknesses regarding the content, quality and coverage (and bias) of each of the individual datasets have been discussed in chapters 4 to 7. This study has major strengths compared with previous ecological studies. It is the only study to link up these datasets at a general practice level for a whole country and examine the relationship using general practices as the unit of analysis. This unit of aggregation was smaller than levels used in other studies, and whilst it is at an ecological level, it is important to examine the association at this level since strategies for enhanced antibiotic prescribing are often targeted at GPs. More sophisticated methodological techniques were used such as multilevel modelling as opposed to simple correlations or regression. Multilevel modelling not only allowed examination of variations in complications and their relationship with antibiotic dispensing at both general practice and LHB levels but confounders such the age structure and deprivation status of the registered practice population and certain practice characteristics could be adjusted for.

Resistance was also examined as a possible modifier of the relationship but the small number of isolates per annum at practice level meant the analysis was either limited to a restricted biased sample of practices with a sufficient number of isolates submitted per annum or to an analysis based on data aggregated to a much larger geographical area (LHB). The LHB level analysis is problematic in itself as it is at the aggregation of a considerable number of practices; results are harder to interpret and it is difficult to account for possible LHB factors that may drive complications (e.g. different types and frequency of hospitals serving in the LHB area).

The main limitation to this study is its ecological nature. It could be speculated that the apparent association between complications and dispensing is spurious and that

we can consider study year is a confounder in this model. That could occur if an unknown factor caused dispensing to fall (such as initiatives to reduce antibiotic prescribing) and another factor caused complications to rise (such as a change in pathways to treatment, for example such as changes in out of hours and organisation of care). However, due to the aggregate nature of the data, the causal pathways are unclear. Whilst we can speculate as to why complications could increase (change in coding or change in presentation of these illnesses) and dispensing decrease, a mechanism linking one to the other cannot be produced.

Another of the limitations of this study was the small numbers of certain hospital events (e.g. mastoiditis) at a general practice level which restricted the scope for examining more complications over all ages and for those in children only. These small numbers of events meant that modelling could not be carried out at a small area level for such diagnoses. Further analyses could only have been carried out for a wider range of complications at LHB level but, as previously discussed, this unit of analysis was too large (with only 22 in Wales) for results to be very meaningful.

True rate of antibiotic dispensing for RTIs, complications

This study has related complications arising from acute RTIs resulting in a hospitalisation with all antibiotic dispensing in primary care from any diagnosis. Some dispensing will not be related to a diagnosis of an acute RTI (for example, tetracyclines in soft tissue and skin infections) and its inclusion here will result in an overestimation of the relevant dispensing rate. Also some antibiotics will not have been consumed (only dispensed) and this in turn will lower the true rate antibiotic exposure in the community. Antibiotic dispensing data in this study does not take into account low or suboptimal dose or the length of treatment controlled by the prescriber. This makes it a weak measure of exposure to antibiotics. The number of defined daily dose (DDD) may be a better measure as it is the assumed average maintenance dose (per day) for a drug used for its main indication in adults.

As discussed in Chapter 7, the incidence of complications may also be underestimated since some are managed in the community and do not result in a hospitalisation. This deficit in complications should be similar across all areas and a comparable underestimate may possibly apply across the whole of Wales. By

observing hospital events of infection, complications at the severest end of the spectrum are compared with overall antibiotic dispensing. Although these complications are the ones of greatest concern, observing all complications is vital if this association is to be thoroughly explored.

Adjusting for confounders

We were able to adjust for a number of practice and practice population based variables believed to be associated with hospital events of acute RTIs and complications and/or antibiotic dispensing. However, there are unmeasured factors that could account for some of the variation, including practice population (e.g. co-morbidity levels) and factors that change the patterns of disease (e.g. vaccination programmes). Whilst the impact of resistance on the relationship was examined it was in a biased sample of practices. Nevertheless, our results at practice and LHB level showed that resistance modified the relationship by only a small amount. This could reflect the positive association between prescribing and resistance.

8.5.3 Comparisons with existing literature

Several papers have examined the relationship between complications and antibiotic dispensing using routine health care databases at a primary care trust (PCT), health authority (HA) or country level. Only one paper could be found that examined the relationship (alongside urinary tract infections) at a GP level but none at a general practice level. Furthermore no papers could be found that examined the impact of resistance on the relationship.

Results from these ecological level analyses also suggest that reductions in GP prescribing of antibiotics may be associated with increases in complications of bacterial infection. Data based on 162 general practitioners in Spain (around 300,000 population) found significant negative associations between antibiotic dispensing rates and hospital admissions due to respiratory and urinary tract infections and complications arising from these infections (Urussuno *et al.* 2008). In another cross-sectional study, Little and colleagues examined primary care prescribing of penicillin and hospital admissions for complications and acute RTIs at the HA level, for the years 1997-1998 (Little *et al*. 2002). They found evidence that higher levels of

primary care prescribing of penicillin were significantly associated with lower rates of admissions for both quinsy and mastoiditis after adjusting for age, gender, deprivation and standardised mortality ratio.

At the country level, a study in the USA compared the percentage of antibiotic prescribing for acute bronchitis and cough, and hospitalisations for RTIs (including pneumonia and empyema), in the US, between 1996 and 2003 (Mainous III *et al*. 2006). Antibiotic prescribing (over the period) had a weak negative correlation with hospitalizations for all RTIs (r_s=-0.22). Another study found that countries practising a restrictive use of antibiotics for acute otitis media (between 1991 and 1998), such as the Netherlands, Norway and Denmark, had a higher incidence rate of mastoiditis when compared to countries such as the UK, Canada, Australia and the US (Van Zuijlen *et al*. 2001). Finally, a study in England and Wales examined aggregate data for pneumonia mortality, and the incidence of primary care visits for influenza or influenza-like illness, and their relationship with antibiotic prescribing for LRTIs in 12-week winter periods between 1993/4 and 1999/2000 (Price *et al*. 2004b). The results demonstrated that antibiotic prescribing for LRTI had a significant association with excess winter pneumonia mortality even after adjusting for influenza incidence.

8.5.4 Implications of findings for clinical practice and future research

At the beginning of this chapter, the hypothesis proposed was that, at the level of general practices in Wales, reduced levels of community antibiotic dispensing in the community were associated with increases in hospital admissions in complications arising from common infections. Although at first glance there seemed to be an association, when study year was included as a confounder this relationship disappeared, suggesting there may be other factors driving complications. In addition, the lack of association found between changes in both dispensing and complications reinforce this finding. Thus we cannot conclude that there is an association but this may be due to the aggregate nature of the data and analysis. The results of these ecological level analyses are therefore unlikely to change current practice although they may be of interest to GPs due to the population that is covered, albeit at a practice level.

The impact of resistance on the model was hard to assess because small numbers of isolates at practice level necessitated a high level of aggregation. To investigate the input at practice level robust general practice level data will rely on practices sending samples more routinely for all sites but especially ENT. This is unlikely to happen in practice. More realistic is the development of near patient testing to identify the bacteria (if any) to prescribe appropriate antibiotics.

In order to assess the true protective effect of antibiotics on complications arising from acute RTIs, individual patient information is required with a large enough sample to be able to examine individual complications. Of particular interest will be examining sub-groups of patients to identify the impact of an absence in antibiotics; will there be a higher risk of complications whether in primary or secondary care? An analysis at individual level is required and this will be examined in the next chapter, albeit in a different geographical area.

8.6 Introduction to individual level analysis of antibiotic prescribing and complications arising from RTIs

The following chapter will be based on individual level data for 60 practices in the UK. An analysis of individual patient level data presenting with an acute RTI, their prescribing behaviour and outcomes will be examined for one year period. This chapter improves on the model tested in this chapter in three ways. Firstly, it circumnavigates the problem of ecological analyses by using data on individual patients. Secondly, further data on patient characteristics is available to allow adjustment for possible confounders of complications and this will allow analysis of important sub-groups such as the children and the elderly.

Chapter 9 Antibiotic prescribing and complications arising from RTIs: Individual patient level analysis

9.1 Introduction to individual level

Chapter 8 examined the association between rates of antibiotic dispensing and hospital events at a general practice level. Whilst these data suggest no association between dispensing and hospital events, the analysis does not provide sufficient evidence to begin to change current practice. To attempt to do this, studies have to be carried out at an appropriate level, in this case at the individual patient level. Datasets should also be of good quality and representative of the larger population so that results are not biased and any inferences made are precise. Also of importance is to improve the inferences made by adjusting for known and measured confounders (risk factors) and using appropriate methods (multivariate analysis or propensity scores).

This chapter attempts to address these issues and aims to investigate the effect of prescribing antibiotics in primary care against the risk of developing a complication arising from an RTI in both primary and secondary care using individual level data. It will also aim to identify sub-groups of patients benefiting most from antibiotics and examine whether this level of protection has changed over time, over a period when antibiotic prescribing declined.

The null hypothesis being tested is that there are no differences in complication rates in patients presenting with an RTI between those prescribed an antibiotic and those not.

9.2 Methods

9.2.1 General Practice Research Database

The General Practice Research Database (GPRD) is the world's largest computerised database of anonymised longitudinal medical records from primary care with around 3.5 million active patients (around 5% of the UK population) from around 460 general practices in the United Kingdom (UK) (GPRD website). It is managed by the

GPRD Group within the Medicines and Healthcare Products Regulatory Agency (MHRA).

Individual patient level data could be obtained for a fee, or free to UK academics through a Medical Research Council (MRC) licence. Although no patient or practice identifiable data are provided, each patient has an encrypted unique number which allows their records to be linked over time. For each patient, GPRD collects and makes available information such as demographic details (gender, year of birth and practice location), all clinical information (diagnoses, symptoms, procedures, and medical history using the Read/OXMIS coding system), all prescriptions issued, referrals to secondary care, test results, and lifestyle information. GPRD data is available from 1987 although the number of practices contributing data and up-to-standard (fulfill the routine quality assurance checks) varies over the years.

The quality of the GPRD records is validated and maintained by the GPRD group with a good relationship maintained with contributing practices to ensure up-to-date data collection. Validation studies show that the quality and completeness of the GPRD data are high (Hollowell J 1997). The 'Up-to-Standard' (UTS) marker is a practice-based quality marker generated for each practice, indicating when data recording by the practice complied with specific quality measures, based on an assessment of the completeness, continuity and plausibility of data recording in key areas.

Data from Full Feature (FF)-GPRD was accessed under an MRC licence which was gained in July 2007. The FF-GPRD has been available since 2001 and has considerably enhanced features compared to the former GPRD dataset. Under the licence, a maximum of 100,000 patient records were available from registered UTS practices across the UK.

9.2.2 Study population

Our study population consisted of patients who had presented in primary care and received a diagnosis of an acute respiratory tract infection (RTI) during 2005. Patients were identified from a number of UTS practices which were chosen at

random by the GPRD analysis team whilst keeping within the 100,000 patient records limit. To ensure that each record was the first presentation of a new acute RTI (called the index RTI), patients must not have presented with an acute RTI in the 8 weeks (60 days) prior to the RTI. Therefore, any prior RTIs were checked for in November and December of 2004, for patients presenting with an RTI in January 2005.

Patients with an RTI diagnosis were identified using a list of Read codes previously identified by Ashworth and colleagues (Ashworth *et al*. 2005) and Smith and colleagues (Smith *et al*. 2006), and were used with permission. These codes were checked by several GP colleagues. These codes are listed in Appendix XI and grouped to allow for sub-group analysis as follows: sore throat, ear infection, sinusitis, laryngitis/tracheitis, chest infection, and pneumonia. A number of codes could not be grouped as they were too vague, such as viral illness and acute respiratory infections. These codes were included in the overall analysis for complications but excluded from any sub-group analyses.

9.2.3 Exposure

We were interested in ascertaining whether patients with an acute RTI were exposed to an antibiotic or not. In this study, we used prescribed antibiotics as a proxy for exposure to antibiotics since no other measures were currently available (such as dispensed or consumed antibiotics). Our primary aim was to investigate, at an individual level, if patients who did not receive an antibiotic prescription at first presentation of the acute RTI (or the index RTI) were more likely to develop a serious complication than those who did receive an antibiotic. This explored the hypothesis that early or immediate prescribing of antibiotics prevented complications.

Patients who are not prescribed an antibiotic on their first presentation with an acute RTI may subsequently consult again and possibly receive an antibiotic. Therefore to avoid under reporting exposure, we also explored the association between patients who were prescribed an antibiotic, either at or after the index RTI event, and presenting with a serious or complicated infection. This was defined as an antibiotic

prescribed either on the *same day* as the index RTI or *subsequently* (defined as between 1 and 60 days of the index RTI); for those who presented with a serious complication, subsequent antibiotic prescribing was only examined up until that event. This explored the hypothesis that prescribing antibiotics in primary care prevented complications.

For patients who were prescribed an antibiotic on the same day as the RTI, the type and strength of antibiotic was ascertained. Data on the dose and duration were available but were either not well populated or not consistently recorded (for example it may have been recorded either as a frequency per day, such as three times a day, or the daily dose such as 250mg three times a day).

Antibiotics of interest are those listed in the British National Formulary (BNF) section 5.1 Antimicrobials (see section 5.2.2), with the exception of the following antibiotics which were not included, as these medications were uncommonly used in the treatment of common RTIs:

- BNF 5.1.1.4 Antipseudomonal penicillins
- BNF 5.1.1.5 Mecillinams
- BNF 5.1.4 Aminoglycosides
- BNF 5.1.6 Clindamycin
- BNF 5.1.7 Some other antibacterials (inc. fusidic acid, chloramphenicol)
- BNF 5.1.9 Antituberculosis drugs
- BNF 5.1.10 Antileprotic drugs
- BNF 5.1.11 Metronidazole and tinidazole
- BNF 5.1.13 Urinary-tract infections (in. nitrofurantoin).

Some patients were prescribed more than one antibiotic on the same day within the same consultation. In these cases, the last prescription was taken as it was assumed that the last prescription printed was a replacement for the first; for example, a possible scenario is that a patient may have first been prescribed amoxicillin but then a history of allergy was identified and it was replaced by erythromycin. Similarly tablets of some antibiotics may have been prescribed initially but then replaced by syrups of the same type of antibiotic, because the patient reported having difficulty swallowing tablets.

9.2.4 Clinical outcome of interest

9.2.4.1 *Complications diagnosed in primary care*

The primary clinical outcomes were any serious or complicated common infections presenting in primary care. These were ascertained using the same methods as in section 7.2.3 and the Read codes are listed in Appendix XII. Complications that presented between day one and day 60 after the RTI were included. Complications that presented on the same day as the index RTI were excluded as it is unlikely that the patient developed the complication as a result of not being prescribed an antibiotic.

9.2.4.2 *Complications diagnosed in secondary care*

A subset of practices had consented to linkage of their patient-level general practice data to hospital admission data (using Hospital Episodes Statistics (HES)). Linkage of these records was carried out in-house by GPRD. As with standard GPRD data, to maximise the quality of data, HES data are limited to acceptable patients only, for example when certain data quality conditions have been met such as no events recorded before the birth date, age <115 years, and a completed gender field. Acceptable patients in GPRD were linked to the HES using a combination of the patient's NHS number, gender, DOB, and postcode (defined as strong matching). Not all patients in GPRD were eligible to be linked to HES data, for example those residing outside England, or without a valid NHS identifier. For some patients, the only record of hospitalisation fell outside their active follow-up period in the GPRD.

Hospital admissions for patients from these consenting practices were arranged into files relating to hospitalisations, and referred to the total period of in-patient hospital stay from admission to discharge (also known as spells in HES and PEDW). A patient may have had more than one HES hospitalisation or spell. Serious or complicated infections presenting in hospital were identified using ICD10 codes (Appendix XIII) and were recorded alongside their discharge date, as opposed to an admission date.

9.2.5 Observation period

Patients presenting with a first episode of acute RTI between 1st January 2005 and 31st December 2005 were identified. For patients with an acute RTI at the end of the study period (December 2005), their consultations were followed up for 60 days to identify any associated serious or complicated infections. The history of all patients was examined for one year prior to the presentation of the index RTI. The study period therefore spanned over two years from 1st January 2004 to 1st March 2006.

9.3 Statistical analysis

9.3.1 Patient level characteristics

Patient level characteristics potentially associated with both antibiotic prescribing and serious or complicated common infections included demographic factors (age at RTI diagnosis and gender), body mass index (BMI) and smoking status (nearest to index date), and co-morbidity. Also examined was the patient's history (number of antibiotics prescribed, whether they had previously been diagnosed with a complication, and number of consultations for any illness) in the one year prior to the index RTI date. The number of consultations was defined as the number of days on which the patient visited their GP, so that multiple attendances on one day would count as a single consultation. It had been hoped to obtain information regarding samples sent for testing for antibiotic resistance but these data fields were poorly populated.

9.3.1.1 *Deprivation*

Deprivation score was calculated by the GPRD team using the Index of Multiple Deprivation (IMD) by linking both the individual patient's postcode and the practice's postcode to a suitable small area and then to an IMD score (Office for National Statistics). Since the score is calculated differently for each of the four countries of the UK, quintiles were created based on the spread of the scores within each country so that they could be compared. A high score (80) and high rank (5) indicated the most deprived and a low score (1) and rank (1) indicated the least

deprived.

9.3.1.2 *BMI*

Recorded BMI was categorized into four groups (underweight, normal, overweight and obesity) using different cut-offs for children and adults. The cut-off points used for adults from 18 years+ were those based on the WHO adult classification (WHO Global Database on Body Mass Index: underweight (< 18.5 kg/m^2); normal weight (18.5 to 24.9 kg/m^2); overweight (25.0 to 29.9 kg/m^2); and obese (≥ 30 kg/m^2). For children aged 2-18, the International Obesity Task Force (IOTF) cut-offs were used to classify BMI into these four groups, the actual cut-offs depending on the child's age and sex, and were chosen to merge smoothly into the adults' cut-offs. Children's cut-off points were calculated by using the Microsoft Excel Add-in module lmsGrowth (www.healthforallchildren.co.uk (Pan H 2007, Cole TJ 2007) and established using survey data from six countries (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States) (Cole *et al*. 2000 and 2007).

9.3.1.3 *Smoking status*

Patients with no recorded smoking codes (recorded from 2004 up until the index RTI date) were categorized as unknown/not recorded. Patients with documented smoking data were categorized as current smoker, former smoker, never smoker, not a current smoker.

9.3.1.4 *Co-morbidity*

Following National Institute of Clinical Excellence (NICE) guidelines, which recommend that antibiotics should be given to patients who are systemically unwell, the following groups were examined: patients with significant heart, lung, renal, liver or neuromuscular disease, recent prescription for immunosuppressive drugs, and cystic fibrosis. We separately identified patients with diabetes and asthma from the GPRD tables provided. A co-morbidity was included if it was diagnosed either on or before the patient's index RTI date as we assumed that a GP was more likely to prescribe an antibiotic if the patient had any co-morbidity. The read codes used to

extract co-morbidities are listed in Appendix XIV.

9.3.2 Predictors of antibiotic prescribing

Predictors of same day antibiotic prescribing were examined using a multilevel logistic regression model using same day antibiotic prescribing as the binary outcome variable (antibiotic prescribed or not). Where numbers at each level allowed, variation in prescribing was accounted for at the level of the region (Wales, Scotland, North West England etc), general practice, and individual, using the second order penalised quasi-likelihood (2^{nd} order PQL) procedure. Patients were considered to have been prescribed an antibiotic for an RTI if the prescription was issued on the day of the index RTI. Associations between certain factors and prescribing were examined firstly at the univariate level and significant predictors retained for the multilevel model. Odds ratios (ORs) were estimated together with 95% confidence intervals (CIs).

9.3.3 Association between antibiotics and complications

Using the same multilevel modelling methods, the risk of developing serious complications in the 60 days after the index RTI was examined (binary outcome of a patient with an acute RTI developing a complication or not). The odds of developing a complication were compared using ORs and 95% CIs. They were compared firstly in those who were prescribed an antibiotic on the same day as the index RTI and those who were not, and secondly in those who were prescribed an antibiotic within 60 days of the index RTI and those who were not, whilst adjusting for significant confounders discussed in section 9.3.1. Therefore, in the univariate model the significant confounders were identified, and in the multilevel model, the effect of antibiotic prescribing was adjusted for these significant confounders.

Complications diagnosed only in primary care were initially examined. For a sub-set of practices linked to secondary care data, explained in section 9.2.4.2, complications diagnosed in either primary or secondary care were explored. For complications observed in both primary and secondary care, the majority of these had the same diagnosis. Where they differed, the earliest recorded complication was taken (and

any antibiotic prescribing taken up to this date).

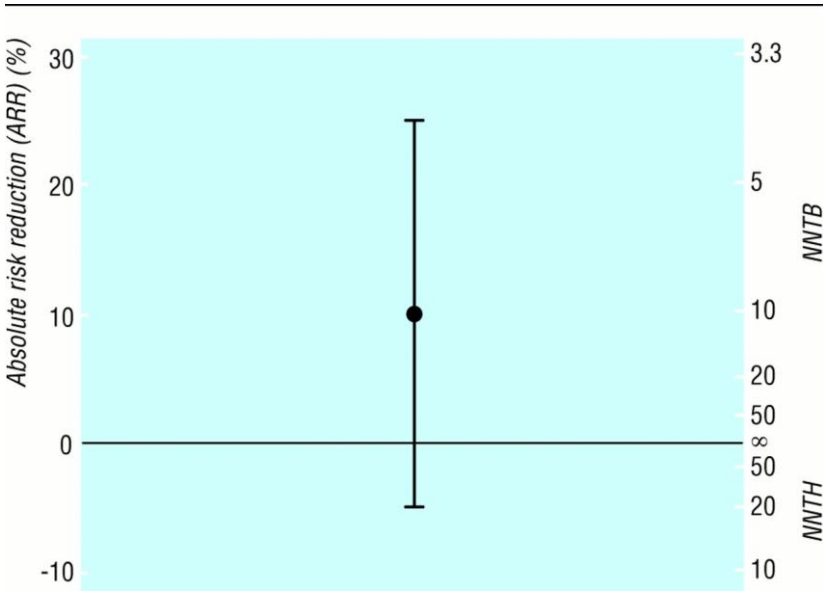
Sore throats and chest infections were examined separately (firstly for complications diagnosed in primary care and then for primary and secondary care diagnosed complications); these were the only infections which were sufficient in numbers to allow secondary analyses.

9.3.4 Numbers needed to treat

The numbers needed to be treated with antibiotics for one additional benefit (prevent a complication) (denoted by NNTB) were estimated from the reciprocal of the absolute risk reduction (ARR), alongside 95% confidence intervals (Cook and Sackett 1995). Confidence intervals for the NNTB were calculated by taking the reciprocals of the limits of 95% confidence intervals for the ARR. A negative absolute risk reduction indicated that the antibiotic had a harmful effect (causing a complication). Therefore a negative number needed to treat (NNT) was called the number needed to harm (and denoted by NNTH).

Where a confidence interval for the positive absolute risk difference included zero, indicating no treatment effect (and NNT is infinite), the corresponding confidence interval for the NNT becomes less informative as it does not include the actual NNTB value. For example, an absolute risk difference of 10% with a wide 95% CI of -5% to 25%, showing a non-significant difference, gives a NNTB=10 (95% CI=-20 to 4). In these cases the approach suggested by Altman (1998) is used with two separate intervals quoted. Altman (1998) suggests using the notation NNTB 4 to infinity (∞) and NNTH 20 to ∞ (or NNTH 20 to ∞ to NNTB 4). Figure 9.1 illustrates the relationship between the ARR and the NNT and their confidence intervals. As a comparison to these NNTs based on crude risk differences, NNTs based on adjusted ORs (obtained from multivariate logistic regression) are also calculated (Bender and Blettner 2002). This adjustment is essential in light of the observational nature of GPRD data where confounding factors have to be taken into account to minimise bias.

Figure 9.1 Relationship between the absolute risk reduction and number needed to treat and their confidence intervals (NNTB=number needed to treat (benefit); NNTH=number needed to treat (harm))



Altman, D. G BMJ 1998;317:1309-1312

BMJ

9.3.5 Exclusions

Patients who were either diagnosed with a complication on the same day as the index date or who died on the index date, were excluded as we could not infer that these patients developed the complication or died as a result of not being prescribed an antibiotic for the initial RTI (n=214). We additionally excluded patients who were diagnosed with an initial RTI of pneumonia (n=411) since only 54 (13.1%) were prescribed an antibiotic on the same day, with an additional 99 (24.1%) patients subsequently prescribed an antibiotic. This is low in comparison with the other RTI groups, especially as guidelines indicate that a diagnosis of pneumonia in the community should be treated with antibiotics (Lim *et al*. 2009). It is possible that these patients were sent straight to hospital as they were too sick to treat.

All multilevel modelling was performed using MLwiN version 2.16 and all other analyses using SPSS version 16.0.

9.4 Results

9.4.1 RTI cohort

In 2005, 90,672 patient individual patients were diagnosed with an acute RTI (with no RTI in the prior 8 weeks) from 60 practices in 2005. Of these 60, 18 were from Wales, 3 from Scotland, 5, from Northern Ireland, 7 from London, 10 from South England, 8 from North West of England, 4 from the North East, and 5 from the East). Table 9.1 shows a summary of the characteristics of these patients. Deprivation was based on the practices' deprivation as opposed to individual patients' deprivation score, since a large proportion (69,416 (77%)) of the latter were missing. Due to the high proportion of missing BMI values, this factor was not included in any multivariate analyses as it may have led to bias in the results.

The index RTI consisted of 151 individual Read code diagnoses, the most common of which were for 'upper respiratory infection not otherwise specified (NOS)' (H05z.00) and 'upper respiratory tract infection NOS' (H05z.11), with 8,901 and 7,694 cases respectively (9.8% and 8.5% of all RTIs), and 'sore throat symptom' (1C9..00) with 8,300 (9.2%) cases (Appendix XI). 'Chest infections/(NOS)' (H06z000 and H06z011) accounted for 13,971 of RTIs (15.4%) and 'acute tonsillitis' (H03..00) for 6,701 (7.4%).

When these individual Read codes were grouped, the majority of diagnoses that could be grouped were classed as sore throats and chest infections (N=23,016 (25.4%) and 22,497 (24.8%) respectively) (Table 9.2). The RTIs that could not be grouped consisted of diagnoses such as upper respiratory (tract) infection NOS.

Table 9.1 Demographics of patients diagnosed with an RTI in 2005 (N(%) unless otherwise specified)

Factors	**N (%)**
Age (years)	
0-4	6,318 (7.0)
5-15	15,163 (16.7)
16-64	53,532 (59.0)
≥65	15,659 (17.3)
Gender	
Male	37,068 (40.9)
Female	53,604 (59.1)
Practice deprivation[i]	
Least deprived 1	14 (23.3)
2	10 (40.0)
3	14 (23.3)
4	14 (23.3)
Most deprived 5	8 (13.3)
Diabetes diagnosed prior to RTI date	
% Yes	6,609 (7.3)
Asthma diagnosed prior to RTI date	
% Yes	13,423 (14.8)
Smoking status	
Current smoker	16,271 (17.9)
Never smoked	37,387 (41.2)
Former smoker	14,167 (15.6)
Status unknown	22,847 (25.2)
Co-morbidity[ii]	
% Yes	18,470 (20.4)
BMI (nearest to index date)	
Underweight	1,439 (2.6)
Normal	22,409 (40.8)
Overweight	18,480 (33.6)
Obese	12,662 (23.0)
Missing	35,682
Died within 60 day follow-up	407 (0.4)
History (1 year prior to index RTI)	
Number of antibiotics	
median (range), mean (sd)	0 (0 to 41), 0.85 (1.58)
None	53,141 (58.6)
1-2	28,953 (31.9)
3+	8,578 (9.5)
Complications (% Yes)	620 (0.7)
Consultations	
Low (0-4 per annum)	34,915 (38.5)
Med (5-10)	28,926 (31.9)
High (>10)	26,831 (29.6)

[i] *Practice deprivation based on Index of Multiple Deprivation score;* [ii] *Based on heart, lung, renal, liver, neuromuscular disease or ever had a prescription for immunosuppressive drugs*

9.4.2 Antibiotic prescribing

A total of 57,337 (63.2%) of the 90,672 patients were prescribed an antibiotic on the same day as the index RTI (Table 9.2); 409 (0.5%) were prescribed more than one antibiotic on the same day but the antibiotic prescribed last was assumed to be the one used, as described in section 9.2.3 above. The most commonly prescribed were broad-spectrum penicillins (N=33,515, 58.5%), benzylpenicillins and phenoxymethylpenicillin (N=10,588, 18.5%), and macrolides (6,710, 11.7%). Cephalosporins and tetracyclines accounted for 5.0% (N=2,863) and 4.4% (N=2,526) of prescribing respectively whilst quinolones, penicillin-resistant penicillins and trimethoprim made up only 2% (N=1,135). Of the patients who were excluded due to having a complication (N=59) or death (N=162) on the index RTI date, 26 (44%) and 2 (1.2%) respectively received an antibiotic on the same day.

Table 9.2 Number (%) of diagnoses by index RTI group alongside N (%) of antibiotic prescribed (no antibiotic prescribed, same day and subsequent) (sorted by % of same day prescribing)

		Antibiotic prescribed		
	Total diagnoses	**Same day**	**Subsequently[i]**	**No antibiotic prescribed**
Index RTI group	**N (%)**	**N (% of total)**		
Sinusitis	6,376 (7.0)	5,713 (89.6)	149 (2.3)	514 (8.1)
Chest infection	22,497 (24.8)	18,954 (84.3)	906 (4.0)	2,637 (11.7)
Ear infection	5,819 (6.4)	4,813 (82.7)	207 (3.6)	799 (13.7)
Sore throat	23,016 (25.4)	14,625 (63.5)	1,421 (6.2)	6,970 (30.3)
Laryngitis/ tracheitis	2,159 (2.4)	1,266 (58.6)	148 (6.9)	745 (34.5)
Not grouped[ii]	30,805 (34.0)	11,966 (38.8)	3,113 (10.1)	15,726 (51.1)
Total	90,672 (100.0)	57,337 (63.2)	5,944 (6.6)	27,391 (30.2)

[i] *1 to 60 days after the initial RTI*
[ii] *Includes diagnoses that could not be grouped such as upper RTIs and bacterial infections*

An additional 5,944 (6.6%) had an antibiotic subsequently prescribed, either between 1 and 60 days of the index RTI or, if a complication did arise sooner than 60 days, up to the date of the complication. Therefore a total of 63,281 patients had an antibiotic prescribed within 60 days of the initial index RTI (69.8% of all RTI consultations). The median (25^{th} to 75^{th} percentiles) number of days between the index RTI and a subsequent antibiotic was 19 days (6 to 40 days). Table 9.2 shows that a high proportion of each RTI group were prescribed an antibiotic on the same day as the

RTI was diagnosed, ranging from 89.6% of patients diagnosed with sinusitis to 38.8% for non-grouped diagnoses (e.g. URTI). Same day antibiotic prescribing varied substantially by practice, between 34% and 92%, and for subsequent prescribing between 2% and 10% (Figure 9.2). Subsequent prescribing was highest (10.1%) in the group including vague diagnoses such as Upper RTI not otherwise specified (NOS).

Figure 9.2 Antibiotic prescribing in 60 GPRD practices

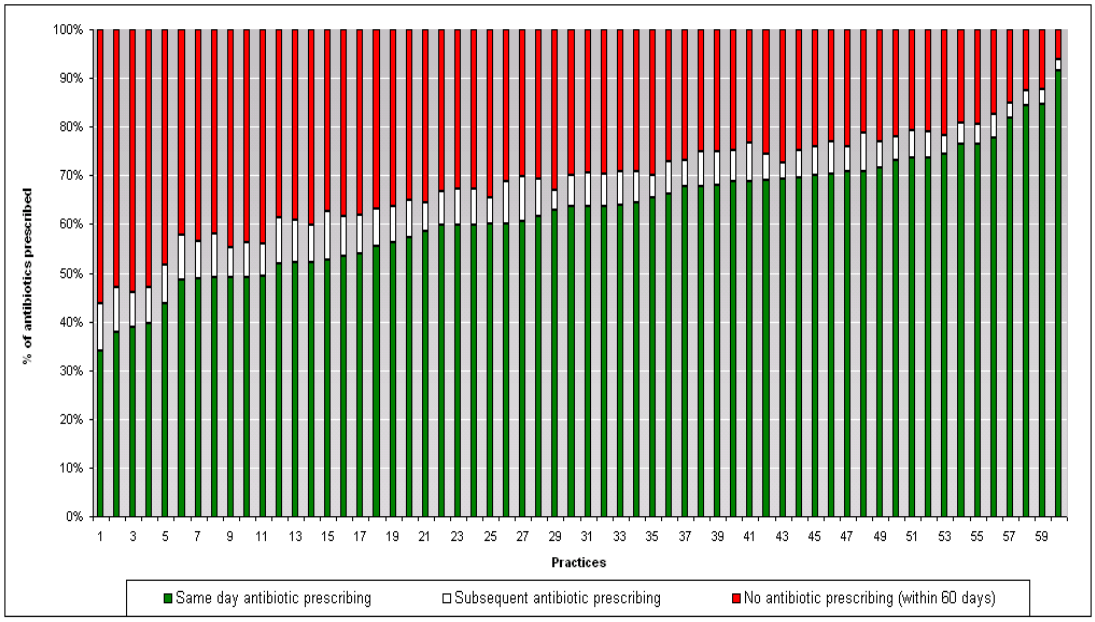


Table 9.3 shows the results from the univariate and multivariate models examining the association between antibiotic prescribing on the same day as the index RTI and individual patient factors. In the univariate model, there was an increased odds of same day antibiotic prescribing for older patients, for those overweight or obese, those diagnosed with diabetes, asthma or another co-morbidity (heart, lung, liver disease etc), in smokers and ex-smokers, and for patients who were prescribed a higher number of antibiotics, consulted their GP more often and had at least one complication in the year prior to the RTI diagnosis. There was a decreased odds of same day antibiotic prescribing for patients who had an unknown smoking status.

When these significant factors were included in a multivariate analysis, age, diabetes, asthma, co-morbidity, smoking, and prior antibiotic were all positively associated

with prescribing on the same day as the index RTI. Again patients with an unknown smoking status had lower odds of receiving an antibiotic on the same day as the RTI. Having a prior complication was no longer significant possibly due to correlation with other variables. There were significant differences between practices in same day antibiotic prescribing (σ^2_{u0}=0.245, (SE=0.049)) but no differences between regions.

Table 9.3 Factors associated with same day antibiotic prescribing (as the index RTI) - univariate and multivariate analyses

	Number of patients (%)		Univariate		Multivariate	
Factors	**No antibiotic prescribed N=33,335**	**Antibiotic prescribed N=57,337**	**Parameter estimate (SE)**	**OR (95% CI)**	**Parameter estimate (SE)**	**OR (95% CI)**
Age (years)						
0-4	3,264 (51.7)	3,054 (48.3)	Ref	1	Ref	1
5-15	7,051 (46.5)	8,112 (53.5)	0.204 (0.031)	1.23 (1.15 to 1.30)	0.190 (0.032)	1.21 (1.14 to 1.29)
16-64	18,566 (34.7)	34,966 (65.3)	0.734 (0.028)	2.08 (1.97 to 2.20)	0.590 (0.041)	1.80 (1.66 to 1.95)
≥65	4,454 (28.4)	11,205 (71.6)	0.996 (0.032)	2.71 (2.54 to 2.88)	0.801 (0.045)	2.23 (2.04 to 2.43)
Gender						
Male	13,739 (37.1)	23,329 (62.9)	Ref	1	-	-
Female	19,596 (36.6)	34,008 (63.4)	0.018 (0.014)	1.02 (0.99 to 1.05)		
Practice deprivation quintile						
Least deprived 1	1,888 (30.8)	4,240 (69.2)	Ref	1	-	-
2	1,393 (36.5)	2,426 (63.5)	-0.264 (0.210)	0.77 (0.51 to 1.16)		
3	1,338 (41.5)	1,885 (58.5)	-0.341 (0.194)	0.71 (0.49 to 1.04)		
4	1,861 (40.7)	2,708 (59.3)	-0.255 (0.198)	0.77 (0.53 to 1.14)		
Most deprived 5	1,392 (39.6)	2,125 (60.4)	0.027 (0.229)	1.03 (0.66 to 1.61)		
BMI						
Underweight	514 (35.7)	925 (64.3)	Ref	1	-	-
Normal	7,683 (34.3)	14,726 (65.7)	0.045 (0.058)	1.05 (0.93 to 1.17)		
Overweight	5,903 (31.9)	12,577 (68.1)	0.149 (0.059)	1.16 (1.03 to 1.30)		
Obese	3,868 (30.5)	8,794 (69.5)	0.230 (0.060)	1.26 (1.12 to 1.42)		
Diabetes	2,131 (32.2)	4,478 (67.8)	0.303 (0.028)	1.35 (1.28 to 1.43)	0.082 (0.030)	1.09 (1.02 to 1.15)
Asthma	4,320 (32.2)	9,103 (67.8)	0.240 (0.021)	1.27 (1.22 to 1.32)	0.063 (0.023)	1.07 (1.02 to 1.11)
Co-morbidity	5,424 (29.4)	13,046 (70.6)	0.404 (0.019)	1.50 (1.44 to 1.55)	0.230 (0.021)	1.26 (1.21 to 1.31)

Table 9.3 Factors associated with same day antibiotic prescribing (as the index RTI) - univariate and multivariate analyses

	Number of patients (%)		Univariate		Multivariate	
Factors	**No antibiotic prescribed N=33,335**	**Antibiotic prescribed N=57,337**	**Parameter estimate (SE)**	**OR (95% CI)**	**Parameter estimate (SE)**	**OR (95% CI)**
Smoking status						
Never smoked	13,364 (35.7)	24,023 (64.3)	Ref	1	Ref	1
Current smoker	4,958 (30.5)	11,313 (69.5)	0.261 (0.021)	1.30 (1.25 to 1.35)	0.256 (0.021)	1.29 (1.24 to 1.35)
Former smoker	4,305 (30.4)	9,862 (69.6)	0.259 (0.022)	1.30 (1.24 to 1.35)	0.179 (0.022)	1.20 (1.15 to 1.25)
Status unknown	10,708 (46.9)	12,139 (53.1)	-0.483 (0.018)	0.62 (0.60 to 0.64)	-0.061 (0.032)	0.94 (0.88 to 1.00)
History (1 year prior to index RTI):						
Antibiotics prescribed						
Low (0 per annum)	20,797 (39.1)	32,344 (60.9)	Ref	1	Ref	1
Med (1-2)	10,029 (34.6)	18,924 (65.4)	0.142 (0.016)	1.15 (1.12 to 1.19)	0.135 (0.017)	1.14 (1.11 to 1.18)
High (>3)	2,509 (29.2)	6,069 (70.8)	0.344 (0.026)	1.41 (1.34 to 1.48)	0.270 (0.028)	1.31 (1.24 to 1.38)
Complications						
No	33,136 (36.8)	56,916 (63.2)	Ref	1	-	-
Yes	199 (32.1)	421 (67.9)	0.221 (0.089)	1.25 (1.05 to 1.49)		
Consultations						
Low (0-4 per annum)	13,785 (39.5)	21,130 (60.5)	Ref	1	Ref	1
Mid (5-10)	10,593 (36.6)	18,333 (63.4)	0.121 (0.017)	1.13 (1.09 to 1.17)	-0.060 (0.018)	0.94 (0.91 to 0.98)
High (>10)	8,957 (33.4)	17,874 (66.6)	0.279 (0.018)	1.32 (1.28 to 1.37)	-0.160 (0.022)	0.85 (0.82 to 0.89)

9.4.3 Complications diagnosed in primary care

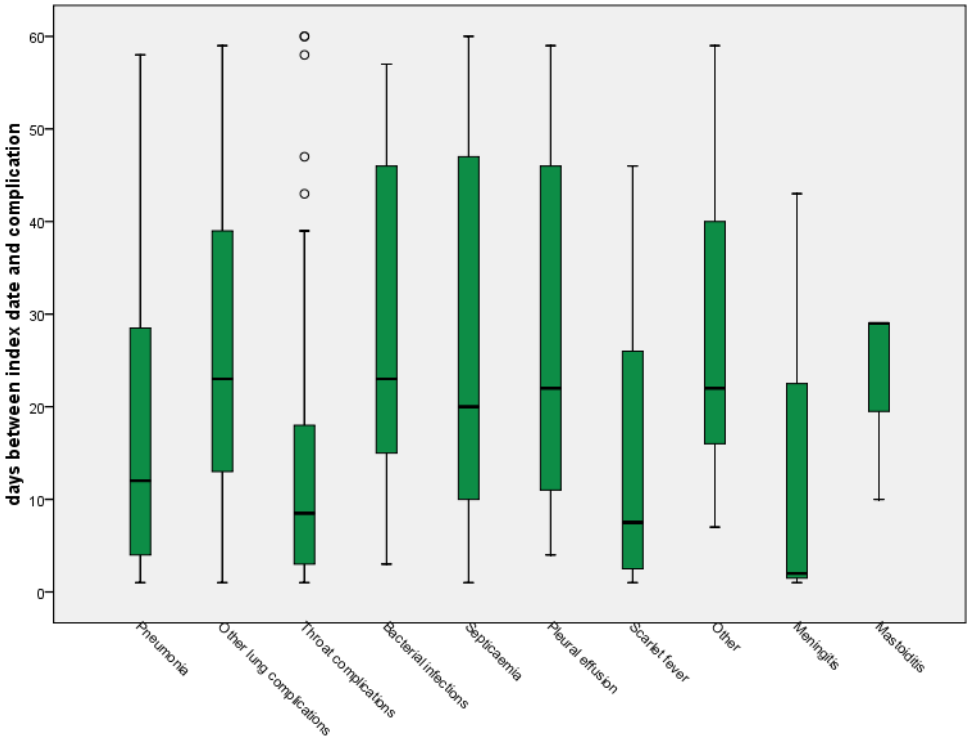
9.4.3.1 *All acute respiratory tract infections*

Of the 90,672 patients with an index RTI, 420 (46.32 per 10,000 patients) had a complication diagnosed by their GP within 60 days. The majority (62.7%) of these were lung complications (pneumonia, acute exacerbation of chronic obstructive pulmonary disease (AE COPD) and other lung complications) and throat complications such as quinsy, epiglottitis, and streptococcal throat/tonsillitis (Table 9.4). The median number of days between the index RTI and the patient's first complication varied by complication group; pneumonia, throat complications and scarlet fever all presented less than a median of 2 weeks after the initial RTI, with the other groups all presenting a median of 20 to 29 days later (Figure 9.3). The exception was meningitis with a median of 2 days (25^{th} to 75^{th} percentiles of 1 to 43 days) but as this was based on only 3 cases, this length of time should be interpreted with caution. Patients that did not receive an antibiotic had a shorter duration to onset of complication (median 9 days (25^{th} to 75^{th} percentile =3 to 23 days). No differences were observed between the group that received an antibiotic on the same or subsequently (median 18 days (7 to 36 days) and 19.50 (9 to 34.50)).

Table 9.4 Complications diagnosed in primary care within 60 days of the RTI

Complication	**N (%)**	**Median days after RTI (25^{th} to 75^{th} percentile)**
Pneumonia	188 (44.8)	12 (4 to 28)
Other lung complications (AE COPD, consolidation, bronchiectasis)	75 (17.9)	23 (13 to 39)
Throat complications (quinsy, epiglottitis, strep throat)	68 (16.2)	8 (3 to 18)
Bacterial infection unspecified (Streptococcal, staphylococcal etc)	26 (6.2)	23 (15 to 46)
Septicaemia	21 (5.0)	20 (10 to 47)
Pleural effusion	13 (3.1)	22 (11 to 46)
Scarlet fever	12 (2.9)	8 (2 to 26)
Other complications (lymphadenitis, cellulitis, reactive arthropathy)	11 (2.6)	22 (12 to 49)
Meningitis	3 (0.7)	2 (1 to 43)
Mastoiditis	3 (0.7)	29 (10 to 29)
Total	**420 (0.5%)**	**14 (5 to 32.75)**

Figure 9.3 Box plot of the number of days between the index RTI and the first complication



9.4.3.2 *Risk of complications by antibiotic prescribing*

Patients prescribed an antibiotic on the same day as the index RTI were found to be at a lower risk of presenting with a complication in primary care in the 60 days after the index RTI (44.47 vs.49.50 per 10,000 patients) (Table 9.5). The absolute risk reduction (ARR) was 5.02 (95% CI=-1.96 to 14.63) although not significant, and the number of antibiotics needed to be prescribed to prevent one complication (NNTB) was 1991 (95% CI= NNTH 5100 to ∞ to NNTB 684). An additional 5,944 patients were prescribed an antibiotic between 1 and 60 days after the index RTI (or until the first complication), of which 34 had a complication (57.20 per 10,000). The ARR for prescribing within any consultation (first or subsequent within 60 days of the initial RTI) was 2.16 (95% CI=-5.35 to 12.34), and the NNT=4637 (NNTH 1870 to ∞ to NNTB 810).

Table 9.5 Risk of complications (diagnosed in primary care) within 60 days of the index RTI (per 10,000 patients)

	Number of patients with a complication (risk per 10,000 patients)		**Absolute risk reduction (ARR) (95% CI)**	**Numbers needed to treat to prevent one complication (NNTB) (95% CI)**
	Not prescribed an antibiotic	**Prescribed an antibiotic**		
Same day prescribing	165/33,335 (49.50)	255/57,337 (44.47)	5.02 (-1.96 to 14.63)	1991 (NNTH[i] 5100 to ∞ to NNTB 684)
Prescribing within 60 days	131/27,391 (47.83)	289/63,281 (45.67)	2.16 (-5.35 to 12.34)	4637 (NNTH 1870 to ∞ to NNTB 810)

[i] *NNTH=number needed to harm*

Table 9.6 shows the results from the univariate and multivariate models examining the association between the risk of complication in the 60 days after the index RTI diagnosis and individual patient factors. In the univariate model, there was an increased risk of a complication for older patients (aged ≥65), males, those diagnosed with diabetes, asthma or another co-morbidity, underweight patients, for patients whose status regarding smoking was unknown, who were prescribed a higher number of antibiotics (>3 per annum), who had a higher number of consultations (>5 per annum) and had previously had a complication in the year prior to the RTI diagnosis.

After adjusting for these significant confounders (excluding diabetes and asthma as they were no longer significant in the multivariate model), patients prescribed an antibiotic on the same day as the index RTI were found to be at a lower risk of developing a complication in primary care in the 60 days after the index RTI (adjusted OR=0.74, 95% CI =0.56 to 0.99) and the number needed to treat with antibiotics to prevent one complication based on the adjusted OR was 780. For prescribing within 60 days of the index RTI, the adjusted OR was 0.78 (95% CI=0.56 to 1.07) and the NNTB=954.

When comparing the number needed to treat between those based on the ARRs and the adjusted ORs, the NNTBs were smaller in the adjusted ORs. For example, for same day antibiotic prescribing the NNTBs were reduced from 1991 to 780 and for prescribing within 60 days of the index RTI, from 4637 to 954.

Table 9.6 Factors associated with complications diagnosed in primary care within 60 days of the index RTI

Factors	Number of patients (%)		Univariate		Multivariate	
	No complication N=90,252	Complication diagnosed N=420	Parameter estimate (SE)	OR (95% Cl)	Parameter estimate (SE)	OR (95% Cl)
Age (years)						
0-4	6,299 (99.7)	19 (0.3)	Ref	1	Ref	1
5-15	15,135 (99.8)	28 (0.2)	-0.485 (0.303)	0.62 (0.34 to 1.12)	-0.343 (0.311)	0.71 (0.39 to 1.31)
16-64	53,363 (99.7)	169 (0.3)	0.056 (0.247)	1.06 (0.65 to 1.72)	0.657 (0.334)	1.93 (1.00 to 3.71)
≥65	15,455 (99.7)	204 (1.3)	1.501 (0.245)	4.49 (2.78 to 7.25)	1.807 (0.343)	6.09 (3.11 to 11.93)
Gender						
Male	36,872 (99.5)	196 (0.5)	Ref	1	Ref	1
Female	53,380 (99.6)	224 (0.4)	-0.234 (0.100)	0.79 (0.65 to 0.96)	-0.330 (0.105)	0.72 (0.59 to 0.88)
Deprivation quintile						
Least deprived 1	25,318 (99.6)	104 (0.4)	Ref	1	-	-
2	14,632 (99.6)	55 (0.4)	-0.035 (0.237)	0.97 (0.61 to 1.54)		
3	15,964 (99.4)	89 (0.6)	0.322 (0.213)	1.37 (0.91 to 2.09)		
4	22,543 (99.6)	99 (0.4)	0.108 (0.209)	1.11 (0.74 to 1.68)		
Most deprived 5	11,795 (99.4)	73 (0.6)	0.448 (0.238)	1.57 (0.98 to 2.50)		
BMI						
Underweight	1,418 (98.5)	21 (1.5)	Ref	1	-	-
Normal	22,288 (99.5)	121 (0.5)	-0.999 (0.243)	0.37 (0.23 to 0.59)		
Overweight	18,380 (99.5)	100 (0.5)	-1.005 (0.247)	0.37 (0.23 to 0.59)		
Obese	12,606 (99.6)	56 (0.4)	-1.217 (0.263)	0.30 (0.18 to 0.50)		
Diabetes	6,536 (98.9)	73 (1.1)	0.951 (0.133)	2.59 (1.99 to 3.36)	-	-
Asthma	13,316 (99.2)	107 (0.8)	0.686 (0.115)	1.99 (1.59 to 2.49)	-	-
Co-morbidity	2,745 (97.8)	63 (2.2)	1.037 (0.102)	2.82 (2.31 to 3.44)	0.409 (0.118)	1.51 (1.19 to 1.90)

Table 9.6 Factors associated with complications diagnosed in primary care within 60 days of the index RTI

Factors	Number of patients (%)		Univariate		Multivariate	
	No complication N=90,252	Complication diagnosed N=420	Parameter estimate (SE)	OR (95% Cl)	Parameter estimate (SE)	OR (95% Cl)
Smoking status						
Never smoked	37,199 (99.5)	188 (0.5)	Ref	1	Ref	1
Current smoker	16,195 (99.5)	76 (0.5)	-0.091 (0.139)	0.91 (0.70 to 1.20)	0.013 (0.144)	1.01 (0.76 to 1.34)
Former smoker	14,074 (99.3)	93 (0.7)	0.254 (0.130)	1.29 (1.00 to 1.66)	-0.257 (0.137)	0.77 (0.59 to 1.01)
Status unknown	22,784 (99.7)	63 (0.3)	-0.601 (0.148)	0.55 (0.41 to 0.73)	0.617 (0.247)	1.85 (1.14 to 3.01)
History (1 year prior to index RTI):						
Antibiotics prescribed						
Low (0 per annum)	52,944 (99.6)	197 (0.4)	Ref	1	Ref	1
Med (1-2)	28,838 (99.6)	115 (0.4)	0.087 (0.120)	1.09 (0.86 to 1.38)	-0.138 (0.127)	0.87 (0.68 to 1.12)
High (>3)	8,470 (98.7)	108 (1.3)	1.277 (0.123)	3.59 (2.82 to 4.56)	0.589 (0.146)	1.80 (1.35 to 2.40)
Complications (Yes)	577 (93.1)	43 (6.9)	2.834 (0.169)	17.01 (12.22 to 23.69)	1.957 (0.189)	7.08 (4.89 to 10.25)
Consultations						
Low (0-4 per annum)	34,826 (99.7)	89 (0.3)	Ref	1	Ref	1
Mid (5-10)	28,817 (99.6)	109 (0.4)	0.402 (0.146)	1.49 (1.12 to 1.99)	0.167 (0.157)	1.18 (0.87 to 1.61)
High (>10)	26,609 (99.2)	222 (0.8)	1.208 (0.129)	3.35 (2.60 to 4.31)	0.365 (0.166)	1.44 (1.04 to 1.99)
Antibiotic prescribing						
Same day prescribing						
No antibiotic	33,170 (99.5)	165 (0.5)	Ref	1	Ref	1
Antibiotic	57,082 (99.6)	255 (0.4)	-0.101 (0.144)	0.90 (0.68 to 1.20)	-0.297 (0.146)	0.74 (0.56 to 0.99)
Prescribing within 60 days[i]						
No antibiotic	27,260 (99.5)	131 (0.5)	Ref	1	Ref	1
Antibiotic	62,992 (99.5)	289 (0.5)	0.023 (0.159)	1.02 (0.75 to 1.40)	-0.254 (0.164)	0.78 (0.56 to 1.07)

[i]*Adjusted for age, gender, co-morbidity, smoking status, and antibiotic prescribing, consultations, and complications in the year prior to the RTI*

9.4.3.3 *Sore throat*

There were 23,016 consultations of sore throats in 2005, with 77 (33.45 per 10,000) complications being diagnosed in the 60 days after the initial RTI. Of these complications, 38 (49%) were for quinsy, 14 (18%) for various streptococcal infections (throat, tonsillitis), 9 (12%) for lung complications and the remainder for complications such as scarlet fever and septicaemia amongst others.

The risk of developing a complication was higher in patients who were prescribed an antibiotic on the same day when compared to those not receiving an antibiotic (34.19 vs. 32.18 per 10,000 patients) and the reduction in risk was negative although not significant (ARR=-2.01, 95% CI=-12.06 to 14.76) (Table 9.7). An additional 1,421 patients were prescribed an antibiotic between 1 and 60 days after the index RTI (or until the first complication), of which 3 had a complication (21.11 per 10,000). By incorporating these patients, the risk of developing a complication was reversed (33.03 vs. 35.35 per 10,000 patients) but the reduction in risk was still not significant (p=0.783). The NNTBs based on absolute risk were -4973 (NNTH 829 to ∞ to NNTB 678) and 4318 (NNTH 1079 to ∞ to NNTB 472) for same day prescribing and prescribing within 60 days respectively.

Only asthma and prior complications were associated with a complication arising from a sore throat diagnosis. After adjusting for these two factors, the OR for same day antibiotic prescribing was 1.07 (95% CI=0.67 to 1.70) and the NNTB was -4455 (or NNTH=4455). For any prescribing within 60 days of the sore throat diagnosis, there was still no significant difference in risk between the two groups (adjusted OR=0.95, 95% CI=0.58 to 1.54) and the NNTB was 5677.

9.4.3.4 *Chest infection*

There were 22,497 patient consultations of chest infections in 2005, with 213 (94.68 per 10,000) complications being diagnosed in the 60 days after the initial infection. Of these complications, 179 (84%) were for pneumonia and other lung complications such as AE COPD and bronchiectasis.

The risk of developing a complication was significantly lower in patients who were prescribed an antibiotic on the same day when compared to those not prescribed (77.56 vs. 186.28 per 10,000 patients) and the risk reduction was 108.73 (95% CI=69.14 to 160.05, p<0.001) (Table 9.7). The number of chest infections needed to treat with antibiotics to prevent one complication arising was 92 (95% CI=62 to 145). An additional 906 patients were prescribed an antibiotic within 60 days of the index RTI (or until the first complication), of whom 15 had a complication (165.56 per 10,000). After incorporating these patients, the risk of developing a complication was still significantly lower in patients who were prescribed an antibiotic within 60 days when compared to those not prescribed (81.57 vs. 193.40) per 10,000 patients) and the reduction in risk was slightly greater (ARR=111.83, 95% CI=65.83 to 172.92, p<0.001). The number of chest infections needed to treat with antibiotics to prevent one complication arising was 89 (95% CI=58 to 152). After adjusting for age, co-morbidity, smoking status, prior complication, and antibiotic in the year prior to the chest infection, the adjusted OR for same day antibiotic prescribing was 0.42 (95% CI=0.28 to 0.64, NNTB=93) and for prescribing within 60 days was 0.39 (95% CI=0.25 to 0.63, NNTB=85).

Table 9.7 Risk of complications (diagnosed in primary care) within 60 days of the index sore throat/chest infection (per 10,000 patients)

	Number of patients with a complication (risk per 10,000 patients)			
	Not prescribed an antibiotic	**Prescribed an antibiotic**	**ARR (95% CI)**	**NNTB[i] (95% CI)**
Sore throats				
Same day prescribing	27/8,391 (32.18)	50/14,625 (34.19)	-2.01 (-12.06 to 14.76)	-4973 (NNTH[ii] 829 to ∞ to NNTB 678)
Prescribing within 60 days	24/6,790 (35.35)	53/16,046 (33.03)	2.32 (-9.27 to 21.18)	4318 (NNTH 1079 to ∞ to NNTB 472)
Chest infections				
Same day prescribing	66/3,543 (186.28)	147/18,954 (77.56)	108.73 (69.14 to 160.05)	92 (62 to 145)
Prescribing within 60 days	51/2,637 (193.40)	162/19,860 (81.57)	111.83 (65.83 to 172.92)	89 (58 to 152)

[i] *NNTB = Number needed to benefit;* [ii] *NNTH = Number needed to harm*

9.4.3.5 *Ear infection, sinusitis, and non specific URTI codes*

There were 5,819 patient consultations of ear infections in 2005, with 10 complications (17.19 per 10,000) being diagnosed in the 60 days after the initial infection. The risk of developing a complication was lower in patients who were prescribed an antibiotic on the same day when compared to those not prescribed (16.62 vs. 19.88 per 10,000 patients) and the number needed to treat with antibiotics to prevent one complication arising was 3068 (95% CI=-895 to 178).

For sinusitis, there were 6,376 patient consultations with 7 developing into complications (10.98 per 10,000). Again the risk of developing a complication was lower in patients who were prescribed an antibiotic on the same day when compared to those not prescribed (10.50 vs. 15.08 per 10,000 patients) and the needed to treat with antibiotics to prevent one complication arising was 2183 (95% CI=-1276 to 134).

For general URTI, there were 30,805 patient consultations with 105 developing into complications (34.09 per 10,000). Again the risk of developing a complication was lower in patients who were prescribed an antibiotic on the same day when compared to those not prescribed (31.76 vs. 35.56 per 10,000 patients) and the needed to treat with antibiotics to prevent one complication arising was 2626 (95% CI=-2674 to 599).

9.4.4 Complications diagnosed in primary and secondary care

A total of 17 practices with 29,473 patients consented to being matched to Hospital Episode Statistics (HES) data (32.5% of the original dataset). Patients can only be matched if they have ever been hospitalised (as an inpatient, outpatient or attended A&E). The majority of patients (N=24,078, 81.7%) were a strong match (linked using NHS, DOB, & gender) and nine (0.03%) were a weak match. A small proportion of patients (N=5,196, 17.6%) could not be linked up to HES data, either because they had not ever been hospitalised or they did not have the required identifiers to allow linkage. Unfortunately, the GPRD data did not distinguish between these two reasons. This group who could not be linked was more likely to consist of young males, with less co-morbidity, non-smokers, of normal weight, with fewer antibiotic prescriptions, complications and consultations in the year prior to their RTI. They were also less likely to have received an antibiotic for the RTI and to have developed a complication. For these reasons it was believed that they were more likely to have not been hospitalised rather than not linked to HES data, and were included in the analysis. Lastly, 190 patients (0.6%) were missing a matching status and were excluded from analysis, leaving 29,283 patients to be analysed

9.4.4.1 *Representativeness of the linked practices*

Rates of complications diagnosed in primary care were slightly higher in linked practices than in non-linked (Table 9.8). Patients in the practices linked to secondary care data were on average younger, more likely to have had asthma, be a smoker or ex-smoker, and have had a complication in the year prior to the RTI. They were less likely to have diabetes, to have had an antibiotic prescribed or a consultation in the year before the RTI diagnosis, and to have been prescribed an antibiotic on the same day or subsequent to the index RTI. Patients were comparable on gender and co-morbidities. Thus there were no indications that this subset of linked data was biased towards patients at a higher risk of complications, thus biasing the rate of complications in the dataset. It is safe to assume that results arising from this subset of data are reliable and any additional complications identified are accurate and not an artefact of the case-mix of patients included. While some comparisons are significant, differences are generally small as the numbers involved are large.

Table 9.8 Demographics of patients diagnosed with an RTI in 2005 (N(%) unless otherwise specified) – practices linked to HES data and those not linked

Factors	**Non-linked practices**	**Linked practices**	**Test statistic, p-value**
Practices (patients)	43 (61,199)	17 (29,283)	
Complications in primary care N (rate per 10,000 patients)	265(43.30)	155 (52.93)	χ^2=3.976, p=0.046
Gender			
Male	24,943 (40.8)	12,048 (41.1)	χ^2=1.222,
Female	36,256 (59.2)	17,235 (58.9)	p=0.269
Age (years) median (25 to 75th percentiles)	38.0 (16 to 58)	37.0 (16 to 56)	MW, p<0.001
Co-morbidity			χ^2=1.295,
% Yes	12,407 (20.3)	6,032 (20.6)	p=0.255
Diabetes diagnosed prior to RTI			χ^2=76.591,
% Yes	4,785 (7.8)	1,816 (6.2)	p<0.001
Asthma diagnosed prior to RTI			χ^2=23.173,
% Yes	8,820 (14.4)	4,576 (15.6)	p<0.001
Smoking status			
Never smoked	10808 (17.7)	5414 (18.5)	χ^2=32.324,
Current smoker	25597 (41.8)	11704 (40.0)	p<0.001
Former smoker	9419 (15.4)	4735 (16.2)	
Status unknown	15375 (25.1)	7430 (25.4)	
History (1 year prior to index RTI)			
Number of antibiotics			
None	35549 (58.1)	17473 (59.7)	χ^2=26.932,
1-2	19689 (32.5)	9207 (31.4)	p<0.001
3+	5961 (9.7)	2603 (8.9)	
Complications			
% Yes	388 (0.6)	232 (0.8)	χ^2=7.291, p=0.007
Consultations			
Low (0-4 per annum)	22,823 (37.3)	12,009 (41.0)	χ^2=120.548,
Med (5-10)	19,785 (32.3)	9,084 (31.0)	p<0.001
High (>10)	18,591 (30.4)	8,190 (28.0)	
Antibiotic prescribed on same day	38,848 (63.5)	18,364 (62.7)	χ^2=4.999, p=0.025
Antibiotic prescribed within 60 days	42,837 (70.0)	20,302 (69.3)	χ^2=4.165, p=0.041

9.4.4.2 *All respiratory tract infections*

Of the 29,283 patients diagnosed with an RTI, 250 (85.37 per 10,000) had a complication diagnosed either in primary or secondary care within 60 days of the index RTI (Table 9.9). Of these, 155 (52.93 per 10,000 patients) presented, and were diagnosed with, a complication in primary care only (n=95) or in both primary and secondary care (n=60). An additional 95 complications (32.44 per 10,000 patients) were diagnosed in secondary care only but were not recorded in primary care during the 60 days after the index RTI. Identifying these secondary care complications was especially significant in the area of lung complications (39% of pneumonia and 54% other lung complications identified), septicaemia where 33% of cases were identified, and pleural effusion where 69% of cases were identified. The 95 patients with complications diagnosed in secondary care only (when compared to patients with a complication presenting in primary care only or in both primary and secondary care) were more likely to be older, have a co-morbidity and a diagnosis of diabetes. They were also more likely to be a smoker or an ex smoker, be prescribed an antibiotic after the index RTI (and less likely to be prescribed an antibiotic on the same day as the index RTI). They had a high number of GP consultations prior to the index RTI but were less likely to have had a complication and a high number of antibiotics prescribed in the year prior to the index RTI.

Table 9.9 Complications diagnosed in primary and secondary care within 60 days of the RTI (N(%) unless otherwise specified)

	Complication presenting in:			Median (25^{th} to 75^{th} percentiles) days after index RTI
Complication	**Primary care only or in both primary and secondary care**	**Secondary care only**	**Total**	
Pneumonia	60 (39)	38 (40)	98 (39)	9 (3 to 23.50)
Other lung complications (AE COPD, pleural empyema etc)	33 (21)	38 (40)	71 (28)	23 (8 to 41)
Throat complications (quinsy, epiglottitis, strep throat)	34 (22)	1 (1)	35 (14)	6 (3 to 15)
Bacterial infections	4 (3)	1 (1)	5 (2)	50 (31.50 to 52.00)
Septicaemia	8 (5)	4 (4)	12 (5)	25 (4.50 to 39.75)
Pleural effusion	4 (3)	9 (9)	13 (5)	25 (9.50 to 39.50)
Scarlet fever	4 (3)	0 (0)	4 (2)	5 (1.25 to 39.50)
Other complications (reactive arthropathy, cellulitis etc)	6 (4)	4 (4)	10 (4)	33.50 (11 to 49.50)
Meningitis	0 (0)	0 (0)	0 (0)	-
Mastoiditis	2 (1)	0 (0)	2 (1)	-
Total complications / Total patients (complication rate per 10,000 patients)	**155/29,283 (52.93)**	**95/29,283 (32.44)**	**250/29,283 (85.37)**	**-**
Median (25^{th} to 75^{th} percentiles) days after index RTI	**11 (4 to 27)**	**22 (7 to 43)**	**14 (4.75 to 31.25)**	**-**

Complications diagnosed in secondary care only had a significantly higher number of days between the index RTI and diagnosis (median= 22 days, 25th to 75th percentiles= 7 to 43 days) than for complications diagnosed in primary care only, or primary and secondary care only (11, 4 to 27 days, p=0.002). As in the main dataset, the majority of complications affected the lung with 80% of those diagnosed only in secondary care had lung complications. The median number of days between the index RTI and the patients' first complication were also comparable to the main datasets of primary care diagnosed complications (Table 9.10). Pneumonia and scarlet fever were diagnosed sooner in secondary care (9 vs. 12 days and 5 vs. 8 days respectively). Of the 60 complications diagnosed at both locations, 25 (42%) had the same dates (date of diagnosis in primary care was the same as the date of discharge from hospital), 27 (45%) had a complication diagnosed in primary care first (with a discharge date in secondary care between 1 and 23 days after), and 8 (13%) were discharged from hospital before the diagnosis had been recorded in primary care.

Table 9.10 Median (25th to 75th percentiles) days after index RTI to first diagnosis of complication by health care setting

Complication	**Diagnosed in:**	
	Primary care	**Secondary care**
Pneumonia	12 (4 to 28)	9 (3 to 23.50)
Other lung complications *(AE COPD, pleural empyema etc)*	23 (13 to 39)	23 (8 to 41)
Throat complications *(quinsy, epiglottitis, strep throat)*	8 (3 to 18)	6 (3 to 15)
Bacterial infections	23 (15 to 46)	50 (31.50 to 52.00)
Septicaemia	20 (10 to 47)	25 (4.50 to 39.75)
Pleural effusion	22 (11 to 46)	25 (9.50 to 39.50)
Scarlet fever	8 (2 to 26)	5 (1.25 to 39.50)
Other complications *(reactive arthropathy, cellulitis etc)*	22 (12 to 49)	33.50 (11 to 49.50)
Meningitis	2 (1 to 43)	0
Mastoiditis	29 (10 to 29)	0

9.4.4.2.1 *Risk of complications by antibiotic prescribing*

Patients prescribed an antibiotic on the same day as the index RTI were found to be at a significantly lower risk of presenting with a complication in primary care and/or secondary care in the 60 days after the index RTI (74.60 vs. 103.49 per 10,000 patients) (Table 9.11). The ARR was 28.89 (95% CI=11.55 to 52.61, p=0.009) and the number of antibiotics needed to be prescribed to prevent one complication (NNTB) was 346 (95% CI=190 to 866). These effects were much higher than in table 9.5.

An additional 1,938 patients were prescribed an antibiotic between 1 and 60 days after the index RTI (or until the first complication), of which 32 had a complication (165.12 per 10,000). This subgroup of patients had a higher risk of complications than those prescribed an antibiotic on the same day. An exploration into this group found that they were more likely to be female, have asthma, diabetes, or a general co-morbidity, a higher number of antibiotics prescribed, higher number of consultations and more likely to have had a prior complication all in the year prior to the index RTI. For this subgroup of patients who were subsequently prescribed an antibiotic, the rates of complications were also higher in the main dataset for RTIs and for chest infections and the patient characteristics of this cohort were consistent with those found above. By including these patients, the ARR was 6.95 (95% CI= -10.61 to 31.61, not significant).

Table 9.11 Risk of complications (diagnosed in primary and/or secondary care) within 60 days of the index RTI (per 10,000 patients)

	Number of patients with a complication (risk per 10,000 patients)			
	Not prescribed an antibiotic	**Prescribed an antibiotic**	**ARR (95% CI)**	**NNTB (95% CI)**
Same day prescribing	113/10,919 (103.49)	137/18,364 (74.60)	28.89 (11.55 to 52.61)	346 (190 to 866)
Prescribing within 60 days	81/8,981 (90.19)	169/20,302 (83.24)	6.95 (-0.61 to 31.61)	1439 (NNTH[i] 942 to ∞ to NNTB 316)

[i] *NNTB = Number needed to benefit*
[ii] *NNTH = Number needed to harm*

Table 9.12 shows the results from the univariate and multivariate models examining the association between the risk of complication in the 60 days after the RTI diagnosis and individual patient factors. In the multivariate analysis, older patients (aged ≥65 years) were at an increased risk of a complication, as were males, patients previously diagnosed with a co-morbidity, previously prescribed a higher number of antibiotics (>3 per annum), with a higher number of consultations (>10 per annum) and with a previous complication in the year prior to the RTI diagnosis.

After adjusting for these significant confounders, the OR for same day antibiotic prescribing was 0.55 (95% CI =0.39 to 0.77) and the number needed to treat with antibiotics to prevent one complication based on the OR was 216. For prescribing within 60 days of the index RTI, the adjusted OR was 0.65 (95% CI=0.46 to 0.93) indicating a significant risk reduction in developing a complication for those prescribed an antibiotic (NNTB=319).

Table 9.12 Factors associated with complications diagnosed in primary and/or secondary care within 60 days of index date for the RTI - univariate and multivariate analyses

Factors	Number of patients (%)		Univariate		Multivariate	
	No complication N=29,033	Complication diagnosed N=250	Parameter estimate (SE)	OR (95% Cl)	Parameter estimate (SE)	OR (95% Cl)
Age (years)						
0-4	2,062 (99.5)	10 (0.5)	Ref	1	Ref	1
5-15	4,824 (99.7)	15 (0.3)	-0.446 (0.412)	0.64 (0.29 to 1.44)	-0.317 (0.417)	0.73 (0.32 to 1.65)
16-64	17,691 (99.5)	94 (0.5)	0.093 (0.336)	1.10 (0.57 to 2.12)	0.141 (0.342)	1.15 (0.59 to 2.25)
≥65	4,456 (97.1)	131 (2.9)	1.810 (0.332)	6.11 (3.19 to 11.71)	1.386 (0.350)	4.00 (2.01 to 7.94)
Gender						
Male	11,924 (99.0)	124 (1.0)	Ref	1	Ref	1
Female	17,109 (99.3)	126 (0.7)	-0.346 (0.128)	0.71 (0.55 to 0.91)	-0.505 (0.132)	0.60 (0.47 to 0.78)
Deprivation quintile						
Least deprived 1	6053 (99.3)	45 (0.7)	Ref	1		
2	3766 (99.2)	31 (0.8)	-0.103 (0.331)	0.90 (0.47 to 1.73)		
3	3172 (99.2)	25 (0.8)	-0.002 (0.332)	1.00 (0.52 to 1.91)		
4	4499 (99.0)	47 (1.0)	0.232 (0.261)	1.26 (0.76 to 2.10)		
Most deprived 5	3443 (98.9)	40 (1.1)	0.298 (0.349)	1.35 (0.68 to 2.67)		
BMI						
Underweight	461 (96.0)	19 (4.0)	Ref	1		
Normal	7,611 (99.0)	75 (1.0)	-1.427 (0.264)	0.24 (0.14 to 0.40)		
Overweight	5,758 (99.1)	52 (0.9)	-1.535 (0.276)	0.22 (0.13 to 0.37)		
Obese	3,803 (99.0)	38 (1.0)	-1.445 (0.289)	0.24 (0.13 to 0.42)		
Diabetes	1,774 (97.7)	42 (2.3)	1.115 (0.173)	3.05 (2.17 to 4.28)	-	-
Asthma	4,498 (98.3)	78 (1.7)	0.963 (0.142)	2.62 (1.98 to 3.46)	-	-
Co-morbidity	5,910 (98.0)	122 (2.0)	1.314 (0.129)	3.72 (2.89 to 4.79)	0.582 (0.147)	1.79 (1.34 to 2.39)

Table 9.12 Factors associated with complications diagnosed in primary and/or secondary care within 60 days of index date for the RTI - univariate and multivariate analyses

Factors	Number of patients (%)		Univariate		Multivariate	
	No complication N=29,033	Complication diagnosed N=250	Parameter estimate (SE)	OR (95% Cl)	Parameter estimate (SE)	OR (95% Cl)
Smoking status						
Never smoked	11,597 (99.1)	107 (0.9)	Ref	1	-	-
Current smoker	5,364 (99.1)	50 (0.9)	-0.014 (0.174)	0.99 (0.70 to 1.39)		
Former smoker	4,672 (98.7)	63 (1.3)	0.373 (0.161)	1.45 (1.06 to 1.99)		
Status unknown	7,400 (99.6)	30 (0.4)	-0.826 (0.209)	0.44 (0.29 to 0.66)		
History (1 year prior to index RTI):						
Antibiotics prescribed						
Low (0 per annum)	17,370 (99.4)	102 (0.6)	Ref	1	Ref	1
Med (1-2)	9,130 (99.2)	77 (0.8)	0.362 (0.153)	1.44 (1.06 to 1.99)	0.095 (0.160)	1.10 (0.80 to 1.50)
High (>3)	2,533 (97.3)	71 (2.7)	1.567 (0.158)	4.79 (3.52 to 6.53)	0.795 (0.184)	2.21 (1.54 to 3.18)
Complications (Yes)	210 (90.5)	22 (9.5)	2.581 (0.236)	13.21 (8.32 to 20.98)	1.445 (0.259)	4.24 (2.55 to 7.05)
Consultations						
Low (0-4 per annum)	11,964 (99.6)	45 (0.4)	Ref	1	Ref	1
Mid (5-10)	9,026 (99.4)	58 (0.6)	0.534 (0.200)	1.71 (1.15 to 2.52)	0.187 (0.211)	1.21 (0.80 to 1.82)
High (>10)	8,043 (98.2)	147 (1.8)	1.583 (0.173)	4.87 (3.47 to 6.84)	0.514 (0.216)	1.67 (1.09 to 2.55)
Antibiotic prescribing						
Same day prescribing						
No antibiotic	10,806 (99.0)	113 (1.0)	Ref	1	Ref	1
Antibiotic	18,227 (99.3)	137 (0.7)	-0.311 (0.158)	0.73 (0.54 to 1.00)	-0.606 (0.174)	0.55 (0.39 to 0.77)
Prescribing within 60 days[i]						
No antibiotic	8,900 (99.1)	81 (0.9)	Ref	1	Ref	1
Antibiotic	20,133 (99.2)	169 (0.8)	-0.037 (0.160)	0.96 (0.70 to 1.32)	-0.427 (0.179)	0.65 (0.46 to 0.93)

[i]*Adjusted for age, gender, co-morbidity, and antibiotic prescribing, consultations, and complications in the year prior to the RTI*

9.4.4.3 *Sore throats*

There were 7,131 episodes of sore throats with 38 (0.53%) complications being diagnosed in either primary or secondary care within 60 days of the initial infection.

The risk of developing a complication was again higher in patients who received an antibiotic on the same day when compared to those not (60.51 vs. 39.94 per 10,000 patients) but the risk reduction was greater but still not significantly different (ARR=20.58, 95% CI= -38.81 to 17.68) (Table 9.13). An additional 409 patients were prescribed an antibiotic between 1 and 60 days after the index RTI (or until the first complication), of which none developed a complication in the 60 days after the sore throat.

The small numbers of complications involved did not allow the multilevel model to be fully fitted and no confounders could be included in the model. The unadjusted OR for same day prescribing was 1.52 (95% CI=0.73 to 3.16) and for prescribing within 60 days was 1.17 (95% CI=0.56 to 2.43).

9.4.4.4 *Chest infections*

There were 6,982 episodes of chest infection, with 134 (1.92%) complications being diagnosed in either primary or secondary care within 60 days of the initial infection. Of these complications, the majority (N=116, 87%) were pneumonia and lung complications.

Once again the risk of developing a complication was significantly lower in patients who received an antibiotic on the same day as the index chest infection compared to those who did not receive an antibiotic (119.27 vs. 575.02, ARR=455.75 (95% CI=333.59 to 610.34, $p<0.001$) (Table 9.13). The number needed to be treated with antibiotics to prevent one complication was 22 (95% CI=16 to 30). An additional 301 patients were prescribed an antibiotic between 1 and 60 days after the index RTI (or until the first complication), of which 19 had a complication (631.23 per 10,000). By incorporating these patients, a similar reduction was seen for any antibiotic

prescribing within 60 days of the chest infection (ARR=409.94, 95% CI=272.49 to 591.26, p<0.001, NNTB=24, 95% CI=17 to 37).

After adjusting for significant confounders (age, co-morbidity and previous antibiotic and complications), the OR for same day prescribing as the chest infection was 0.19 (95% CI=0.12 to 0.31, NNTB=22). For any prescribing within 60 days of the chest infection, the OR was 0.21 (95% CI=0.11 to 0.39, NNTB=23).

Table 9.13 Risk of complications (diagnosed in primary and/or secondary care) within 60 days of the index sore throat/chest infection (per 10,000 patients)

	Number of patients with a complication (risk per 10,000 patients)			
	Not prescribed an antibiotic	**Prescribed an antibiotic**	**ARR (95% CI)**	**NNTB (95% CI)**
Sore throats				
Same day prescribing	10/2,504 (39.94)	28/4,627 (60.51)	-20.58 (-38.81 to 17.68)	-486 (NNTH 28 to ∞ and NNTB 566)
Prescribing within 60 days	10/2,095 (47.73)	28/5,036 (55.60)	-7.87 (-29.65 to 35.56)	-1271 (NNTH 337 to ∞ to NNTB 281)
Chest infections				
Same day prescribing	64/1,113 (575.02)	70/5,869 (119.27)	455.75 (333.59 to 610.34)	22 (16 to 30)
Prescribing within 60 days	45/812 (554.19)	89/6,170 (144.25)	409.94 (272.49 to 591.26)	24 (17 to 37)

9.4.5 Summary of results

Table 9.14 summarises the results from this chapter examining the risk of complications arising from an acute RTI by antibiotic prescribing, firstly using the main set of GPRD patients (Table 9.14a) and then looking at the cohort of patients that were linked to hospital admissions data (Table 9.14b).

Complications diagnosed in primary care were almost three times as likely to occur after a chest infection than they were after a sore throat (94.68 vs. 33.45 per 10,000). For all acute RTIs and chest infections, the risk of a complication arising was higher in patients that had not received an antibiotic when compared to those prescribed an antibiotic (either on the same day as the index RTI or within 60 days). In chest infections, the protective effect of antibiotic prescribing was most apparent with an absolute risk reduction of 108.73 per 10,000 for same day prescribing, resulting in low numbers needed to treat with antibiotics to benefit one patient avoiding a complication (NNTB=92). There was no evidence of a protective effect of antibiotic prescribing in diagnoses of sore throats.

The risk of a complication was higher in patients subsequently prescribed an antibiotic (one to 60 days after the index RTI); for example in chest infections, patients subsequently prescribed an antibiotic had a rate of complication of 165.56 per 10,000 compared to 77.56 per 10,000 in patients prescribed an antibiotic on the same day as the index RTI. These patients (subsequently prescribed an antibiotic) had more co-morbidities and were possible sicker than patients prescribed on the same day or not prescribed at all. Presumably these patients returned to the GP because they were still unwell and the complication may have been starting to develop when the antibiotic was subsequently prescribed.

There was no evidence to suggest that the subset of patients linked to secondary care data were a biased sample of the whole set and no more likely to experience a complication (not a sicker cohort). The impact of including complications diagnosed in secondary care (not previously diagnosed in primary care) can be seen, with higher risks observed across all RTI groups. The impact of including secondary care diagnosed complications was most pronounced for all RTIs and chest infections,

where including secondary care complications increased the risk from 52.93 to 85.37 per 10,000 patients, and from 88.80 to 191.92 per 10,000 patients respectively. Complications diagnosed in primary and/or secondary were again more frequently diagnosed in chest infections than in all RTIs (191.92 vs. 85.37 per 10,000) and lower in sore throats.

Again for all acute RTIs and chest infections, the risk of complications identified in primary and secondary care was higher in patients that had not received an antibiotic when compared to those prescribed an antibiotic (either on the same day as the index RTI or within 60 days). In chest infections, the protective effect of antibiotics was most apparent with an absolute risk reduction of 455.75 per 10,000 for same day prescribing (an increase from when primary care complications were included), resulting in even lower numbers needed to treat (NNTB=22). Even when we considered secondary care complications, there was no evidence of a protective effect of antibiotic in diagnoses of sore throats, with only an additional 4 complications identified in secondary care.

In patients who had a complication diagnosed in secondary care, the rates of complications were high (32.44 per 10,000 for all RTIs and 103.12 per 10,000 in chest infections) compared to those diagnosed in primary care. In this cohort there were no differences between patients who were prescribed an antibiotic on the same day (n=42) compared to those who were not (n=53) with respect to their demographics. When we examined subsequent prescribing (n=65) vs. no prescribing (n=30) in the same cohort, then patients that were not prescribed an antibiotic were more likely to be older, less likely to have a co-morbidity, had a antibiotic prescribed in the year prior, had a complication in the year prior and less likely to have had a high number of consultations in the year prior.

Table 9.14 Complication rates (per 10,000) by index RTI group and antibiotic prescribing status

a. Complications diagnosed in primary care					
	Not prescribed an antibiotic	**Same day prescribing**	**Subsequent prescribing (1-60 days)**	**Prescribing within 60 days**	**Total**
All RTIs	131/27,391 (47.83)	255/57,337 (44.47)	34/5,944 (57.20)	289/63,281 (45.67)	420/90,972 (46.32)
Sore throat	24/6,790 (35.35)	50/14,625 (34.19)	3/1,421 (21.11)	53/16,046 (33.03)	77/23,016 (33.45)
Chest infection	51/2,637 (193.40)	147/18,954 (77.56)	15/906 (165.56)	162/19,860 (81.57)	213/22,497 (94.68)

b. Complications diagnosed in primary and/or secondary care						**Secondary care only**
	Not prescribed an antibiotic	**Same day prescribing**	**Subsequent prescribing (1-60 days)**	**Prescribing within 60 days**	**Total**	**Total**
All RTIs	81/8,891 (90.19)	137/18,364 (74.60)	32/1,938 (165.12)	169/20,302 (83.24)	250/29,283 (85.37)	95
Sore throat	10/2,095 (47.73)	28/4,627 (60.51)	0/409 (0.00)	28/5,036 (55.60)	38/7,131 (53.29)	4
Chest infection	45/812 (554.19)	70/5,869 (119.27)	19/301 (631.23)	89/6,170 (144.25)	134/6,982 (191.92)	72

9.5 Discussion

9.5.1 Main findings

The risk of developing a serious complication diagnosed in primary care after an acute RTI was higher in those not prescribed an antibiotic (either on the same day or in the 60 days subsequently) . However the absolute risk reduction (ARR) was non-significant and the number of patients needing to be treated with an antibiotic to prevent one complication was high (1991). After adjusting for identified confounding factors, same day prescribing of antibiotics had a weak but significant protective effect against complications diagnosed in primary care, and although the numbers required to treat with antibiotics to prevent one complication had reduced, they remained high. In complications following a diagnosis of a sore throat, the risk of complication was lower for patients not prescribed an antibiotic and again the ARR was non-significant. In chest infections however, the risk of complications was higher in those not prescribed an antibiotic on the same day as the RTI with a significant decrease in risk with treatment of antibiotics. The number of patients with a chest infection needed to be prescribed an antibiotic to prevent one complication was much lower (92).

Complications diagnosed in secondary care only (and not in primary care) were especially identified for lung complications, septicaemia and pleural effusion. When complications identified in primary and secondary care were taken into account, the risk of developing a complication was higher across all the RTI groups examined. The risk of complication was significantly higher for patients not being prescribed an antibiotic on the same day as the index RTI than for those prescribed an antibiotic. In chest infections, there was a substantial risk of complication, which was again significantly reduced in those prescribed an antibiotic (same day and at any time) and the number of patients with a chest infection needed to be prescribed an antibiotic to prevent one complication was 22.

9.5.2 Strengths and weaknesses of the study

Only a small number of studies have examined the effect of antibiotic prescribing on complications arising from acute RTIs at the individual patient level, whilst adjusting

for significant confounders. Although we were restricted in the size of our cohort (a maximum of 100,000 patient records), one of the main advantages was that we were able to obtain secondary care data for a sub-set of practices, thus identifying additional complications presenting in secondary care, not previously recorded in primary care and quantifying the number of these. Complications were identified by using Read codes and included all types of consultations such as surgery consultations and letter from outpatients. Thus we can be confident that the extra information derived from linking to HES is a very important finding as it indicates that the assumption of many researchers that most major diagnoses are recorded in primary care data, may be misleading.

Not only did including secondary care complications increase the risk of complications, but it also increased the risk of complication in those not receiving an antibiotic on the same day as the index RTI. In RTIs, the risk of complications increased over two-fold (from 49.50 per 10,000 in the primary dataset to 103.49 in the dataset linked to secondary care data). The effect of linking to secondary care data was more evident in complications arising from chest infections where the risk increased from 186.28 to 575.02 per 10,000 patients in those not prescribed an antibiotic, and from 77.56 to 119.27 per 10,000 patients in those prescribed an antibiotic. Identifying secondary care complications increased the ARR which in turn reduced the NNTs (Table 9.15).

Table 9.15 Numbers needed to treat (NNT) with antibiotics to prevent one complication by healthcare setting

	Complication diagnosed in…	
	Primary care only	**Primary and/or secondary care**
All RTIs		
Unadjusted model	1991	346
Adjusted model	780	216
Sore throat		
Unadjusted	-4973	-486
Adjusted	-4455	NA
Chest		
Unadjusted	92	22
Adjusted	93	22

NA = complications too rare to perform logistic regression modelling

The increases in complications rates found by incorporating secondary care complications could not be attributed to any differences in the case-mix of patients between the two datasets, suggesting that the increase in complications was a true reflection of the incidence of complications in the population.
The under-recording that can occur by only assessing GP records for complications was minimised, and the population of complications more accurately estimated. The entire population of complications, however, is still under-recorded as it excludes patients who are seen in out of hours clinics and not recorded in the GP notes, and also patients presenting to emergency departments and sent home without being admitted to hospital.

This study was also able to assess the impact of prescribing an antibiotic after the initial RTI was diagnosed (between 1 and 60 days). This could be interpreted as delayed prescribing but it was impossible to know if the delay was due to the GP or due to the patient re-consulting independently. This group of patients had higher complication rates (identified in primary and/or secondary care) for patients diagnosed with any RTIs and also chest infections. In fact these rates were higher than those not prescribed antibiotics.

This was an observational study using routinely collected data, and therefore possible confounders may be unequally distributed between those prescribed an antibiotic and those not. In this study, however, we fitted models to assess patient characteristics which appeared to influence the decisions of GPs to prescribe an antibiotic or not, for example to sicker patients and to those who were at a higher risk of complications though. Data on individuals' resistance levels was not available. We then adjusted for these confounders in the main analysis, estimating the effect of prescribing antibiotics on the risk of complications. Sufficient data were not available to examine the risk of complications by antibiotic type and dose as planned, nor were there enough to examine the interaction between age and antibiotic prescribing as seen in other studies (Petersen *et al.* 2007). Although we were able to identify the characteristics of patients more likely to receive an antibiotic prescription, we were not able to adjust for severity of the presenting infections; patients with more severe disease would have been more likely to receive a prescription for an antibiotic.

There was also insufficient outcome data to examine complications presenting in 30 days as planned, in addition to 60 days. A variety of follow-up times have been used in other studies, varying from 30 days to 3 months (Dunn *et al*. 2007 and Winchester *et al*. 2009 respectively). However, whilst the average time between an RTI and a complication for all complications was 14 (25^{th} to 75^{th} percentiles 5 to 32.75) days, they varied greatly by type of complication. For example, the average time between an RTI and pneumonia was 12 (4 to 28) days while for septicaemia the average was 20 (10 to 47) days. This variation was also found in the study by Thompson *et al.* (2009a) where the average time between an episode of otitis media and mastoiditis was 21.5 (6.0 to 51.5) days.

Whilst GPRD data is a very useful data source into gaining an insight into primary care observational data, it has some limitations. Firstly, patients who choose to present with RTI symptoms to their GP may be unrepresentative in respect of clinical factors such as age, duration of symptoms, and co morbidity (McKinlay 1972; Van Duijn *et al*. 2007). It has been estimated that between 10% and 30% of patients with an episode of respiratory tract symptoms consult a GP (Bruijnzeels *et al*. 1998; Van Duijn *et al*. 2007). The outcomes for those patients who do not present are either that the RTI would be self-limiting, and resolve without antibiotics, or else the patient would deteriorate and present to primary or secondary care with a complication. Therefore assessing the impact of this bias is difficult. For patients who do present to their GP it has been suggested that a potential limitation is that not all consultations for such minor infections are recorded in GP records (Hayward *et al*. 2007), leading to a possible underestimation in the number of patients not receiving an antibiotic. Diagnoses recorded by GPs may be influenced by their prescribing decisions (also referred to as diagnostic drift) but hard evidence of this is limited. Indeed, several studies have claimed that no evidence exists to support a shift in diagnostic preference (Fleming *et al*. 2003; Ashworth *et al*. 2005a). Nonetheless this bias would lead to an overestimation of the proportion of patients who received an antibiotic.

We acknowledge that antibiotic prescribing is an imperfect proxy for antibiotic consumption. However, evidence suggests that only 6-8% of prescriptions are not dispensed (personal communication, *Dr Efrosini Setakis, GPRD*) and that the majority of adults in the UK (90%) claim to finish their course of antibiotics

(Pecherer 2001). This would therefore lead to only a small bias in prescribing data although this bias may vary by the type of acute RTI (the more serious the infection, the higher the likelihood of dispensing the prescription and adhering to the antibiotic). Adjusting for the possible bias found in the group prescribed antibiotics is likely to increase any effect found between the two groups and so any conclusions made are likely to be conservative. Lastly, we are not able to demonstrate causality as we cannot assert that the patients who did not have an antibiotic but then went on to have a complication could have avoided the complication if they had in fact received the antibiotic.

We excluded pneumonia as an RTI since the percentage of patients receiving an antibiotic was low; 13.1% on the same day as pneumonia was diagnosed. This low percentage could be attributed not to inadequate care by the GP but as a result of a referral to hospital for additional treatment (such as a chest x-ray alongside antibiotics).

9.5.3 Comparisons with existing literature

Before comparing our results with other literature we first assess whether our cohort is comparable to the whole GPRD database, and therefore representative of GP consultations and prescribing in the UK, (with respect to the proportion of RTIs seen and the proportion prescribed an antibiotic). A comparison will then be made with the literature examining the relationship between antibiotics and complications.

9.5.3.1 *External validity of the GPRD RTI cohort*

Comparing our cohort of patients with an RTI to the general population with an RTI is difficult as little comparative data exists. However, output from a study funded by the Department of Health for a collaboration between the University College London Centre for Infectious Disease Epidemiology and the Health Protection Agency (http://www.idrn.org/antimicrobial_prescribing) showed that in data from 179 practices in the GPRD (for 2000/01) (with an age sex structure similar to the UK population), the proportions of consultations for sore throats, ear infections, sinusitis, URTIs and LRTIs were similar to those found in our cohort of patients. For

example, in our study, 25.4% and 7.0% of RTIs were for consultations of sore throats and sinusitis respectively (compared to 20.9% and 7.6% respectively in the larger dataset).

The proportion of antibiotics prescribed to RTIs in our study was similar to that found in GPRD based studies which included a larger population of GPs. Table 9.16 shows comparative figures from this and two other studies and the differences are minimal.

Table 9.16 Proportion of antibiotics prescribed by type of RTI

	Petersen and Hayward (2007)	**Ashworth *et al.* (2004)**	**Cannings-John (2012)**
Study period	*1991 to 2001*	*1994 to 2000*	*2005*
N practices (patients)	*108 (642,685)*	*162 (not stated)*	*60 (90,672)*
Chest infection	82.2%	89%	84.3%
Ear infection	82.5%	81%	82.7%
Sore throat	64.3%	60%	63.5%
Upper RTI	44.2%	47%	34.0%

9.5.3.2 *Predictors of complications*

Until recently the role of antibiotics in the development of complications arising from RTIs had been examined only by ecological studies or meta-analyses of trials in which complications were not the primary outcome. Randomised controlled trials are the gold standard but the large numbers required to power studies to examine the rare events of complications mean they have not been carried out. Additionally the study populations of these RCTs have generally been selective (e.g. patients with streptococcal sore throat). Lately, observational studies, mainly using the general practice research database (GPRD), have been used to examine this association.

We were able to show that in patients with a diagnosis of any RTI in primary care, whilst antibiotics had a protective effect, the number needed to treat to prevent complications was high. However, the relatively small sample size did not allow us

to explore the protective effect of antibiotics in all RTI groups especially by age groups, apart from in sore throats and chest infections (followed by any complication). In sore throats, a meta-analysis has shown that antibiotics had a protective effect against acute rheumatic fever and quinsy (Spinks *et al*. 2006) but these were based on studies in the 1950s-60s, a period where the background incidences of these infections were much higher in Western society. A large observational study in primary care by Petersen *et al.* (2007) showed that same day antibiotic prescribing did reduce the risk of quinsy diagnosed in primary care (after adjusting for age, gender, deprivation), but the number needed to treat to prevent one serious complication was high. Conversely, a case-control study by Dunn *et al*. (2006) showed that antibiotic exposure had no effect on the occurrence of quinsy arising from sore throats. However, there was some evidence to suggest that antibiotics may reduce the risk of quinsy in patients with a diagnosis of tonsillitis.

The study by Petersen *et al.* (2007) also showed that antibiotics reduced the risk of pneumonia (following a chest infection) across all ages, and the risk of pneumonia was particularly high in the 65 plus age group. The number of patients needed to treat with antibiotics to prevent one complication of pneumonia following a chest infection was smaller than in other RTI groups and also reduced with age. Winchester *et al*. (2009) additionally examined patients diagnosed with LRTIs and found that an antibiotic prescription on the same day was less likely to result in hospitalisations and death from pneumonia. We also found that exposure to antibiotics reduced the risk of developing any complication (diagnosed in primary care) arising from chest infections, with relatively small numbers needed to treat. Additionally we found that when complications recorded in secondary care were considered, the number of patients needed to be treated with antibiotics was reduced drastically.

9.5.4 Implications of findings for clinical practice and future research

These observational studies concluded that antibiotic prescribing could be reduced in primary care, especially for sore throats, ear infections and URTI, since the numbers needed to treat were so high that few complications would be likely to arise. Research should also focus on developing clinical algorithms to identify which

symptoms and signs patients present with at the diagnosis of an RTI are more likely to predict if a complication will occur, so that prescribing can be targeted more precisely at high-risk patients. This is especially relevant in chest infections where the numbers needed to treat were much lower, especially in older patients. Targetting a more specific group of patients based on their symptoms or bacterial infections has been shown to reduce complications, when a subset of patients with higher clinical likelihood of group A β-hemolytic streptococcus (GABHS) showed more benefit from antibiotics in prevention of quinsy (Dagnelie *et al*. 1996; Zwart *et al*. 2000). We suggest that before further reductions are made in antibiotic prescribing for URTIs, sore throats and otitis media, a large scale observational study (using the GPRD or equivalent) should be carried out to examine the risk associated with withholding antibiotics on complications diagnosed in primary *and* secondary care. Ideally it would be useful to examine this association over a longer time period to see if, as antibiotic prescribing in RTIs decreased in primary care (albeit the proportion of prescribing being high), the numbers required to treat with antibiotics to prevent one complication changed over time. The sample size would have to be sufficiently large to permit examination of risk by certain RTI groups (sore throats, otitis media, sinusitis, URTI, chest infection) and by age group. It would also be of interest to see whether risk varies by type and dose of antibiotic.

9.6 Introduction to Chapter 10

The current chapter concludes the research into the possible risks associated with antibiotic prescribing with respects to complications. Within each chapter, results and discussion have been presented enabling each to be read independently (albeit that the research theme connects each chapter). The final chapter synthesises the research presented in each chapter and provides a summary of the thesis, reflects on the main strengths and weaknesses and implications of the results to clinical practice and suggests future areas of research.

Chapter 10 Discussion

The aim of this thesis was to investigate the relationship between antibiotic prescribing, resistance and complications arising from acute RTIs and objectives were set out in Chapter 1. Rather than address each individual objective and repeat the results in respective chapters, this chapter will summarise the results, highlight the study strengths and weaknesses, and discuss the implications of the results to both clinical practice and future research.

10.1 Main findings

10.1.1 Antibiotic dispensing

This study covers an era where UK general practitioners were advised that a strategy of no or delayed antibiotic prescribing should generally apply to patients presenting with certain acute RTIs (acute otitis media, sore throat/pharyngitis/tonsillitis, common cold, acute rhinosinusitis, acute cough/bronchitis) (SMAC 1998, NICE Clinical Guidelines 69, 2008). This resulted in a decline in antibiotic dispensing which is replicated in this research for the Welsh population between 1996 and 2006. Reductions were seen in overall dispensing for antibiotics used in the treatment of RTIs and for the majority of antibiotic classes, for all ages and children (using liquid oral antibiotics). The exception to this was flucloxacillin which significantly increased over the period. Dispensing rates and trends vary widely amongst Welsh practices; practices with the highest initial rates decreased their dispensing the most. Worryingly the trend in dispensing rates had slowed down by 2004/05 and in 2005/06 had started to turn.

10.1.2 The benefits of reducing antibiotic dispensing

The main benefit of the reduction in dispensing is the belief that antimicrobial resistance will be contained. This study showed significant reductions in resistance to amoxicillin and tetracycline in *H. influenzae* isolates for all samples (including wound and urine) submitted by GPs over the same time period. Resistance to erythromycin in *S. pneumoniae* isolates increased over time. Similar trends to these are seen in samples taken from the respiratory tract (ear, nose and throat and sputum

samples). Evidence suggests a positive association between lagged antibiotic dispensing and resistance, even after adjusting for confounders indicating that resistance was more likely to occur in patients from a practice dispensing at a higher rate. However, reducing total antibiotic dispensing at a practice level did not impact favourably on resistance in RTI samples. No clear pattern was found between change in dispensing and change in resistance for any of the organism/ antibiotic combinations that were examined although the study lacked power.

10.1.3 The risks of reducing antibiotic dispensing

With little evidence of a relationship between reductions in dispensing and resistance at a practice level, the research addressed the possible disadvantages of reductions in primary care dispensing; namely a possible increased risk of developing a serious infection or complication. Trends from all-Wales data suggest that overall, complications presenting in secondary care and outcomes such as pneumonia, septicaemia, and pleural empyema increased. Albeit from a small number of practices, primary care diagnosed pneumonia and empyema demonstrated a conflicting trend and decreased between 1996 and 2000.

The reasons for these increases in complications are unknown but one possible contributing factor is the reduction in antibiotics dispensing in RTIs, that is, a blanket reduction of antibiotics occurred instead of targeting antibiotics to those that they should be offered to (for example in patients that were systemically unwell or had a pre-existing co-morbidity). Trends in complications appear to have coincided with reductions in dispensing. Initial results showed a negative relationship between hospitalised complications and dispensing in the community even after adjusting for practice characteristics. However, this relationship disappeared after adjusting for study year, suggesting it was acting as a confounder representing unknown factors causing dispensing to fall and complications to rise. The relationship also disappeared after excluding the early period (1996 and 1997) where the greatest reduction in antibiotic dispensing was observed. There was also a lack of association found between changes in dispensing and changes in complications, reinforcing this finding. There was insufficient resistance data at general practice level to examine the possible modifying effect on the relationship between complications and

dispensing.

We cannot conclude a cause-effect relationship between antibiotic dispensing and adverse outcomes of acute RTIs, but this may be due to the aggregate level of the data. It does lead however to testing the hypothesis further, to an assessment at the individual patient level. For patients presenting to primary care with an acute RTI, same day antibiotics were more likely to be prescribed to older patients, patients with a co-morbidity, diabetes, or asthma, current and ex-smokers, and patients who had been previously prescribed antibiotics. Same day antibiotics were less likely to have been prescribed to patients frequently consulting for any illness in the prior year.

Same day prescribing of antibiotics had a weak but significant protective effect against complications diagnosed in primary care, although the numbers required to treat (NNT) with antibiotics to prevent one complication were very large. The absolute risk of a complication was small (49.50 per 10,000 patients). When secondary care complications were considered in a subset of patients and practices, the risk of developing a complication was significantly higher for patients not prescribed an antibiotic on the same day as the index RTI than for those prescribed an antibiotic and the NNT reduced from 780 to 216. Following a diagnosis of a sore throat, the risk of complication was lower for patients not prescribed an antibiotic and the reduction in risk was non-significant. In chest infections, the risk of primary care recorded complication was higher in those not prescribed an antibiotic on the same day as the RTI with a significant decrease in risk with treatment of antibiotics. When secondary care complications were included the NNT reduced from 92 to 22.

10.2 Study strengths and limitations

The strengths and weaknesses of the datasets used as well as the methods and analyses used have previously been discussed at length, and hence will be summarised here.

10.2.1 Strengths - Practice level

Three national high quality datasets were successfully obtained and linked,

something that can be achieved in a country such as Wales where good links exist between the NHS and academia. Relatively few people are responsible for the datasets and this makes it easier to obtain sharing agreements. There does not appear to be anything unique about Welsh general practices that would limit the applicability of these findings to other settings. To date this is one of only a few studies to examine the variation in trends of the three outcomes amongst general practices and on such a large scale, over a large period of time, and using detailed data. In addition we were able to look at liquid oral antibiotic dispensing, a proxy for dispensing in children and only once previously examined. A comprehensive list of ICD10 codes for acute RTIs and their complications was produced which enabled an examination of a wide set of complications which had not previously been carried out. This level of detail made each dataset very rich and resulted in multiple outputs. It also allowed an exploration of the trends in the proportion of submitted isolate samples tested for resistance in *H. influenzae*, *S. pyogenes* and *S. pneumoniae* isolates. It is very rare to obtain sampling data and to assess the sampling rate per practice and the association with resistance rates.

This study allowed not only an exploration of the relationship between individual resistance data and practice based antibiotic dispensing data but also to examine the link between reduced dispensing and reductions in resistance at a practice level. This has not previously been examined in these particular isolates relating to RTIs. This is also the first time an ecological level study has examined the relationship between dispensing, resistance and complications in a large population. Including resistance data was important and strengthened the analysis as it allowed an exploration of how resistance modified any relationship between complications and dispensing. This is also the first observational study to examine the association between change in the rate of antibiotic dispensing and change in complication rates over time.

10.2.2 Strengths - Individual patient level

To date, this is one of only a small number of observational studies to examine the effect of antibiotic prescribing on complications arising from acute RTIs at the individual patient level, whilst adjusting for significant confounders. Although the size of the cohort was restricted, one of the main strengths of this study was that

secondary care data was obtained for a sub-set of practices, thus identifying additional complications presenting in secondary care and not previously recorded in primary care. This, to our knowledge, has not been done before in this research area. Therefore the under-recording that can occur by only assessing GP records for complications was minimised, and the population of complications more accurately estimated. This translated into reduced NNTs in this subgroup as more complications were identified, especially in lung infections. We were able to examine the difference in risk associated with being prescribed an antibiotic and the number of antibiotic prescriptions needed to prevent one complication.

Identified patients from primary care and linking to secondary care data enabled a patient journey to be built, through primary care and, for a proportion, secondary care. Thus each patient could be flagged as being prescribed an antibiotic (either on the same day as the acute RTI or subsequently) or not, as were any complications diagnosed and recorded in primary care and/or secondary care. This study is the also the first to assess the risk of complications on prescribing an antibiotic after the initial RTI was diagnosed. In addition to all acute RTIs, the protective effect of antibiotics against overall complications was examined in patients presenting with sore throats and chest infections.

10.2.3 Limitations - Practice level

There are also limitations to each of these datasets. The largest was that dispensing data was only available at a practice level and thus individual dispensing data could not be linked to resistance and hospital data which was available at an individual patient level. For dispensing data, antibiotics given for all types of indications were used and not just for RTIs, thus overestimating the antibiotics prescribed for RTIs. There is also a risk of an underestimation in dispensing due to out of hours (OOH) data not being captured. Dispensing of antibiotics is an imperfect proxy for antibiotic consumption but is an improvement of those prescribed. This would lead to a very small bias in dispensing data although this bias may vary by the type of acute RTI. Dispensing in children could be overestimated since liquid oral antibiotics are also dispensed in the elderly. These biases are bound to reduce associations compared to examining individual data as Donnan *et al.* (2004) showed.

Patient Episode Dataset for Wales (PEDW) data is based on episodes of consultant care which are usually combined to create hospital admissions (or spells) to ensure that double counting of diagnoses is kept to a minimum. The use of a 91 day cut-off (linking episodes within 91 days of the initial infection) to create an *event* of infection may mean that we have under-estimated the number of complications. Our measure of infection is therefore likely to be conservative. The study was also limited in that it does not capture the true incidence rate of complications in the population since those presenting to primary care only or A&E are not captured. This data was also limited in the rarity of some of the complications such as quinsy which restricted modelling at a practice level.

Resistance data was more limited than dispensing and complications data; data could only be obtained from 11 of the 18 laboratories which serve Welsh general practices although the practices were broadly similar to the remaining Welsh practices. Routinely collected data using samples submitted by GPs may not necessarily be typical of all infections presenting to primary care but little is known about how representative reported levels of resistance are as samples submitted to microbiology by general practices vary widely. To limit the bias, laboratories demonstrating selectivity in the samples that were tested were excluded from all analyses. Practices submitting a small number of samples were not more likely to have higher resistance rates. Following this, the largest weakness of the resistance data was the small number of samples (with *H. influenzae, S. pneumoniae* and *S. pyogenes* identified) and resistance rates per annum for a large proportion of practices. This made examining resistance rates at a practice level very restrictive, especially in samples taken from the respiratory tract (Sputum and ENT). Aggregating at the LHB level is a large level and thus not informative as we would not especially expect differences in rates at this level.

The main weakness in all these analyses is that results are offered at the level of general practice and suffer from the 'ecological fallacy' in which erroneous inferences regarding individuals within the same area are made from ecological models based on aggregate data. However, it is probably the lowest and most relevant level to use with this type of data.

10.2.4 Limitations - Individual patient level

Whilst GPRD data is a very useful data source into gaining an insight into primary care observational data, it has some limitations. This was a relatively limited cohort of patients with an acute RTI with a small number of complications identified (at most only 0.85% of all RTIs). Thus sufficient data were not available to examine the risk of complications by severity of the acute RTI, antibiotic type and dose as planned, nor were there enough to examine the interaction between age and antibiotic prescribing. There was also insufficient outcome data to examine complications presenting in 30 days as planned, in addition to 60 days. Also, due to the rarity of some complications, specific complications after an acute RTI such as quinsy after a sore throat or mastoiditis after acute otitis media could not be examined. Although primary and secondary care complications were obtained for 32.5% of the original cohort, the entire population of complications is still under-recorded. It excludes patients who are seen in OOH clinics and not recorded in the GP notes, and also patients presenting to emergency departments and sent home without being admitted to hospital.

Some biases are not confined to this research and would be difficult to remove in any epidemiological study using routine primary care data. Patients who choose to present with an RTI symptom to their GP may be unrepresentative in respect of clinical factors such as age, duration and severity of symptoms, and co morbidity. For those patients who do not present, the RTI will either be self-limiting and resolve without antibiotics or else deteriorate and present eventually to primary or secondary care in the form of a complication (without a prior acute RTI) but we have no data on the chances of these outcomes. Assessing the impact of this bias is difficult but as Fleming (2007) stated "The surveillance of persons presenting for healthcare is as close to complete population-based surveillance as is realistically achievable". For patients who do present to their GP, it has been suggested that a potential limitation is that not all consultations for such minor infections are recorded in GP records (Hayward et al. 2007), leading to a possible underestimate of the number of patients not receiving an antibiotic, although this is increasingly unlikely with record computerisation. Diagnoses recorded by GPs may be influenced by their prescribing decisions (also referred to as diagnostic drift) but without examining trends to

identify any evidence of a change in diagnostic behaviour, it is difficult to speculate whether this happens. Missing data was also a potential weakness as some factors, especially lifestyle factors such as BMI and smoking, may not be up-to-date, only being measured at registration at the practice. These data are not strictly missing but rather not measured, since there was no cause for concern. Patients with more regularly measured BMI are more closely monitored due to a health problem. Therefore including BMI would potentially be a misleading factor and a proxy for a comorbidity or ill health.

As already acknowledged in previous sections, antibiotic prescribing is an imperfect proxy for antibiotic consumption. This would lead to only a small bias in estimating consumption although this bias may vary by the type of acute RTI (the more serious the infection, the higher the likelihood of dispensing the prescription and adhering to the antibiotic). Lastly, we are not able to demonstrate causality as there is no evidence to suggest that the patients who did not have an antibiotic but then went on to have a complication could have avoided the complication if they had in fact received the antibiotic.

10.3 Implications of main findings for clinical practice

10.3.1 Should ecological level data be used to inform clinical decision?

We cannot conclude that at a practice level antibiotic dispensing is the main driver in the rise in complications. This may be due to the aggregate nature of the data and analysis by 'concealing' information, which made it difficult to come to a firm conclusion regarding associations. Making recommendations that might be implemented in practice is then impossible especially since it has been shown here and in other studies that group level data may hide associations found at individual level (Donnan *et al*. 2004). The discrepancy in results between Chapters 8 and 9 meant that using aggregate data has great dangers. The natural path for future work is then to obtain individual patient level data to assess the true protective effect of antibiotics on complications.

Despite a number of limitations, using these datasets is the only way to reliably

estimate antibiotic dispensing, resistance and complications in primary care at a macro and micro level for the whole population of Wales and practice level respectively. We can be reasonably confident that our findings are reliable and generalisable as they are based on an entire population and results are in agreement with the majority of the body of published evidence.

10.3.2 Should antibiotics be prescribed to prevent complications?

The results from the individual patient level data show that in the 60 days after an RTI diagnosis, complications are rare (46 per10,000 patients). Prescribing antibiotics for acute RTIs was seen to have a protective effect over suppurative and non-suppurative complications *diagnosed in primary care* but the absolute risk reduction (ARR) was small. This was after adjusting for confounding variables, in other words patients with a higher likelihood to be prescribed an antibiotic such as age and comorbidity. Similarly, for any complication following a sore throat diagnosis, the risk reduction was small.

In contrast, the reduction in risk of complications following a chest infection was larger with an NNT was 92. These findings are supported by other studies, three of which were retrospective cohort studies using the GPRD (Dunn *et al*. (2006), Petersen *et al.* (2007), and Winchester *et al*. (2009)) and a case-control study in children (Crocker *et al*. 2012). These studies concluded that antibiotic prescribing could be reduced in primary care, especially for sore throats, ear infections and URTI, since the NNT were so high that few complications would be likely to arise. The results from this work support this recommendation.

However, in a sub-group of the original sample of nearly 30,000 patients, when secondary care complications are also included to give a more accurate reflection of complications in the population, the NNTs in all RTIs are reduced. This is due to 39% of total pneumonia cases, 54% of other lung complications, 33% of septicaemia cases, and 69% of pleural effusion cases being identified only in secondary care. Even so, for complications following all RTIs and sore throat, the NNTs are still large. This is most probably due to few quinsy cases being identified in secondary care within this year. The NNT in chest infection however is considerably reduced

from 92 to 22. Primary and secondary care complications have not been examined in previous studies; this component of the study is therefore a valuable addition and greatly improves the evidence base.

10.4 Key messages for general practitioners

- Antibiotic prescribing for nonspecific coding in URTIs is low and complications in this subgroup are rare. GPs can be confident that not prescribing an antibiotic for a patient presenting with vague RTI symptoms will not result in an adverse outcome.
- Antibiotics should not be considered for sore throat as the risk of developing a complication is low unless presenting in patients with asthma or who have previously developed a complication in the year prior to the new throat infection.
- Complications occurring in ears and sinuses were also rare but over 80% of those presenting with these symptoms were prescribed antibiotics.
- GPs cannot be confident about withholding antibiotics for patients presenting with chest infections and should be especially considered in the elderly (65 plus years), those with a comorbidity, and those with a prior complication in the previous year.

10.5 Implications of main findings for future research

10.5.1 Study design

Routinely collected data analysed at an aggregate level is particularly useful in the monitoring of trends at a macro level. At a micro level, using aggregate data can be a stepping stone to using individual data as it can be used to generate hypotheses, especially as routinely collected data is more readily available than individual patient level data. However, as we have shown, there is strong evidence to demonstrate that aggregate level data can obscure important associations occurring at an individual level.

RCTs are the gold standard when it comes to study design as through randomisation

they reduce the problem of confounding, an important limitation of observational studies. In this clinical area RCTs would need to be very large to be adequately powered to examine differences in rare complications. Also patients recruited would not be representative of routine practice as trials would exclude the most sick or those at a higher risk for ethical reasons. Therefore using datasets containing individual patient data are most appropriate. Can we use them to evaluate the efficacy of treatment in real life to bridge results from RCTs to clinical practice using cohort data? Is it possible that results of a cohort study could change clinical practice?

10.5.2 Blanket reductions in dispensing or in inappropriate dispensing?

We were restricted to examining dispensing at a general practice level and found a decrease in most antibiotics over the period. For mainstream patients this reduction in antibiotics would pose no risk but for patients at risk it might. It would therefore be worth exploring the reasons for the variations and reductions found in antibiotic dispensing by GPs and practices. There is a need to clarify whether GPs are following national guidelines, whether appropriate dispensing is being achieved by GPs by reducing inappropriate dispensing or whether a blanket reduction is being practiced over time. Analysing changes in inappropriate prescribing would be more powerful than overall antibiotic dispensing. Defining what is appropriate dispensing will depend on patient symptoms and diagnoses as well as characteristics and thus individual patient data and medical history would be required in those presenting with a suspected infection.

10.5.3 Identifying those that will benefit from antibiotics

Before further reductions are made in antibiotic prescribing for ear infections, chest infections, sore throats and sinusitis, a large scale observational study should be carried out to examine the risk associated with withholding antibiotics on complications diagnosed in primary *and* secondary care (including A&E and Out of Hours). Ideally it would be useful to examine this association over a longer time period to see if, as antibiotic prescribing in RTIs decreased in primary care (albeit the proportion of prescribing remaining high), the numbers required to treat with

antibiotics to prevent one complication changed over time. The sample size would have to be sufficiently large to permit examination of risk by certain RTI groups (sore throats, otitis media, sinusitis, URTI, chest infection) and severity (using signs and symptoms or evidence of a bacterial infection) and by age group. This would help to identify, at the diagnosis of an RTI, which patient characteristics and signs and symptoms are more likely to predict if a complication will occur, so that prescribing can be targeted more precisely at high-risk patients. This is especially relevant in chest infections where the numbers needed to treat were much lower. It would also be of interest to see whether risk varies by type, dose and duration of the antibiotic. Shorter higher dose courses can achieve the same outcomes but with less impact on resistance selection, but at what cost to complications (Wise *et al.* 2011)? This would then determine how short treatment can be before an impact is seen on adverse outcomes.

It would be important to examine the difference between patients who do receive an antibiotic, but still go on to develop a complication, and those who did receive the antibiotic and did not develop a complication. What makes this subgroup different? In addition, a proportion of patients do not present to primary care with an acute RTI but subsequently end up in A&E or are hospitalised with a complication. We hypothesise that these patients are different to patients who do consult with an acute RTI (and subsequently present with a serious or complicated infection in hospital).

All of this work could be achieved by using routinely collected data from Wales from the Secure Anonymised Information Linkage (SAIL) Databank established by the Health Information Research Unit (HIRU) in Swansea and the newly established Clinical Practice Research Datalink (CPRD) which links GRPD data to HES. The main aim of SAIL is to link together the widest possible range of anonymised, electronically-held, person-based, routinely-collected data for the purpose of conducting and supporting health-related research. Datasets that have been linked in SAIL include primary care data from GPs in Wales, secondary care data on hospital in-patients from the Patient Episode Database for Wales (PEDW), accident and emergency data, and local authority social services data. These data allow a patient to be followed-up over time utilising several datasets and thus creating a patient's clinical pathway. Similar conclusions were found in a review of the evidence of the

role of antibiotics in preventing serious complications of URTIs in children (Keith *et al.* 2010). In their conclusions for further research, the only feasible option to examine risk factors of patients who develop complications would be through linkage of large national datasets such as these. Although routinely collected data sets are, by their nature, restricted to data that have been recorded for a reason (such as in the case with BMI recording), there are great benefits from obtaining a very large sample size with resulting high power. The possibility of using these linked datasets in Wales must be a natural step forward in this research area. This would improve the evidence base, allowing clinicians to make better informed decisions in the prescribing of antibiotics when faced with an acute RTI and helping to identify which patient groups antibiotics should be targeted to protect individuals from harm.

10.6 Conclusions

This thesis has contributed to the important debate of the relationship between antibiotic use in primary care and complications arising from acute RTIs. As in other countries, Wales' general practitioners have followed national guidelines and, over the study period, reduced their dispensing of antibiotics most commonly used in the treatment of acute RTIs. This trend appears to have changed in the later study years. Although variations in dispensing rates and trends were observed between practices, the majority changed their antibiotic dispensing behaviour. What is unknown is whether the reduction was restricted to those who need them the most or whether a blanket reduction was implemented. One rationale for limiting antibiotic consumption is to contain or reduce antibiotic resistance. Whilst certain resistance rates, such as amoxicillin resistance in *H.influenzae* isolates, have decreased, trends in others (erythromycin resistance in *S. pneumoniae* isolates) are upwards. We have shown that, at a general practice level, a relationship exists between lagged dispensing and resistance but no clear patterns were found between a change in dispensing and resistance. The possible benefit of reducing antibiotic consumption in the community is counter balanced by the risk of developing a serious infection or complication. At an all-Wales level, trends in certain complications diagnosed in secondary care are increasing whilst the opposite trends are seen for the same complications diagnosed in primary care (albeit in a small sample of practices), possibly an indication of a change of where patients present. Again no clear

relationship was evident between dispensing and complications at the general practice level. It is clear that ecological level evidence will not change clinical practice and that individual level evidence is required from large observational studies. This thesis showed that, from a large cohort diagnosed with an acute RTI, the absolute risk of developing any complication was small. Antibiotics are not justified to reduce the risk of a complication in those diagnosed with an acute RTI or sore throat. However, for patients presenting with a chest infection, the risk of developing a complication is high and antibiotics appears to reduce the risk of a complication. Further research is required to identify subgroups of patients or certain risk factors for these complications to assist GPs to prescribe antibiotics appropriately, ensuring that those needing antibiotics the most receive them and do not come to unnecessary harm.

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Appendices

Appendix I Literature search terms by databases

1. Relationship between antibiotic prescribing and resistance.

MEDLINE

#	Search History	Results
1	exp anti-bacterial agents/	344750
2	anti?biot$.mp.	151921
3	anti?microb$.mp.	43527
4	or/1-3	425041
5	prescri$.mp.	67453
6	Dispens$.mp.	12631
7	Prescriptions, Drug/	14246
8	exp Drug Utilization/	12312
9	or/5-8	84736
10	4 and 9	8591
11	drug resistance, microbial/ or drug resistance, bacterial/ or drug resistance, multiple/ or drug resistance, multiple, bacterial/	65011
12	resistan$.mp.	424233
13	susceptib$.mp.	158821
14	or/11-13	540820
15	10 and 14	2639
16	limit 15 to humans	2482
17	Limit 16 to English language	1991

EMBASE

#	Search History	Results
1	exp Antibiotic Agent/	444426
2	anti?biot$.mp.	216454
3	anti?microb$.mp.	47854
4	or/1-3	502601
5	drug utilization/ or "utilization review"/	5969
6	prescri$.mp.	75155
7	dispens$.mp.	9558
8	"drug use"/ or prescription/	63559
9	or/5-8	111879

10	4 and 9	15667
11	antibiotic sensitivity/ or antibiotic resistance/ or penicillin resistance/	57582
12	exp drug resistance/	83599
13	susceptib$.mp.	139533
14	resistan$.mp.	357922
15	or/11-14	467563
16	10 and 15	4410
17	limit 16 to human	3719
18	Limit 17 to English language	3058

EBM Review

#	Search History		Results
1	anti?biotic$.mp.		11526
2	anti?microbi$.mp.		2552
3	anti?bacteri$.mp.		4983
4	or/1-3		15432
5	prescri$.mp.		6823
6	dispens$.mp.		543
7	utili$.mp.		9715
8	or/5-7		16095
9	4 and 8		1200
10	resistan$.mp.		17274
11	susceptib$.mp.		3505
12	or/10-11		19919
13	9 and 12		305
14	remove duplicates from 13		302

2. Relationship between antibiotic prescribing and infections

MEDLINE
1966 to February Week 3 2006

#	Search History	Results
1	Acute Disease/	10733
2	exp Bacterial Infections/	248645
3	exp Community-Acquired Infections/	1908
4	Communicable Diseases/	1908
5	exp Respiratory Tract Infections/	75860
6	exp Pneumonia/	58991
7	suppuration/ or brain abscess/ or lung abscess/ or peritonsillar	11889

	abscess/	
8	exp Otitis Media/	13091
9	exp bronchitis/ or exp laryngitis/ or pleural diseases/ or exp empyema, pleural/	20447
10	exp Urinary Tract Infections/	25328
11	exp Sepsis/	30775
12	exp skin diseases, infectious/ or exp soft tissue infections/	51719
13	exp Impetigo/	1068
14	exp Nephritis/	29918
15	exp Lymphangitis/	472
16	Wound Infection/	11566
17	exp Pharyngeal Diseases/	18322
18	exp aspergillosis/	4691
19	quinsy.mp.	63
20	infection$.mp.	631203
21	sore throat$.mp.	3397
22	Staphylococcal Infections/ or exp Streptococcal Infections/	10841
23	Cough/	17496
24	acute disease$.mp.	11854
25	communicable disease$.mp.	2684
26	pneumonia.mp.	65565
27	(suppuration or abscess$).mp.	34297
28	(otitis media or bronchitis or laryngitis or pleural disease$ or empyema or pleural).mp.	51376
29	UTI.mp.	2652
30	RTI.mp.	778
31	cough.mp.	13706
32	(sepsis or impetigo or nephritis or lymphangitis or pharyngeal disease$ or aspergillosis).mp.	66865
33	(skin disease$ or soft tissue$).mp.	76763
34	or/1-33	986810
35	exp anti-bacterial agents/	881475
36	anti?biot$.mp.	216454
37	anti?microb$.mp.	47854
38	anti?bacter$.mp.	28737
39	or/35-38	923724
40	Prescriptions, Drug/	36645

41	exp drug utilization/	4562
42	drug util$.mp.	5241
43	prescri$.mp.	75155
44	dispens$.mp.	9558
45	or/40-44	85815
46	39 and 45	16476
47	34 and 46	8379
48	limit 47 to humans	7798
49	limit 48 to english language	6142

EMBASE
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#	Search History	Results
1	exp Respiratory Tract Infection/	75860
2	exp Urinary Tract Infection/	25328
3	exp ear infection/ or exp otitis media/	14411
4	skin infection/ or exp bacterial skin disease/	26340
5	exp Soft Tissue Infection/	2459
6	exp Bacterial Infection/	248645
7	exp Abscess/	23560
8	Communicable Disease/	1908
9	exp dermatitis/ or exp respiratory tract inflammation/ or exp urinary tract inflammation/	191116
10	exp Pharyngitis/	6379
11	exp Sinusitis/	10981
12	Lymphangitis/	472
13	exp Aspergillosis/	4691
14	quinsy/	7
15	cough.mp.	13706
16	infection$.mp.	631203
17	sore throat$.mp. or Sore Throat/	3397
18	quinsy.mp.	63
19	(Aspergillosis or lymphangitis or sinusitis or pharyngitis).mp.	23951
20	(RTI or UTI).mp.	3393
21	otitis media.mp.	13749
22	skin diseas$.mp.	26230
23	abscess.mp.	31078

24	communicable disease.mp.	2248
25	(dermatitis or respiratory tract inflammmation or urinary tract inflammation).mp.	33919
26	or/1-25	941139
27	exp antibiotic agent/	444426
28	anti?biot$.mp.	216454
29	anti?microb$.mp.	47854
30	anti?bacter$.mp.	28737
31	or/27-30	511487
32	drug utilization/ or "utilization review"/	5969
33	prescri$.mp.	75155
34	dispens$.mp.	9558
35	"drug use"/ or prescription/	63559
36	or/32-35	111879
37	31 and 36	15765
38	37 and 26	8843
39	limit 38 to human	8197
40	limit 39 to english language	6456

EBM Review

#	Search History	Results
1	exp Respiratory Tract Infection/	5769
2	exp Urinary Tract Infection/	1545
3	exp ear infection/ or exp otitis media/	744
4	skin infection/ or exp bacterial skin disease/	195
5	exp Soft Tissue Infection/	28
6	exp Bacterial Infection/	9151
7	exp Abscess/	337
8	exp dermatitis/ or exp respiratory tract inflammation/ or exp urinary tract inflammation/	1718
9	exp Pharyngitis/	464
10	exp Sinusitis/	354
11	Lymphangitis/	9
12	exp Aspergillosis/	48
13	cough.mp.	2507
14	infection$.mp.	30624
15	sore throat$.mp. or Sore Throat/	800
16	quinsy.mp.	13
17	(Aspergillosis or lymphangitis or sinusitis or pharyngitis).mp.	1833
18	(RTI or UTI).mp.	428
19	otitis media.mp.	1452

20	skin diseas$.mp.	1024
21	abscess.mp.	856
22	communicable disease.mp.	54
23	(dermatitis or respiratory tract inflammmation or urinary tract inflammation).mp.	2428
24	anti?biot$.mp.	11576
25	anti?microb$.mp.	2562
26	anti?bacter$.mp.	4985
27	drug utilization/ or "utilization review"/	201
28	prescri$.mp.	6823
29	dispens$.mp.	543
30	"drug use"/ or prescription/	0
31	or/1-23	42402
32	or/24-26	15478
33	or/27-30	7311
34	32 and 33	840
35	31 and 34	646
36	remove duplicates from 35	631

Appendix II Antibiotics used in the treatment of respiratory tract infections

		Dataset	
BNF Sub-Section	**BNF Chemical**	**1996-2003**	**2000-2006**
5.1.1 Penicillins			
5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin			✓
	Benzylpenicillin		✓
	Phenoxymethylpenicillin Benzathine	✓	✓
	Penicillin		✓
	Procaine		✓
	Benzylpenicillin		✓
5.1.1.2 Penicillinase-resistant penicillins		✓	✓
	Flucloxacillin Sodium		✓
	Flucloxacillin Magnesium		✓
5.1.1.3 Broad-spectrum penicillins		✓	✓
	Amoxicillin	✓	✓
	Amoxicillin Sodium		✓
	Ampicillin		✓
	Co-Amoxiclav	✓	✓
	Co-Fluampicil		✓
5.1.2 Cephalosporins and other beta-lactams		✓	✓
	Meropenem		✓
	Cefpirome Sulphate		✓
	Aztreonam		✓
	Cefprozil		✓
	Cefuroxime Axetil		✓
	Cefamandole		✓
	Cefazolin Sodium		✓
	Imipenem with cilastatin		✓
	Cefadroxil (1^{st} generation)		✓
	Cefalexin (1^{st})		✓
	Cefradine (1^{st})		✓
	Cefaclor (2^{nd})		✓
	Cefuroxime Sodium (2^{nd})		✓
	Cefixime (3^{rd})		✓
	Cefotaxime Sodium (3^{rd})		✓
	Cefpodoxime (3^{rd})		✓
	Ceftriaxone Sodium (3^{rd})		✓
	Ceftazidime Pentahydrate (3^{rd})		
5.1.3 Tetracyclines		✓	✓
	Demeclocycline Hydrochloride		✓
	Doxycycline Hyclate		✓
	Lymecycline		✓
	Minocycline Hydrochloride		✓
	Oxytetracycline		✓
	Tetracycline		✓
	Tetracycline combined preps		✓
5.1.5 Macrolides		✓	✓
	Erythromycin	✓	✓
	Erythromycin Estolate		✓
	Erythromycin Ethylsuccinate		✓
	Erythromycin Lactobionate		✓
	Erythromycin Stearate		✓
	Azithromycin		✓

		Dataset	
BNF Sub-Section	**BNF Chemical**	**1996-2003**	**2000-2006**
	Clarithromycin		✓
	Telithromycin		
5.1.8 Sulphonamides and trimethoprim		✓	✓
	Trimethoprim		✓
5.1.12 Quinolones		✓	✓
	Ciprofloxacin		✓
	Levofloxacin		✓
	Moxifloxacin		✓
	Ofloxacin		✓
	Nalidixic acid		✓
	Norfloxacin		✓

Appendix III Liquid oral antibiotic preparations

BNF Sub Section	Chemical	Preparation
Aminoglycosides	Gentamicin Sulphate	Gentamicin Sulph_Pdr
	Tobramycin With Sodium Chloride	Tobramycin/sod Chlor_Inf 80mg/20ml
	Tobramycin	Tobramycin_Liq Spec 40mg/5ml
	Gentamicin Sulphate	Cidomycin_Ster Pdr
Benzylpenicillin & Phenoxymethylpenicillin	Phenoxymethylpenicillin (Penicillin V)	Phenoxymethylpenicillin_Soln 250mg/5mlSF
		Apsin Vk_Gran For Syr 250mg/5ml
		Phenoxymethylpenicillin_Soln 125mg/5ml
		Phenoxymethylpenicillin_Soln 250mg/5ml
		Tenkicin_Pdr For Elix 125mg/5ml
		Tenkicin_Pdr For Elix 250mg/5ml
		Phenoxymethylpenicillin_Soln 125mg/5mlSF
Broad-Spectrum Penicillins	Ampicillin	Penbritin_Pdr For Syr Fte 250mg/5ml
	Ampicillin	Ampicillin_Oral Susp 125mg/5ml
	Amoxicillin	Respillin_Pdr For Syr 250mg/5ml S/f
	Ampicillin	Ampicillin_Oral Susp 125mg/5ml S/f
	Ampicillin	Ampicillin_Oral Susp 250mg/5ml
	Ampicillin	Penbritin_Pdr For Paed Susp 125mg/1.25ml
	Amoxicillin	Respillin_Pdr For Syr 250mg/5ml
	Ampicillin	Penbritin_Pdr For Syr 125mg/5ml
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Augmentin_Pdr For Susp 125/31mg/5ml S/f
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Augmentin_Pdr For Susp 250/62mg/5ml S/f
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Augmentin_Tab Disper 375mg
	Amoxicillin	Respillin_Pdr For Syr 125mg/5ml S/f
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Co-Amoxiclav_Susp 125mg/31mg/5ml S/f

BNF Sub Section	Chemical	Preparation
Broad Spectrum Penicillins	Amoxicillin	Amoxil Sf_Pdr For Syr 250mg/5ml
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Co-Amoxiclav_Tab Disper 250mg/125mg
	Amoxicillin	Almodan_Syr 125mg/5ml
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Ranclav_Pdr For Susp 250mg/62mg/5ml S/f
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Augmentin-Duo 400/57_Pdr For Susp S/f
	Amoxicillin	Amoxicillin_Oral Susp 250mg/5ml S/f
	Amoxicillin	Almodan_Syr 125mg/5ml S/f
	Amoxicillin	Almodan_Syr 250mg/5ml
	Amoxicillin	Almodan_Syr 250mg/5ml S/f
	Amoxicillin	Amix 125_Pdr For Susp 125mg/5ml S/f
	Amoxicillin	Amix 250_Pdr For Susp 250mg/5ml S/f
	Amoxicillin	Amoxicillin_Gran Sach 125mg S/f
	Amoxicillin	Amoxicillin_Oral Pdr Sach 3g S/f
	Amoxicillin	Amoxicillin_Oral Susp 125mg/5ml
	Amoxicillin	Amoxil_Pdr For Paed Susp 125mg/1.25ml
	Amoxicillin	Amoxicillin_Oral Susp 250mg/5ml
	Amoxicillin	Respillin_Pdr For Syr 125mg/5ml
	Amoxicillin	Amoxicillin_Oral Susp Paed 125mg/1.25ml
	Amoxicillin	Amoxicillin_Tab Disper 500mg
	Amoxicillin	Amoxil Sf_Pdr For Syr 125mg/5ml
	Co-Fluampicil(Flucloxacillin/Ampicillin)	Co-Fluampicil_Syr 125mg/125mg/5ml
	Amoxicillin	Amoxil Sf_Sach 3g
	Co-Fluampicil(Flucloxacillin/Ampicillin)	Magnapen_Pdr For Syr 250mg/5ml
	Amoxicillin	Galenamox_Susp

BNF Sub Section	Chemical	Preparation
		125mg/5ml S/f
Broad Spectrum Penicillins	Amoxicillin	Galenamox_Susp 250mg/5ml S/f
	Amoxicillin	Amoxicillin_Oral Susp 125mg/5ml S/f
	Co-Amoxiclav (Amoxicillin/Clavul Acid)	Ranclav_Pdr For Susp 125mg/31mg/5ml S/f
Cephalosporins,Cephamycins & Betalactams	Cefpodoxime	Cefpodoxime_Susp 40mg/5ml
	Cefuroxime Axetil	Zinnat_Gran For Susp 125mg/5ml
	Cefalexin	Ceporex_Gran For Syr 250mg/5ml
	Cefalexin	Ceporex_Gran For Syr 500mg/5ml
	Cefalexin	Keflex_Gran For Paed Susp 125mg/5ml
	Cefalexin	Keflex_Gran For Susp 250mg/5ml
	Cefalexin	Tenkorex_Pdr For Susp 125mg/5ml
	Cefalexin	Tenkorex_Pdr For Susp 250mg/5ml
	Cefalexin	Cefalexin_Oral Susp 500mg/5ml
	Cefixime	Suprax_Pdr For Oral Susp Paed 100mg/5ml
	Cefalexin	Cefalexin_Oral Susp 250mg/5ml S/f
	Cefpodoxime	Orelox Paed_Gran For Susp 40mg/5ml
	Cefprozil	Cefzil_Gran For Susp 250mg/5ml
	Cefradine	Cefradine_Oral Soln 250mg/5ml
	Cefradine	Velosef_Pdr For Syr 250mg/5ml
	Cefuroxime Axetil	Cefuroxime Axetil_Gran Sach 125mg
	Cefuroxime Axetil	Cefuroxime Axetil_Susp 125mg/5ml
	Cefixime	Cefixime_Oral Susp 100mg/5ml
	Cefadroxil	Baxan_Pdr For Susp 250mg/5ml
	Cefaclor	Cefaclor_Oral Susp 125mg/5ml
	Cefaclor	Cefaclor_Oral Susp

BNF Sub Section	Chemical	Preparation
		125mg/5ml S/f
Cephalosporins,Cephamycins & Betalactams	Cefaclor	Cefaclor_Oral Susp 250mg/5ml
	Cefaclor	Cefaclor_Oral Susp 250mg/5ml S/f
	Cefaclor	Distaclor_Gran For Susp 125mg/5ml
	Cefaclor	Distaclor_Gran For Susp 250mg/5ml
	Cefaclor	Keftid_Pdr For Susp 125mg/5ml S/f
	Cefalexin	Ceporex_Gran For Syr 125mg/5ml
	Cefadroxil	Baxan_Pdr For Susp 125mg/5ml
	Cefuroxime Axetil	Zinnat_Gran Sach 125mg
	Cefadroxil	Baxan_Pdr For Susp 500mg/5ml
	Cefadroxil	Cefadroxil_Susp 125mg/5ml
	Cefadroxil	Cefadroxil_Susp 250mg/5ml
	Cefadroxil	Cefadroxil_Susp 500mg/5ml
	Cefalexin	Cefalexin_Oral Susp 125mg/5ml
	Cefalexin	Cefalexin_Oral Susp 125mg/5ml S/f
	Cefalexin	Cefalexin_Oral Susp 250mg/5ml
	Cefaclor	Keftid_Pdr For Susp 250mg/5ml S/f
Clindamycin and Lincomycin	Clindamycin Hydrochloride	Clindamycin Hcl_Liq Spec 75mg/5ml
Macrolides	Erythromycin Estolate	Erythromycin Estolate_Mix 250mg/5ml
	Erythromycin Estolate	Ilosone_Susp Fte 250mg/5ml
	Erythromycin Ethylsuccinate	Arpimycin_Gran For Susp 125mg/5ml
	Erythromycin Ethylsuccinate	Arpimycin_Gran For Susp 125mg/5ml S/f
	Erythromycin Ethylsuccinate	Arpimycin_Gran For Susp 250mg/5ml
	Erythromycin Ethylsuccinate	Arpimycin_Gran For Susp 250mg/5ml S/f

BNF Sub Section	Chemical	Preparation
Macrolides	Erythromycin Ethylsuccinate	Erycen_Susp 250mg/5ml
	Erythromycin Ethylsuccinate	Erythroden_Gran For Susp 125mg/5ml
	Erythromycin Ethylsuccinate	Erythroden_Gran For Susp 250mg/5ml
	Erythromycin Ethylsuccinate	Erythromycin_Ethylsuc Sach 250mg
	Erythromycin Ethylsuccinate	Erythromycin_Ethylsuc Susp 125mg/5ml S/f
	Erythromycin Estolate	Erythromycin Estolate_Mix 125mg/5ml
	Erythromycin Ethylsuccinate	Erythromycin_Ethylsuc Susp 500mg/5ml
	Erythromycin Ethylsuccinate	Erythromycin_Ethylsuc Susp 125mg/5ml
	Erythromycin Ethylsuccinate	Erythromycin_Ethylsuc Susp 500mg/5ml S/f
	Erythromycin Ethylsuccinate	Erythroped Fte Sf_Gran For Susp 500mg/5m
	Erythromycin Ethylsuccinate	Erythroped Fte_Gran For Susp 500mg/5ml
	Erythromycin Ethylsuccinate	Erythroped Pi Sf_Susp 125mg/5ml
	Erythromycin Ethylsuccinate	Erythroped Pi_Susp 125mg/5ml
	Erythromycin Ethylsuccinate	Erythroped Sf_Gran For Susp 250mg/5ml
	Erythromycin Ethylsuccinate	Erythroped_Gran For Susp 250mg/5ml
	Erythromycin Ethylsuccinate	Primacine_Gran For Susp 125mg/5ml S/f
	Erythromycin Ethylsuccinate	Rommix 125_Susp 125mg/5ml
	Azithromycin	Zithromax_Pdr For Oral Susp 200mg/5ml
	Azithromycin	Azithromycin_Oral Susp 200mg/5ml
	Erythromycin Ethylsuccinate	Erythromycin_Ethylsuc Susp 250mg/5ml S/f
	Clarithromycin	Klaricid_Pdr Sach 250mg
	Clarithromycin	Klaricid_Gran For Paed Susp 125mg/5ml
	Clarithromycin	Clarosip_Gran Straw 250mg
	Clarithromycin	Clarosip_Gran Straw

BNF Sub Section	Chemical	Preparation
		125mg
Macrolides	Clarithromycin	Clarithromycin_Pdr Sach 250mg
	Clarithromycin	Clarithromycin_Oral Susp 250mg/5ml
	Clarithromycin	Clarithromycin_Oral Susp 125mg/5ml
	Clarithromycin	Clarithromycin_Gran Straw 250mg
	Clarithromycin	Clarithromycin_Gran Straw 187.5mg
	Clarithromycin	Klaricid_Gran For Paed Susp 250mg/5ml
	Clarithromycin	Clarithromycin_Gran Straw 125mg
	Erythromycin Ethylsuccinate	Erythromycin_Ethylsuc Susp 250mg/5ml
Metronidazole, Tinidazole & Ornidazole	Metronidazole	Metronidazole_Oral Susp 200mg/5ml
	Metronidazole	Flagyl-S_Susp 200mg/5ml
	Metronidazole	Norzol_Susp 200mg/5ml
Penicillinase-Resistant Penicillins	Flucloxacillin Magnesium	Floxapen_Pdr For Syr 125mg/5ml
	Flucloxacillin Sodium	Flucloxin_Pdr For Syr 125mg/5ml
	Flucloxacillin Sodium	Fluclox Sod_Oral Soln 250mg/5ml
	Flucloxacillin Magnesium	Floxapen_Pdr For Syr 250mg/5ml
	Flucloxacillin Magnesium	Fluclox Mag_Oral Susp 125mg/5ml
	Flucloxacillin Magnesium	Fluclox Mag_Oral Susp 250mg/5ml
	Flucloxacillin Sodium	Fluclox Sod_Oral Soln 125mg/5ml
	Flucloxacillin Sodium	Fluclox Sod_Oral Soln 125mg/5ml S/f
Quinolones	Nalidixic Acid	Nalidixic Acid_Oral Susp 300mg/5ml S/f
	Nalidixic Acid	Negram_Susp 300mg/5ml S/f
	Nalidixic Acid	Nalidixic Acid_Oral Susp 300mg/5ml
	Nalidixic Acid	Mictral_Gran Sach 7g
	Nalidixic Acid	Gppe Gran Sach_Mictral 7g

BNF Sub Section	Chemical	Preparation
Quinolones	Ciprofloxacin	Ciprofloxacin_Gran For Susp 250mg/5ml
	Nalidixic Acid	Uriben_Susp 300mg/5ml
	Ciprofloxacin	Ciproxin_Gran For Susp 250mg/5ml
Some Other Antibiotics	Chloramphenicol	Chloramphen Palm_Liq Spec 125mg/5ml
	Colistin Sulphate	Colistin Sulph_Elix 250,000u/5ml
	Fusidic Acid	Fucidin_Paed Susp 250mg/5ml
	Fusidic Acid	Fusidic Acid_Mix 250mg/5ml
	Colistin Sulphate	Colomycin_Pdr For Syr 250,000u/5ml
Sulphonamides And Trimethoprim	Co-Trimoxazole(Trimethoprim/Sulfamethox	Chemotrim_Susp Paed 240mg/5ml
	Co-Trimoxazole(Trimethoprim/Sulfamethox	Co-Trimoxazole_Oral Susp 480mg/5ml
	Co-Trimoxazole(Trimethoprim/Sulfamethox	Co-Trimoxazole_Oral Susp 480mg/5ml @gn
	Co-Trimoxazole (Trimethoprim/Sulfamethox	Co-Trimoxazole_Oral Susp Paed 240mg/5ml
	Co-Trimoxazole(Trimethoprim/Sulfamethox	Co-Trimoxazole_Susp Paed 240mg/5ml S/f
	Trimethoprim	Trimopan_Susp 50mg/5ml S/f
	Co-Trimoxazole(Trimethoprim/Sulfamethox	Laratrim_Paed Susp 240mg/5ml
	Trimethoprim	Monotrim_Susp 50mg/5ml S/f
	Trimethoprim	Trimethoprim_Oral Susp 50mg/5ml S/f
	Co-Trimoxazole (Trimethoprim/Sulfamethox	Septrin_Paed Susp 240mg/5ml S/f
Tetracyclines	Oxytetracycline	Oxytetracycline_Susp 250mg/5ml
	Oxytetracycline	Oxytetracycline_Oral Liq @spec
	Oxytetracycline	Oxytetracycline_Liq Spec 250mg/5ml
	Oxytetracycline	Oxytetracycline_Liq Spec 100mg/5ml

BNF Sub Section	Chemical	Preparation
	Oxytetracycline	Oxytetracycline_Liq Spec 125mg/5ml
Tetracyclines	Tetracycline	Tetracycline_Liq Spec 125mg/5ml
	Doxycycline Hyclate	Doxycycline Hyclate_Tab Disper 100mg
	Chlortetracycline Hydrochloride	Chlortet Hcl_Pdr @gn
	Chlortetracycline Hydrochloride	Aureomycin_Pdr
	Doxycycline Hyclate	Vibramycin-D_Tab Disper 100mg

Appendix IV Broad- and narrow-spectrum classifications

BNF Chemical	BNF sub-section	Broad (B)/ Narrow (N)-spectrum
Co-Amoxiclav	Broad-spectrum penicillins	B
Amoxicillin	Broad-spectrum penicillins	B
Amoxicillin Sodium	Broad-spectrum penicillins	B
Ampicillin	Broad-spectrum penicillins	B
Co-Fluampicil	Broad-spectrum penicillins	B
Cefaclor	Cephalosporins	B
Cefamandole	Cephalosporins	B
Cefixime	Cephalosporins	B
Cefotaxime Sodium	Cephalosporins	B
Cefpodoxime	Cephalosporins	B
Cefprozil	Cephalosporins	B
Ceftazidime Pentahydrate	Cephalosporins	B
Ceftriaxone Sodium	Cephalosporins	B
Cefuroxime Axetil	Cephalosporins	B
Cefuroxime Sodium	Cephalosporins	B
Aztreonam	Cephalosporins	B
Cefadroxil	Cephalosporins	B
Cefalexin	Cephalosporins	B
Cefazolin Sodium	Cephalosporins	B
Cefpirome Sulphate	Cephalosporins	B
Cefradine	Cephalosporins	B
Imipenem With Cilastatin	Cephalosporins	B
Meropenem	Cephalosporins	B
Azithromycin	Macrolides	B
Clarithromycin	Macrolides	B
Cinoxacin	Quinolones	B
Ciprofloxacin	Quinolones	B
Levofloxacin	Quinolones	B
Moxifloxacin	Quinolones	B
Nalidixic Acid	Quinolones	B
Norfloxacin	Quinolones	B
Ofloxacin	Quinolones	B
Chlortetracycline Hydrochloride	Tetracyclines	B
Demeclocycline Hydrochloride	Tetracyclines	B
Doxycycline Hyclate	Tetracyclines	B
Lymecycline	Tetracyclines	B
Minocycline Hydrochloride	Tetracyclines	B
Oxytetracycline	Tetracyclines	B
Tetracycline	Tetracyclines	B
Tetracycline Combined Preparations	Tetracyclines	B
Flucloxacillin Magnesium	Flucloxacillin	N
Flucloxacillin Sodium	Flucloxacillin	N
Erythromycin	Macrolides	N
Erythromycin Estolate	Macrolides	N
Erythromycin Ethylsuccinate	Macrolides	N

BNF Chemical	BNF sub-section	Broad (B)/ Narrow (N)-spectrum
Erythromycin Lactobionate	Macrolides	N
Erythromycin Stearate	Macrolides	N
Telithromycin	Macrolides	N
Benzathine Penicillin	Phenoxymethylpenicillin	N
Benzylpenicillin Sodium (Pen G)	Phenoxymethylpenicillin	N
Phenoxymethylpenicillin (Pen V)	Phenoxymethylpenicillin	N
Procaine Benzylpenicillin	Phenoxymethylpenicillin	N
Trimethoprim	Trimethoprim	N

Appendix V Modelling for antibiotic resistance and lagged dispensing in *H. influenzae*, *S. pneumoniae* and *S. pyogenes* in sputum/ENT isolates.

Organism	Antibiotic resistance	Lagged antibiotic dispensing	Parameter estimate	Standard error	Dispensing rate IQR[i]	OR (IQR)[ii] (95% CI)	Adjusted OR (95% CI)
H. influenzae	Amoxicillin	BSPs	0.58	0.20	0.12	1.07 (1.02 to 1.13)	1.06 (1.01 to 1.12)
		Tetracyclines	1.15	1.30	0.02	1.03 (0.97 to 1.08)	-
		Macrolides	1.20	0.57	0.05	1.06 (1.00 to 1.12)	1.04 (0.98 to 1.10)
		Beta-lactams	0.35	0.16	0.18	1.07 (1.01 to 1.13)	1.05 (0.98 to 1.12)
H. influenzae	Tetracycline	BSPs	1.24	0.84	0.12	1.17 (0.96 to 1.43)	-
		Tetracyclines	8.25	5.04	0.02	1.19 (0.97 to 1.48)	-
		Macrolides	1.44	2.29	0.05	1.07 (0.87 to 1.32)	-
		Beta-lactams	0.52	0.63	0.18	1.10 (0.88 to 1.38)	-
S. pneumoniae	Erythromycin	BSPs	-0.69	0.48	0.12	0.92 (0.82 to 1.03)	-
		Tetracyclines	0.93	2.91	0.02	1.02 (0.90 to 1.15)	-
		Macrolides	-1.17	1.27	0.05	0.95 (0.84 to 1.06)	-
		Beta-lactams	-0.62	0.35	0.18	0.89 (0.78 to 1.01)	-
S. pneumoniae	Penicillin	BSPs	0.71	0.64	0.12	1.09 (0.94 to 1.27)	-
		Tetracyclines	6.73	4.01	0.02	1.16 (0.98 to 1.37)	-
		Macrolides	1.82	1.74	0.05	1.09 (0.93 to 1.28)	-
		Beta-lactams	0.15	0.50	0.18	1.03 (0.86 to 1.23)	-
S. pyogenes	Erythromycin	BSPs	0.49	0.61	0.12	1.06 (0.92 to 1.23)	-
		Tetracyclines	5.71	3.50	0.02	1.13 (0.98 to 1.31)	-
		Macrolides	3.67	1.35	0.05	1.19 (1.05 to 1.35)	1.29 (1.12 to 1.48)
		Beta-lactams	0.72	0.42	0.18	1.14 (0.98 to 1.33)	-

[i] *Inter quartile range (IQR) is the difference between the 75th and 25th percentile of the dispensing rate distribution*
[ii] *Odds Ratio (OR) is the odds of resistance at 75th percentile of dispensing distribution compared to the 25th percentile*

Appendix VI Changes (%) in resistance to amoxicillin and tetracycline over an 8-year period, in Sputum and ENT *H. influenzae* isolates, by quartile of reductions in:

(a) Total antibiotic dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Amoxicillin resistance					
1998, %	20.1	22.2	18.7	18.0	19.7
2005, %	19.3	16.7	15.4	15.5	16.7
Change, % (95% CI)	↓0.8 (-4.9 to 6.5)	↓5.5 (0.2 to 10.6)	↓3.3 (-2.1 to 8.6)	↓2.5 (-2.3 to 7.2)	↓3.0 (0.4 to 5.6)
Tetracycline resistance					
1998, %	2.5	3.2	3.5	3.1	3.2
2005, %	2.8	0.4	2.7	0.41	1.6
Change, % (95% CI)	↑0.3 (-2.6 to 3.5)	↓2.8 (0.4 to 5.4)	↓0.8 (-3.0 to 4.0)	↓2.7 (0.4 to 5.1)	↓1.5 (0.2 to 2.8)

(b) Broad Spectrum Penicillin dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Amoxicillin resistance					
1998, %	21.7	19.8	19.0	18.9	19.7
2005, %	19.5	15.3	18.5	14.1	16.7
Change, % (95% CI)	↓2.2 (-3.8 to 8.1)	↓4.5 (-0.4 to 9.4)	↓0.5 (-4.7 to 5.7)	↓4.8 (-0.2 to 9.7)	↓3.0 (0.4 to 5.6)

(c) Tetracycline dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Tetracycline resistance					
1998, %	2.2	2.6	3.5	4.3	3.1
2005, %	1.5	2.1	1.5	1.5	1.6
Change, % (95% CI)	↓0.7 (-1.5 to 2.9)	↓0.5 (3.7 to 4.1)	↓2.0 (-0.8 to 4.6)	↓2.9 (-0.5 to 6.2)	↓1.5 (0.2 to 2.8)

Appendix VII Changes (%) in resistance to erythromycin and penicillin over an 8-year period, in Sputum and ENT *S. pneumoniae* isolates, by quartile of reductions in:

(a) Total antibiotic dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance					
1998, %	8.9	7.4	4.0	10.6	7.9
2005, %	10.6	13.3	7.2	10.6	10.6
Change, % (95% CI)	↑1.7 (-5.1 to 8.9)	↑6.0 (-0.4 to 12.7)	↑3.2 (-2.2 to 8.2)	=0.0 (-6.4 to 6.0)	↑2.7 (-0.4 to 5.7)
Penicillin resistance					
1998, %	5.6	3.3	7.2	5.2	5.4
2005, %	3.7	6.7	3.6	3.2	4.4
Change, % (95% CI)	↓1.9 (-3.1 to 7.3)	↑3.4 (-1.4 to 8.4)	↓3.6 (-1.4 to 8.7)	↓1.9 (-2.3 to 6.0)	↓1.0 (-1.3 to 3.3)

(b) Macrolide dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance					
1998, %	10.3	6.0	8.7	6.1	7.9
2005, %	10.7	9.4	9.7	13.2	10.6
Change, % (95% CI)	↑0.5 (-6.6 to 7.5)	↑3.5 (-1.9 to 9.2)	↑1.0 (-4.8 to 6.5)	↑7.1 (0.0 to 14.3)	↑2.7 (-0.4 to 5.7)

(c) BSP dispensing

	Reduced dispensing most		Reduced dispensing least		
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Penicillin resistance					
1998, %	6.6	3.4	5.3	6.4	5.4
2005, %	5.5	4.6	4.1	3.6	4.4
Change, % (95% CI)	↓1.0 (-4.9 to 7.5)	↑1.2 (-5.5 to 3.1)	↓1.2 (-3.6 to 6.1)	↓2.8 (-1.6 to 7.1)	↓1.0 (-1.3 to 3.3)

Appendix VIII Changes (%) in resistance to erythromycin over an 8-year period, in Sputum and ENT *S. pyogenes* isolates, by quartile of reductions in:

(a) Total antibiotic dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance					
1998, %	4.3	1.7	1.6	4.3	3.2
2005, %	6.7	4.5	4.4	0.6	4.1
Change, % (95% CI)	↑2.4 (-2.1 to 7.4)	↑2.8 (-1.3 to 7.8)	↑2.8 (-0.9 to 7.9)	↓3.7 (0.4 to 6.8)	↑0.9 (-1.0 to 3.0)

(b) Macrolide dispensing

	Reduced dispensing most			Reduced dispensing least	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Overall**
Erythromycin resistance					
1998, %	4.0	2.6	2.9	2.9	3.2
2005, %	4.7	4.4	5.2	1.6	4.1
Change, % (95% CI)	↑0.6 (-3.1 to 5.0)	↑1.8 (-2.3 to 6.4)	↑2.3 (-1.7 to 7.6)	↓1.3 (-3.1 to 5.2)	↑0.9 (-1.0 to 3.0)

Appendix IX List of respiratory infections seen in hospital (ICD10 codes)

ICD10	**ICD10 DESCRIPTION**
J00	Acute nasopharyngitis [common cold]
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute tracheitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J22	Unspecified acute lower respiratory infection
H650	Acute serous otitis media
H651	Other acute nonsuppurative otitis media
H660	Acute suppurative otitis media
H659	Nonsuppurative otitis media, unspecified (acute or chronic)
H664	Suppurative otitis media, unspecified (acute or chronic)
H669	Otitis media, unspecified (NOS, acute, chronic)
J20 (exc J203, J204, J205, J206, J207)	Acute bronchitis exc viruses

Appendix X Complications arising from RTIs (ICD10 codes)

ICD10	ICD10 DESCRIPTION
A36	Diptheria
A38	Scarlet fever
A39	Meningococcal infection
A40	Streptococcal septicaemia
A41	Other septicaemia
A481	Legionnaires disease
A491	Streptococcal infection, unspecified
A492	Haemophilus influenzae infection, unspecified
A493	Mycoplasma infection, unspecified
A70	Chlamydia psittaci infection
B960	Mycoplasma pneumoniae as the cause of diseases classified to other chapters
B961	Klebsiella pneumoniae as the cause of diseases classified to other chapters
G00	Bacterial meningitis, not elsewhere classified
G01*	Meningitis in bacterial diseases classified elsewhere
G042	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified
G048	Other encephalitis, myelitis and encephalomyelitis
G050*	Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
G06	Intracranial and intraspinal abscess and granuloma
G08	Intracranial and intraspinal phlebitis and thrombophlebitis
H67*	Otitis media in diseases classified elsewhere
H70	Mastoiditis and related conditions
H75*	Other disorders of middle ear and mastoid in diseases classified elsewhere
I00	Rheumatic fever without heart involvement
I01	Rheumatic fever with heart involvement
I02	Rheumatic chorea
I301	Infective pericarditis

ICD10	ICD10 DESCRIPTION
I33	Acute and subacute endocarditis
I38	Endocarditis, valve unspecified
J051	Acute epiglottitis
J13	Pneumonia due to Strep p
J14	Pneumonia due to H influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms (not elsewhere classified)
J170*	Pneumonia in bacterial diseases classified elsewhere
J178*	Pneumonia in other diseases classified elsewhere
J18	Pneumonia, organism unspecified
J340	Abscess, furuncle and carbuncle of nose
J36	Abscess of peritonsillar
J390	Retropharyngeal and parapharyngeal abscess
J391	Other abscess of pharynx
J398	Other specified diseases of upper respiratory tract
J399	Disease of upper respiratory tract, unspecified
J40	Bronchitis (not acute or chronic)
J440	COPD with acute lower respiratory infection
J441	COPD with acute exacerbation, unspecified
J47	Bronchiectasis
J85	Abscess of lung and mediastinum
J86	Pyothorax
J90	Pleural effusion, not elsewhere classified
J91*	Pleural effusion in conditions classified elsewhere
L040	Acute lymphadenitis of face, head and neck
L048	Acute lymphadenitis of other sites
L049	Acute lymphadenitis, unspecified
L540*	Erythema marginatum in acute rheumatic fever
M001	Pneumococcal arthritis and polyarthritis
M002	Other streptococcal arthritis and polyarthritis
M008	Arthritis and polyarthritis due to other specified bacterial agents

Appendix X

ICD10	ICD10 DESCRIPTION
M009	Pyogenic arthritis, unspecified (infective arthritis)
M010*	Meningococcal arthritis
M013*	Arthritis in other bacterial diseases classified elsewhere
M028	Other reactive arthropathies
M029	Reactive arthropathy, unspecified
M03*	Post infective and reactive arthropathies in disease classified elsewhere
N00	Acute nephritic syndrome (glomerulonephritis)
N01	Rapidly progressive nephritic syndrome

Appendix XI List of respiratory tract infections (Read codes) by type and the number of patients identified with each code

(a) Sore throats

Read code	Description	N	%
1C9..00	Sore throat symptom	8,300	9.2
1C9..11	Throat soreness	2,706	3.0
1C92.00	Has a sore throat	49	0.1
1C93.00	Persistent sore throat	0	0.0
1C9Z.00	Sore throat symptom NOS	2	0.0
1CA..00	Hoarseness symptoms	135	0.1
1CA..11	Hoarseness - throat symptoms	6	0.0
1CB3.00	Throat pain	191	0.2
1CB3.11	Pain in throat	23	0.0
2DB6.00	O/E - follicular tonsillitis	5	0.0
2DC1.00	O/E - pharynx hyperaemic	21	0.0
2DC1.11	O/E - fauces injected	27	0.0
2DC2.00	O/E - granular pharyngitis	0	0.0
2DC3.00	Inflamed throat	135	0.1
A340.00	Streptococcal sore throat	16	0.0
A340200	Streptococcal pharyngitis	1	0.0
A340300	Streptococcal tonsillitis	26	0.0
H00..00	Acute nasopharyngitis	7	0.0
H02..00	Acute pharyngitis	2,168	2.4
H02..11	Sore throat NOS	477	0.5
H02..12	Viral sore throat NOS	114	0.1
H02..13	Throat infection - pharyngitis	784	0.9
H020.00	Acute gangrenous pharyngitis	0	0.0
H021.00	Acute phlegmonous pharyngitis	3	0.0
H022.00	Acute ulcerative pharyngitis	0	0.0
H023.00	Acute bacterial pharyngitis	0	0.0
H023000	Acute pneumococcal pharyngitis	0	0.0
H023100	Acute staphylococcal pharyngitis	0	0.0
H023z00	Acute bacterial pharyngitis NOS	0	0.0

Appendix XI

Read code	Description	N	%
H024.00	Acute viral pharyngitis	78	0.1
H02z.00	Acute pharyngitis NOS	172	0.2
H03..00	Acute tonsillitis	6,701	7.4
H03..11	Throat infection - tonsillitis	66	0.1
H03..12	Tonsillitis	542	0.6
H030.00	Acute erythematous tonsillitis	1	0.0
H031.00	Acute follicular tonsillitis	45	0.0
H032.00	Acute ulcerative tonsillitis	0	0.0
H033.00	Acute catarrhal tonsillitis	0	0.0
H034.00	Acute gangrenous tonsillitis	0	0.0
H035.00	Acute bacterial tonsillitis	12	0.0
H035000	Acute pneumococcal tonsillitis	0	0.0
H035100	Acute staphylococcal tonsillitis	0	0.0
H035z00	Acute bacterial tonsillitis NOS	0	0.0
H036.00	Acute viral tonsillitis	24	0.0
H037.00	Recurrent acute tonsillitis	31	0.0
H03z.00	Acute tonsillitis NOS	140	0.2
H050.00	Acute laryngopharyngitis	2	0.0
H052.00	Pharyngotracheitis	4	0.0
H053.00	Tracheopharyngitis	0	0.0
H055.00	Pharyngolaryngitis	2	0.0
H121100	Atrophic pharyngitis	0	0.0
H121200	Granular pharyngitis	0	0.0
H121300	Hypertrophic pharyngitis	0	0.0
H14y600	Lingular tonsillitis	0	0.0
H271100	Influenza with pharyngitis	0	0.0
Hyu0100	[X]Acute pharyngitis due to other specified organisms	0	0.0
Hyu0200	[X]Acute tonsillitis due to other specified organisms	0	0.0

(b) Sinusitis

Read code	Description	N	%
1BA5.11	Pain in sinuses	624	0.7
1CC..00	Blocked sinuses	35	0.0
2DA2.00	O/E - maxillary sinus tenderness	6	0.0
2DA3.00	O/E - frontal sinus tenderness	5	0.0
H01..00	Acute sinusitis	4,422	4.9
H01..11	Sinusitis	1,154	1.3
H010.00	Acute maxillary sinusitis	56	0.1
H010.11	Antritis - acute	1	0.0
H011.00	Acute frontal sinusitis	17	0.0
H012.00	Acute ethmoidal sinusitis	1	0.0
H013.00	Acute sphenoidal sinusitis	1	0.0
H01y.00	Other acute sinusitis	0	0.0
H01y000	Acute pansinusitis	1	0.0
H01yz00	Other acute sinusitis NOS	0	0.0
H01z.00	Acute sinusitis NOS	0	0.0
H130.12	Maxillary sinusitis	35	0.0
H131.11	Frontal sinusitis	11	0.0
H135.00	Recurrent sinusitis	7	0.0
H13y.00	Other chronic sinusitis	0	0.0
H13y100	Pansinusitis	0	0.0
Hyu0000	[X]Other acute sinusitis	0	0.0
Hyu2200	[X]Other chronic sinusitis	0	0.0
SN31.11	Aerosinusitis	0	0.0

(c) Laryngitis/ tracheitis

Read code	Description	N	%
H04..00	Acute laryngitis and tracheitis	7	0.0
H040.00	Acute laryngitis	983	1.1
H040000	Acute oedematous laryngitis	0	0.0
H040100	Acute ulcerative laryngitis	0	0.0
H040200	Acute catarrhal laryngitis	1	0.0

Read code	Description	N	%
H040300	Acute phlegmonous laryngitis	1	0.0
H040400	Acute haemophilus influenzae laryngitis	0	0.0
H040500	Acute pneumococcal laryngitis	0	0.0
H040600	Acute suppurative laryngitis	0	0.0
H040w00	Acute viral laryngitis unspecified	30	0.0
H040x00	Acute bacterial laryngitis unspecified	0	0.0
H040z00	Acute laryngitis NOS	0	0.0
H041.00	Acute tracheitis	782	0.9
H041000	Acute tracheitis without obstruction	0	0.0
H041100	Acute tracheitis with obstruction	0	0.0
H041z00	Acute tracheitis NOS	0	0.0
H042.00	Acute laryngotracheitis	60	0.1
H042.11	Laryngotracheitis	23	0.0
H042000	Acute laryngotracheitis without obstruction	0	0.0
H042100	Acute laryngotracheitis with obstruction	0	0.0
H042z00	Acute laryngotracheitis NOS	0	0.0
H044.00	Croup	271	0.3
H04z.00	Acute laryngitis and tracheitis NOS	1	0.0
H271000	Influenza with laryngitis	0	0.0

(d) Ear infections

Read code	Description	N	%
F51..00	Nonsuppurative otitis media + eustachian tube disorders	1,314	1.4
F510.00	Acute non suppurative otitis media	280	0.3
F510000	Acute otitis media with effusion	4	0.0
F510011	Acute secretory otitis media	55	0.1
F510100	Acute serous otitis media	146	0.2
F510200	Acute mucoid otitis media	1	0.0
F510300	Acute sanguinous otitis media	0	0.0
F510z00	Acute nonsuppurative otitis media NOS	4	0.0
F514.00	Unspecified nonsuppurative otitis media	3	0.0

Read code	Description	N	%
F514100	Serous otitis media NOS	6	0.0
F514200	Catarrhal otitis media NOS	55	0.1
F514300	Mucoid otitis media NOS	0	0.0
F514z00	Nonsuppurative otitis media NOS	1	0.0
F52..00	Suppurative and unspecified otitis media	671	0.7
F520.00	Acute suppurative otitis media	276	0.3
F520000	Acute suppurative otitis media tympanic membrane intact	4	0.0
F520100	Acute suppurative otitis media tympanic membrane ruptured	0	0.0
F520300	Acute suppurative otitis media due to disease EC	0	0.0
F520z00	Acute suppurative otitis media NOS	0	0.0
F524.00	Purulent otitis media NOS	0	0.0
F524000	Bilateral suppurative otitis media	2	0.0
F525.00	Recurrent acute otitis media	6	0.0
F526.00	Acute left otitis media	308	0.3
F527.00	Acute right otitis media	357	0.4
F528.00	Acute bilateral otitis media	84	0.1
F52z.00	Otitis media NOS	1,839	2.0
F52z.11	Infection ear	401	0.4
F540.00	Acute myringitis without otitis media	2	0.0
FyuP000	[X]Other acute nonsuppurative otitis media	0	0.0
FyuP300	[X]Otitis media in bacterial diseases classified elsewhere	0	0.0
FyuP400	[X]Otitis media in viral diseases classified elsewhere	0	0.0
FyuP500	[X]Otitis media in other diseases classified elsewhere	0	0.0
SN30.11	Aero-otitis media	0	0.0

(e) Chest infection

Read code	Description	N	%
1712	Dry cough	767	0.8
1713	Productive cough - clear sputum	122	0.1
1714	Productive cough - green sputum	418	0.5
1715	Productive cough - yellow sputum	269	0.3
1716	Productive cough – NOS	176	0.2
1719	Chesty cough	2,091	2.3
171E	Unexplained cough	0	0.0
171F	Cough with fever	3	0.0
171Z	Cough symptoms NOS	66	0.1
A79A.00	Respiratory syncytial virus infection	3	0.0
H06..00	Acute bronchitis and bronchiolitis	0	0.0
H060.00	Acute bronchitis	2,384	2.6
H060.11	Acute wheezy bronchitis	298	0.3
H060000	Acute fibrinous bronchitis	0	0.0
H060100	Acute membranous bronchitis	0	0.0
H060200	Acute pseudomembranous bronchitis	0	0.0
H060300	Acute purulent bronchitis	0	0.0
H060400	Acute croupous bronchitis	3	0.0
H060500	Acute tracheobronchitis	90	0.1
H060600	Acute pneumococcal bronchitis	0	0.0
H060700	Acute streptococcal bronchitis	0	0.0
H060800	Acute haemophilus influenzae bronchitis	0	0.0
H060A00	Acute bronchitis due to mycoplasma pneumoniae	0	0.0
H060B00	Acute bronchitis due to coxsackievirus	0	0.0
H060C00	Acute bronchitis due to parainfluenza virus	0	0.0
H060D00	Acute bronchitis due to respiratory syncytial virus	0	0.0
H060E00	Acute bronchitis due to rhinovirus	0	0.0
H060F00	Acute bronchitis due to echovirus	0	0.0
H060w00	Acute viral bronchitis unspecified	9	0.0

Read code	Description	N	%
H060x00	Acute bacterial bronchitis unspecified	1	0.0
H060z00	Acute bronchitis NOS	0	0.0
H062.00	Acute lower respiratory tract infection	395	0.4
H06z.00	Acute bronchitis or bronchiolitis NOS	0	0.0
H06z000	Chest infection NOS	6,940	7.7
H06z011	Chest infection	7,031	7.8
H06z100	Lower resp tract infection	506	0.6
H06z112	Acute lower respiratory tract infection	0	0.0
H06z200	Recurrent chest infection	17	0.0
H07..00	Chest cold	128	0.1
H24..11	Chest infection with infectious disease EC	0	0.0
H260000	Lung consolidation	11	0.0
H30..00	Bronchitis unspecified	293	0.3
H30..11	Chest infection - unspecified bronchitis	1	0.0
H30..12	Recurrent wheezy bronchitis	8	0.0
H300.00	Tracheobronchitis NOS	5	0.0
H301.00	Laryngotracheobronchitis	3	0.0
H302.00	Wheezy bronchitis	94	0.1
H30z.00	Bronchitis NOS	1	0.0
H312200	Acute exacerbation of chronic obstructive airways disease	361	0.4
H3y0.00	Chronic obstruct pulmonary disease with acute lower respiratory infection	3	0.0
Hyu1000	[X]Acute bronchitis due to other specified organisms	0	0.0

(f) Not grouped – Lower RTIs

Read code	Description	N	%
A3A4.00	Legionella	0	0.0
Hyu1.00	[X]Other acute lower respiratory infections	0	0.0

(g) Not grouped –Upper RTIs

Read code	Description	N	%
Hyu0400	[X]Flu+oth respiratory manifestations,'flu virus identified	0	0.0
Hyu0600	[X]Influenza+oth respiratory manifestatns,virus not identifd	0	0.0
Hyu0500	[X]Influenza+other manifestations,influenza virus identified	0	0.0
Hyu0300	[X]Other acute upper respiratory infections/multiple sites	0	0.0
AyuD.00	[X]Other viral diseases	0	0.0
H051.00	Acute upper respiratory tract infection	2,631	2.9
A790.00	Adenovirus	1	0.0
1C86	Blocked nose	160	0.2
H00..11	Common cold	286	0.3
H00..12	Coryza - acute	292	0.3
H00..13	Febrile cold	2	0.0
1652	Feels hot/ feverish	239	0.3
165..11	Fever symptoms	588	0.6
1653	Fever with sweating	0	0.0
1656	Feverish cold	55	0.1
H27z.11	Flu like illness	1,806	2.0
H27..00	Influenza	205	0.2
H27z.12	Influenza like illness	13	0.0
H27z.00	Influenza NOS	3	0.0
H271.00	Influenza with other respiratory manifestation	0	0.0
H271z00	Influenza with respiratory manifestations NOS	0	0.0
1C83	Nasal discharge present	44	0.0
H1y1z14	Nasal infection	163	0.2
2D2..00	O/E - nasal discharge	30	0.0
2D2Z.00	O/E - nasal discharge - NOS	0	0.0
2D2..11	O/E - nose discharge	2	0.0
2E34.00	O/E - temperature elevated	1	0.0

Read code	Description	N	%
2D24.00	O/E - nasal discharge - mucopurulent	3	0.0
H05..00	Other acute upper respiratory infections	1	0.0
H05y.00	Other upper respiratory infections of multiple sites	0	0.0
2D26.00	Postnasal discharge	70	0.1
H00..15	Pyrexial cold	17	0.0
H054.00	Recurrent upper respiratory tract infection	11	0.0
H00..16	Rhinitis - acute	218	0.2
A793.00	Rhinovirus	0	0.0
165Z.00	Temperature symptom NOS	7	0.0
165..00	Temperature symptoms	407	0.4
H05z.00	Upper respiratory infection NOS	8,901	9.8
H05z.11	Upper respiratory tract infection NOS	7,694	8.5
A79z.11	Viral illness	960	1.1
A79z.00	Viral infection NOS	2,374	2.6
H05z.12	Viral upper respiratory tract infection NOS	305	0.3
Hyu0.00	[X]Acute upper respiratory infections	0	0.0
2D22.00	O/E - rhinorrhoea	2	0.0
2D23.00	O/E - nasal discharge - foul smell	1	0.0

(h) Not grouped – RTIs

Read code	Description	N	%
A3Bz.00	Bacterial infection NOS	0	0.0
A3y..00	Other specified bacterial diseases	0	0.0
A3z..00	Other bacterial disease NOS	0	0.0
H0...00	Acute respiratory infections	1,051	1.2
H06z111	Respiratory tract infection	2,180	2.4
H0y..00	Other specified acute respiratory infections	1	0.0
H0z..00	Acute respiratory infection NOS	61	0.1
H5yy.11	Respiratory infection NOS	20	0.0

(i) Pneumonia

Read code	Description	N	%
A3BXB00	Klebsiella pneumoniae/cause/disease classified/other chapters	2	0.0
A3By400	Pleuropneumonia-like organism (PPLO) infection	0	0.0
AyuK900	[X]Mycoplasma pneumoniae [PPLO] /cause/disease classified/other chapters	0	0.0
AyuKA00	[X]Klebsiella pneumoniae/cause/disease classified/other chapters	0	0.0
H2...00	Pneumonia and influenza	13	0.0
H20..00	Viral pneumonia	6	0.0
H20..11	Chest infection - viral pneumonia	1	0.0
H200.00	Pneumonia due to adenovirus	0	0.0
H201.00	Pneumonia due to respiratory syncytial virus	0	0.0
H202.00	Pneumonia due to parainfluenza virus	0	0.0
H20y.00	Viral pneumonia NEC	0	0.0
H20z.00	Viral pneumonia NOS	2	0.0
H21..00	Lobar (pneumococcal) pneumonia	58	0.1
H21..11	Chest infection - pneumococcal pneumonia	0	0.0
H22..00	Other bacterial pneumonia	8	0.0
H22..11	Chest infection - other bacterial pneumonia	1	0.0
H220.00	Pneumonia due to klebsiella pneumoniae	0	0.0
H221.00	Pneumonia due to pseudomonas	0	0.0
H222.11	Pneumonia due to haemophilus influenzae	0	0.0
H223.00	Pneumonia due to streptococcus	1	0.0
H223000	Pneumonia due to streptococcus, group B	0	0.0
H224.00	Pneumonia due to staphylococcus	0	0.0
H22y.00	Pneumonia due to other specified bacteria	1	0.0
H22y000	Pneumonia due to escherichia coli	0	0.0
H22y011	E.coli pneumonia	0	0.0
H22y100	Pneumonia due to proteus	0	0.0
H22y200	Pneumonia - Legionella	1	0.0

Read code	Description	N	%
H22yX00	Pneumonia due to other aerobic gram-negative bacteria	0	0.0
H22yz00	Pneumonia due to bacteria NOS	0	0.0
H22z.00	Bacterial pneumonia NOS	0	0.0
H23..00	Pneumonia due to other specified organisms	7	0.0
H23..11	Chest infection - pneumonia organism OS	0	0.0
H230.00	Pneumonia due to Eaton's agent	0	0.0
H231.00	Pneumonia due to mycoplasma pneumoniae	0	0.0
H232.00	Pneumonia due to pleuropneumonia like organisms	0	0.0
H233.00	Chlamydial pneumonia	0	0.0
H23z.00	Pneumonia due to specified organism NOS	0	0.0
H24..00	Pneumonia with infectious diseases EC	0	0.0
H240.00	Pneumonia with measles	0	0.0
H241.00	Pneumonia with cytomegalic inclusion disease	0	0.0
H243.00	Pneumonia with whooping cough	0	0.0
H243.11	Pneumonia with pertussis	0	0.0
H24y400	Pneumonia with salmonellosis	0	0.0
H24y700	Pneumonia with varicella	0	0.0
H24z.00	Pneumonia with infectious diseases EC NOS	0	0.0
H25..00	Bronchopneumonia due to unspecified organism	128	0.1
H25..11	Chest infection - unspecified bronchopneumonia	0	0.0
H26..00	Pneumonia due to unspecified organism	202	0.2
H26..11	Chest infection - pnemonia due to unspecified organism	0	0.0
H260.00	Lobar pneumonia due to unspecified organism	14	0.0
H261.00	Basal pneumonia due to unspecified organism	26	0.0
H262.00	Postoperative pneumonia	0	0.0
H270.00	Influenza with pneumonia	0	0.0
H270.11	Chest infection - influenza with pneumonia	0	0.0

Read code	Description	N	%
H270000	Influenza with bronchopneumonia	1	0.0
H270100	Influenza with pneumonia, influenza virus identified	0	0.0
H270z00	Influenza with pneumonia NOS	0	0.0
H28..00	Atypical pneumonia	6	0.0
H2y..00	Other specified pneumonia or influenza	0	0.0
H2z..00	Pneumonia or influenza NOS	46	0.1
H530200	Gangrenous pneumonia	0	0.0
H540000	Hypostatic pneumonia	0	0.0
H540100	Hypostatic bronchopneumonia	0	0.0
H56y100	Interstitial pneumonia	2	0.0
H571.00	Rheumatic pneumonia	0	0.0
Hyu0800	[X]Other viral pneumonia	0	0.0
Hyu0900	[X]Pneumonia due to other aerobic gram-negative bacteria	0	0.0
Hyu0A00	[X]Other bacterial pneumonia	0	0.0
Hyu0B00	[X]Pneumonia due to other specified infectious organisms	0	0.0
Hyu0C00	[X]Pneumonia in bacterial diseases classified elsewhere	0	0.0
Hyu0D00	[X]Pneumonia in viral diseases classified elsewhere	0	0.0
Hyu0G00	[X]Pneumonia in other diseases classified elsewhere	0	0.0
Hyu0H00	[X]Other pneumonia, organism unspecified	0	0.0

Appendix XII Complications arising from respiratory tract infections (Read codes)

Read code	Description
A32..	**Diphtheria**
A320.	Faucial
A321.	Nasopharyngeal
A322.	Anterior nasal
A323.	Laryngeal
A32y.	Other specific diphtheria
A32z.	Diphtheria NOS
A34..	**Streptococcal sore throat and scarlatina**
A340.	Streptococcal sore throat
A341.	Scarlet fever
A342.	Streptococcal sore throat with scarlatina NOS
A36..	**Meningococcal infection**
A360.	Meningococcal meningitis
A361.	Meningococcal encephalitis
A362.	Meningococcal septicaemia
A363.	Waterhouse-Friderichsen syndrome (E35.1*)
A364.	Meningococcal carditis
A365.	Meningococcal meningitis with acute meningococcal septicaemia
A366.	Meningococcal meningitis with meningococcal septicaemia
A36y.	Other specified meningococcal infection
A36z.	Meningococcal infection NOS
A38..	**Septicaemia**
A380.	Streptococcal septicaemia
A3800	Septicaemia due to streptococcus, group A
A3801	Septicaemia due to streptococcus, group B
A3802	Septicaemia due to streptococcus, group D
A3803	Septicaemia due to streptococcus pneumoniae
A3804	Septicaemia due to enterococcus
A3805	Vancomycin resistant enterococcal septicaemia
A381.	Staphylococcal septicaemia

Read code	Description
A382.	Pneumococcal septicaemia
A383.	Septicaemia due to anaerobes (includes Lemierre's disease)
A384.	Septicaemia due to other gram negative organisms
A38y.	Other specified septicaemia
A38z.	Septicaemia NOS
A3B..	**Bacterial infections - causative organisms**
A3B0.	Streptococcal infection
A3B1.	Staphylococcal infection
A3B2	Pneumococcal infection
A3B5.	Haemophilus influenzae infection
A3B7.	Pseudomonas infection
A3BX.	Bacterial causes of diseases classified elsewhere
A3Bx.	Bacteria causing diseases classified elsewhere
A3By.	Other specified bacterial infection
A3Bz.	Bacterial infection NOS
A73..	**Ornithosis - psittacosis**
A730.	Ornithosis with pneumonia
A73x.	Ornithosis with other specified complications
A73y.	Ornithosis with unspecified complications
A73z.	Unspecified Ornithosis
F00..	**Bacterial meningitis**
F000.	Haemophilus meningitis
F001.	Pneumococcal meningitis
F002.	Streptococcal meningitis
F003.	Staphylococcal meningitis
F005.	Meningitis - meningococcal
F007.	Meningitis in other bacterial disease classified elsewhere
F00y.	Other specified bacterial meningitis
F00z.	Bacterial meningitis NOS
F0330	**Encephalitis due to meningococcus**
F033z	**Unspecified encephalitis due to other infection EC**
F03X.	**Bacterial meningoencephalitis and meningomyelitis, not**

Read code	Description
	elsewhere classified
F03z.	**Encephalitis NOS**
F04..	**Intracranial and intraspinal abscesses**
F040.	Intracranial abscess
F041.	Intraspinal abscess
F04X.	Extradural and subdural abscess, unspecified
F04z.	Intracranial or intraspinal abscess NOS (epidural abscess)
F53..	**Mastoiditis**
F530.	Acute mastoiditis
F531.	Chronic mastoiditis
F532.	Petrositis
F53z.	Mastoiditis NOS
F551.	**Adhesive middle ear disease**
F552.	**Other acquired abnormality of ear ossicles**
F55y.	**Other middle ear and mastoid disorders OS**
F55z.	**Middle ear or mastoid disorder NOS**
Fyu00	**[X]Other bacterial meningitis**
Fyu05	**[X]Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified**
Fyu06	**[X]Other encephalitis, myelitis and encephalomyelitis**
Fyu07	**[X]Encephalitis, myelitis and encephalomyelitis in bacterial diseases classified elsewhere**
Fyu0B	**[X]Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere**
G0...	**Acute rheumatic fever**
G00..	Rheumatic fever without heart involvement
G01..	Rheumatic fever with heart involvement
G02..	Rheumatic chorea
G0y..	Other specified acute rheumatic fever
G0z..	Acute rheumatic fever NOS
G50z2	**Acute pericarditis - pneumococcal**
G50z3	**Acute pericarditis - staphylococcal**

Read code	Description
G50z4	**Acute pericarditis - streptococcal**
G50z5	**Acute purulent pericarditis unspecified**
G51..	**Acute and subacute endocarditis**
G510.	Acute and subacute bacterial endocarditis
G511.	Acute and subacute infective endocarditis in diseases EC
G51z.	Acute and subacute endocarditis unspecified
H043.	**Acute epiglottitis (non strep)**
H0430	Acute epiglottitis without obstruction
H0431	Acute epiglottitis with obstruction
H043z	Acute epiglottitis NOS
H14..	**Chronic tonsil and adenoid disease**
H140.	Chronic tonsillitis/adenoiditis
H141.	Tonsil and/or adenoid hypertrophy
H142.	Adenoid vegetations
H143.	Chronic adenotonsillitis
H14y.	Other chronic diseases of tonsils and adenoids
H14z.	Chronic tonsil and adenoid disease NOS
H15..	**Peritonsillar abscess - quinsy**
H1y21	Pharynx or nasopharynx cellulitis
H1y22	Parapharyngeal abscess
H1y23	Retropharyngeal abscess
H1y26	Pharynx or nasopharynx abscess
H1y8.	Upper respiratory tract hypersensitivity reaction NOS
2DB5.	O/E – quinsy present
H21..	**Lobar (pneumococcal) pneumonia**
H22..	**Other bacterial pneumonia**
H23..	**Pneumonia due to other specified organisms**
H24..	**Pneumonia with infectious diseases EC**
H25..	**Bronchopneumonia due to unspecified organism**
H26..	**Pneumonia due to unspecified organism**
H28..	**Atypical pneumonia**
H313.	Mixed simple and mucopurulent chronic bronchitis

Read code	Description
H34..	**Bronchiectasis**
H3y1.	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
H5016	**Pyothorax**
H510B	Streptococcal pleurisy
H511.	Bacterial pleurisy with effusion
H51y.	Other pleural effusion excluding mention of tuberculosis
H51z.	Pleural effusion NOS
H51zz	Pleural effusion NOS
H53..	**Abscess of lung and mediastinum**
H530.	Abscess of lung
H531.	Abscess of mediastinum
H53z.	Abscess of lung and mediastinum NOS
K0A0.	**Acute nephritic syndrome**
K0A1.	**Rapidly progressive nephritic syndrome**
M0002	Carbuncle of nasal septum
M0102	Boil of nasal septum
M0301	Cellulitis and abscess of nose
M043.	Acute lymphadenitis of face, head and neck
M15y6	Erythema marginatum in acute rheumatic fever
N0108	Staphylococcal arthritis and polyarthritis
N0109	Pneumococcal arthritis and polyarthritis
N010z	Pyogenic arthritis NOS
N014.	Arthropathy associated with other bacterial diseases
N01w.	Reactive arthropathy, unspecified
N0380	Postmeningococcal arthritis
N0381	Postinfective arthropathy in syphilis
N0420	Rheumatic carditis
Nyu00	[X]Other streptococcal arthritis and polyarthritis
R0555	[D] septic shock

Appendix XIII ICD10 codes for complications

ICD10 Code	Description
A36	**Diptheria**
A38	**Scarlet fever**
A39	**Meningococcal infection**
A39.0+	Meningococcal meningitis (G01*)
A39.1+	Waterhouse-Friderichsen syndrome (E35.1*)
A39.2	Acute meningococcaemia
A39.3	Chronic meningococcaemia
A39.4	Meningococcaemia, unspecified
A39.5+	Meningococcal heart disease
A39.8	Other meningococcal infections
A39.9	Meningococcal infection, unspecified
A40	**Streptococcal septicaemia**
A40.0	Septicaemia due to streptococcus, group A
A40.1	Septicaemia due to streptococcus, group B
A40.2	Septicaemia due to streptococcus, group D
A40.3	Septicaemia due to Streptococcus pneumoniae. Pneumococcal septicaemia
A40.8	Other streptococcal septicaemia
A40.9	Streptococcal septicaemia, unspecified
A41	**Other septicaemia**
A41.0	Septicaemia due to Staphylococcus aureus
A41.1	Septicaemia due to other specified staphylococcus
A41.2	Septicaemia due to unspecified staphylococcus
A41.3	Septicaemia due to Haemophilus influenzae
A41.4	Septicaemia due to anaerobes
A41.5	Septicaemia due to other Gram-negative organisms
A41.8	Other specified septicaemia
A41.9	Septicaemia, unspecified inc septic shock
A48.1	**Legionnaires disease**
A49.1	**Streptococcal infection, unspecified**

ICD10 Code	Description
A49.2	**Haemophilus influenzae infection, unspecified**
A49.3	**Mycoplasma infection, unspecified**
A70	**Chlamydia psittaci infection**
B96.0	**Mycoplasma pneumoniae [M. pneumoniae] as the cause of diseases classified to other chapters**
B96.1	**Klebsiella pneumoniae [K. pneumoniae] as the cause of diseases classified to other chapters**
G00	**Bacterial meningitis, not elsewhere classified**
G00.0	Haemophilus meningitis: Meningitis due to Haemophilus influenzae
G00.1	Pneumococcal meningitis
G00.2	Streptococcal meningitis
G00.3	Staphylococcal meningitis
G00.8	Other bacterial meningitis: Meningitis due to escherichia coli, Friedländer bacillus, Klebsiella
G00.9	Bacterial meningitis, unspecified: Meningitis purulent NOS, pyogenic NOS, suppurative NOS
G01*	**Meningitis in bacterial diseases classified elsewhere**
G04.2	**Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified**
G04.8	**Other encephalitis, myelitis and encephalomyelitis** (Postinfectious encephalitis and encephalomyelitis NOS)
G05.0*	**Encephalitis, myelitis and encephalomyelitis in bacterial diseases classified elsewhere**
G06	**Intracranial and intraspinal abscess and granuloma**
G06.0	Intracranial abscess and granuloma
G06.1	Intraspinal abscess and granuloma
G06.2	Extradural and subdural abscess, unspecified
G08	**Intracranial and intraspinal phlebitis and thrombophlebitis**
H67*	**Otitis media in diseases classified elsewhere**
H70	**Mastoiditis and related conditions**
H70.0	Acute mastoiditis (Abscess, Empyema)
H70.1	Chronic mastoiditis (Caries, Fistula)

ICD10 Code	Description
H70.2	Petrositis (inflammation of petrous bone (acute)(chronic))
H70.8	Other mastoiditis and related conditions
H70.9	Mastoiditis, unspecified
H75*	**Other disorders of middle ear and mastoid in diseases classified elsewhere**
H75.0*	Mastoiditis in infectious and parasitic diseases classified elsewhere
H75.8*	Other specified disorders of middle ear and mastoid in diseases classified elsewhere
I00	**Rheumatic fever without mention of heart involvement (Arthritis, rheumatic, acute or subacute)**
I01	**Rheumatic fever with heart involvement**
I01.0	Acute rheumatic pericarditis (Any condition in I00 with pericarditis)
I01.1	Acute rheumatic endocarditis (Any condition in I00 with endocarditis or valvulitis)
I01.2	Acute rheumatic myocarditis (Any condition in I00 with myocarditis)
I01.8	Other acute rheumatic heart disease (Any condition in I00 with other or multiple types of heart involvement)
I01.9	Acute rheumatic heart disease, unspecified (Any condition in I00 with unspecified type of heart involvement)
I02	**Rheumatic chorea**
I02.0	Rheumatic chorea with heart involvement
I02.9	Rheumatic chorea without heart involvement
I30.1	**Infective pericarditis**
I33	**Acute and subacute endocarditis**
I33.0	Acute and subacute infective endocarditis
I33.9	Acute endocarditis, unspecified
I38	**Endocarditis, valve unspecified**
J05.1	**Acute epiglottitis**
J13	**Pneumonia due to Streptococcus pneumoniae**
J14	**Pneumonia due to Haemophilus influenzae**
J15	**Bacterial pneumonia, not elsewhere classified**

ICD10 Code	Description
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to Pseudomonas
J15.2	Pneumonia due to staphylococcus
J15.3	Pneumonia due to streptococcus, group B
J15.4	Pneumonia due to other streptococci
J15.5	Pneumonia due to Escherichia coli
J15.6	Pneumonia due to other aerobic Gram-negative bacteria
J15.7	Pneumonia due to Mycoplasma pneumoniae
J15.8	Other bacterial pneumonia
J15.9	Bacterial pneumonia, unspecified
J16	**Pneumonia due to other infectious organisms, not elsewhere classified**
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
J17.0*	**Pneumonia in bacterial diseases classified elsewhere**
J17.8*	**Pneumonia in other diseases classified elsewhere**
J18	**Pneumonia, organism unspecified**
J18.0	Bronchopneumonia, unspecified
J18.1	Lobar pneumonia, unspecified
J18.2	Hypostatic pneumonia, unspecified
J18.8	Other pneumonia, organism unspecified
J18.9	Pneumonia, unspecified
J34.0	**Abscess, furuncle and carbuncle of nose**
J36	**Peritonsillar abscess**
J39	**Other diseases of upper respiratory tract**
J39.0	Retropharyngeal and parapharyngeal abscess
J39.1	Other abscess of pharynx
J39.8	Other specified diseases of upper respiratory tract
J39.9	Disease of upper respiratory tract, unspecified
J40	**Bronchitis, not specified as acute or chronic**
J44.0	**Chronic obstructive pulmonary disease with acute lower respiratory infection**

ICD10 Code	Description
J44.1	**Chronic obstructive pulmonary disease with acute exacerbation, unspecified**
J47	**Bronchiectasis**
J85	**Abscess of lung and mediastinum**
J86	**Pyothorax**
J86.0	Pyothorax with fistula
J86.9	Pyothorax without fistula
J90	**Pleural effusion, not elsewhere classified**
J91*	**Pleural effusion in conditions classified elsewhere**
L04.0	**Acute lymphadenitis of face, head and neck**
L04.8	**Acute lymphadenitis of other sites**
L04.9	**Acute lymphadenitis, unspecified**
L54.0*	**Erythema marginatum in acute rheumatic fever (I00+)**
M00.1	**Pneumococcal arthritis and polyarthritis**
M00.2	**Other streptococcal arthritis and polyarthritis**
M00.8	**Arthritis and polyarthritis due to other specified bacterial agents**
M00.9	**Pyogenic arthritis, unspecified**
M01.0*	**Meningococcal arthritis (A39.8+)**
M01.3*	**Arthritis in other bacterial diseases classified elsewhere**
M02.8	**Other reactive arthropathies**
M02.9	**Reactive arthropathy, unspecified**
M03*	**Postinfective and reactive arthropathies in diseases classified elsewhere**
M03.0*	Postmeningococcal arthritis
M03.1*	Postmeningococcal arthritis
M03.2*	Other postinfectious arthropathies in diseases classified elsewhere
M03.6*	Reactive arthropathy in other diseases classified elsewhere
N00	**Acute nephritic syndrome (glomerulonephritis)**
N01	**Rapidly progressive nephritic syndrome**

Appendix XIV List of Read codes used to identify co-morbidities
(a) Lung Disease

Read Code	Description
C370%	Cystic fibrosis
H31%	Chronic bronchitis
H32%	Emphysema
H34%	Bronchiectasis
H35%	Extrinsic allergic alveolitis
H36%	Mild chronic obstructive pulmonary disease
H37%	Mod chronic obstructive pulmonary disease
H38%	Severe chronic obstructive pulmonary disease
H3y%	Chronic obstructive airway disease.OS
H3z%	Chronic obstructive airway disease NOS
H40-H46	Lung disease due to external agents
H47y0	Detergent asthma
H48-H4z	Lung disease due to external agents
H5410	Chronic pulmonary oedema
H55	Postinflammatory pulmonary.fibrosis
H563%	Idiopath.fibrosing alveolitis
H57%	Lung involvement in disease
H583	Pulmonary eosinophilia
H591	Chronic respiratory failure
Hyu3%	[X]Chronic lower respiratory disease
Hyu4000	[X]Pneumoconiosis due to other dust containing silica
Hyu4100	[X]Pneumoconiosis due to other specified inorganic dusts
Hyu5%	[X]Oth resp dis aff interstit
Q3170	Chronic lung disease of prematurity

(b) Renal Disease

Read code	Description
7B00%	Transplantation of kidney
7B012	Bilateral nephrectomy
7B015	Transplant nephrectomy
7B063	Exploration of renal transplant

Read code	Description
8L50	Renal transplant planned
G220.00	Malignant hypertensive renal disease
G222.00	Hypertensive renal disease with renal failure
G23..00	Hypertensive heart and renal disease
K01%	Nephrotic syndrome
K02%	Chronic glomerulonephritis
K05%	Chronic renal failure
K0A3%	Chronic nephritic syndrome
K0D	End-stage renal disease
Kyu21	[X]Other chronic renal failure
SP083	Kidney transplant failure and rejection
TB001	Kidney transplant with complication, without blame
ZV420	[V]Kidney transplanted CTV3

(c) Neuromuscular Disease

Read code	Description
C370.00	Cystic fibrosis
C370.11	Fibrocystic disease
C370.12	Mucoviscidosis
F12%	Parkinson's disease
F134%	Huntington's chorea
F150.00	Werdnig - Hoffmann disease
F150.11	Infantile spinal muscular atrophy
F151%	Spinal muscular atrophy
F152000	Amyotrophic lateral sclerosis
F20..00	Multiple sclerosis
F380.00	Myasthenia gravis
F39..00	Muscular dystrophies and other myopathies
G61..12	Stroke due to intracerebral haemorrhage
G64..13	Stroke due to cerebral arterial occlusion
G66..00	Stroke and cerebrovascular accident unspecified
G66..12	Stroke unspecified

(d) Liver Disease

Read code	Description
J6%	Liver, biliary, pancreas + gastrointestinal diseases NEC
J61%	Cirrhosis and chronic liver disease
J62%	Liver abscess and sequelae of chronic liver disease
J62..%	Liver abscess and sequelae of chronic liver dis
J6353	Toxic liver dis with chronic persist.hepatitis
J6353	Toxic liver disease with chronic persistent hepatitis
J6354	Toxic liver dis with chronic lobular hepatitis
J6354	Toxic liver disease with chronic lobular hepatitis
J6355	Toxic liver dis with chronic active hepatitis
J6355	Toxic liver disease with chronic active hepatitis
J6356	Toxic liver dis with fibrosis & cirrhosis of liver
J6356	Toxic liver disease with fibrosis & cirrhosis of liver
J63B	Autoimmune hepatitis
PB61%	Biliary atresia
PB63%	Congenital absence of liver & gallbladder
PB6yl	Congenital hepatomegaly CTV3

(e) Heart Disease

Read code	Description
7919600	Percutaneous transluminal pulmonary valve replacement
G1%	Chronic rheumatic heart disease
G21%	Hypertensive heart disease
G220	Malignant hypertensive renal disease
G222	Hypertensive renal disease with renal failure
G23%	Hypertensive heart+renal dis.
G3%	Ischaemic heart disease
G41%	Chronic pulmonary heart diseas
G55%	Cardiomyopathy
G58%	Heart failure
G5yy9	Left ventricul systol dysfunc
G5yyA	Left ventric diastolic dysfunc

Read code	Description
P5%	Bulb.cordis/cardiac sept.anom.
P60-P6X	Other congenital heart anomal.
P6y	Other congenital heart anomal.
P6y0-P6y3	Other congenital heart anomal.
P6y63-P6y6z	Other congenital heart anomal.
P6yy-P6zz	Other congenital heart anomal.
P6z%	Congenital heart anomaly NOS
SP08400	Heart transplant failure and rejection
TB00000	Heart transplant with complication, without blame
ZV42100	[V]Heart transplanted
ZVu6e00	[X]Presence of other heart valve replacement

(f) Immunosuppressant drugs

BNF chapter	Description
6.3.1	Replacement corticosteroids for endocrine conditions
6.3.2	Glucocorticoid therapy
8.1.1	Alkylating Drugs
8.1.2	Cytotoxic Antibiotics
8.1.3	Anti metabolites
8.1.4	Vinca Alkaloids etc
8.1.5	Other anti neoplastic drugs
8.1.6	Chemotherapy induced mucositis and myelosuppression
8.2.1	Anti proliferative immunosuppressants
8.2.2	Cortico-steroids and other immunosuppressants
8.2.3	Rituximab
8.2.4	Interferons