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Development and validation of an indicator to compare antibiotic usage in secondary care in England.

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Doctor of Philosophy

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November 2005

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Summary

The use of antibiotics was investigated in twelve acute hospitals in England. Data was collected electronically and by questionnaire for the financial years 2001/2,2002/3 and 2003/4. Hospitals were selected on the basis of their Medicines Management Self-Assessment Scores (MMAS) and included a cohort of three hospitals with integrated electronic prescribing systems. The total sample size was 6.65% of English NHS activity for 2001/2 based on Finished Consultant Episode (FCE) numbers. Data collected included all antibiotics dispensed (ATC category J01), hospital activity FCE's and bed-days, Medicines Management Self-assessment scores, Antibiotic Medicines Management scores (AMS), Primary Care Trust (PCT) of origin of referral populations, PCT antibiotic prescribing rates, Index of Multiple Deprivation for each PCT.

The DDD/FCE (Defined Daily Dose/FCE) was found to correlate with the DDD/100beddays ($r = 0.74$ $p<0.01$) indicating this is a useful additional indicator for identifying hospitals that require further study. Antibiotic use increased from a mean 4.16 DDD/FCE in 2001/2 to 4.35 DDD/FCE in 2003/4. Antibiotic use in the electronic prescribing cohort was found to be lower, than the sample mean at 3.48 DDD/FCE in 2001/2 and 3.34 DDD/FCE in 2003/4.

The MMAS and AMS were found to correlate ($r = 0.74$ $p<0.01$) thus validating the use of the MMAS as an indication of control of antibiotic use. No correlation was found between the MMAS and a range of qualitative indicators of antibiotic use. A number of indicators are proposed as triggers for further investigation including a proportion of 0.24 for the ratio of third generation to first/second generation cephalosporin use, and five percent as the limit for parenteral quinolone DDD of total quinolone DDD usage.

It was possible to demonstrate a correlation between the IMD 2000 and primary care antibiotic prescribing rates but not between primary and secondary care antibiotic prescribing rates for the same referral population or between the weighted mean IMD 2000 for each hospital's referral population and the hospital antibiotic prescribing rate.

Keywords: antibiotic use, defined daily doses, medicines management, deprivation, electronic prescribing

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List of Abbreviations

ADD	Average Daily Dose
ADQ	Average Daily Quantity
AMS	Antibitoic medicines Management score
APUA	Alliance for the Prudent Use of Antibiotics
ARM	Antibiotic Resistance Management database
ASTRO-PU	Age-sex, temporary resident originated prescribing units
ATC	Anatomical, Therapeutic Chemical Index
BNF	British National Formulary
CDC	Centers for Disease Control (United States)
CME	Continuing Medical Education
CPD	Continuing Professional Development
DDD	Defined Daily Dose
DUR	Drug Utilisation Review
EARSS	European Antimicrobial Resistance Surveillance System
EC	European Community
EHR	Electronic Health Record
EPR	Electronic Patient Record
ESCMID	European Society for Clinical Microbiology and Infectious Disease
ESGAP	European Study Group on Antibiotic Policies
FCE	Finished Consultant Episode
FDA	Food and Drugs Agency (United States)
IFAR	International Forum on Antibiotic Resistance
IMD	Index of Multiple Deprivation

LISI	Low Income Scheme Index
MIC	Minimum Inhibitory Concentration
MMAS	Medicines Management Self-Assessment score
MMD	Minimum Marketed Dose
MRSA	Methicillin-Resistant Staphylococcus aureus
MYSTIC	Meropenem Yearly Susceptibility Test Information Collection
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PACT	Prescribing Analysis and Cost
PCT	Primary Care Trust
PDD	Prescribed Daily Dose
PHLS	Public Health Laboratory Service
PPA	Prescription Pricing Agency
PRISMS	Prescribing Information System for Scotland
RPI	Rational Prescribing Indicator
SMAC	Standing Medical Advisory Committee
SMR	Standardised Mortality Ratio
SPC	Summary of Product Characteristics
STAR-PU	Specific therapeutic group age-sex related prescribing unit
TC	Therapeutic Course
VRE	Vancomycin Resistant *Enterococcus*
WHO	World Health Organisation

1. Introduction

1.1 Background

The use of medicines within the secondary care environment has been the subject of debate for many years. In the United Kingdom, with the National Health Service being funded from general taxation, it is rightly subject to scrutiny as to how resources are used. The service is subject to annual efficiency gain targets, together with efforts to reduce waiting lists for patient treatments and a focus on reduction in length of stay. These factors together with a desire to ensure the cost-effective use of resources, ensures that expenditure on medicines retains a high profile with both the public and with politicians. There is a paucity of aggregated data relating to the use of medicines within the United Kingdom secondary care sector. Pilot work, has been carried out by the National Prescribing Centre (National prescribing Centre,1999) with a group of nineteen hospitals, to analyse their expenditure on medicines. This work found that during the period January 1997 to December 1998, expenditure on antibiotics accounted for nineteen percent of total expenditure on medicines. This was the highest spend of all categories of medicinal product. It was noted in the report that participants had raised the need for a suitable denominator to facilitate benchmarking between hospitals.

The publication in 2001 of the Audit Commission report on Medicines Management within hospitals (Audit Commission 2001) raised the profile of medicines management as a central element of the clinical governance framework in a hospital. The report found that expenditure on medicines within the National Health Service secondary care sector during 1999/2000 was in

excess of £1.5 billion. This expenditure is growing owing to the ageing population, the introduction of new medicines, increasing numbers of patients being treated by the health care system and the trend to use medicines in preference to invasive treatments.

The emergence of 'evidence based practice' during the NHS policy reforms of the 1990's is part of the change to create a culture where clinical governance drives individual hospital practitioners to examine their practice and compare it with their peers. In order to optimise the use of medicines, it is vital that therapeutic categories of medicines where there is high-volume and high-cost are reviewed. It has been established that antibiotics are high-volume and high-cost. In addition, workers have demonstrated (Castle et al., 1977), that a large percentage of antibiotic use in hospitals is inappropriate. There is a requirement for multi-centre clinical audit of antibiotic usage. In order to benchmark the use of antibiotics in different hospitals, a robust measure is needed. Which enables comparisons to be made and which is independent of workload.

To understand the scale of antibiotic use globally it is necessary to be aware of the incidence of infectious disease. These diseases are one of the leading causes of death across the world and in 1998 accounted for 13.3 million deaths; twenty five percent of all deaths (World Health Organisation, 1999; Cassell and Mekalanos 2001). Data from the United States (Pinner *et al.*, 1996), shows that deaths from infectious diseases rose by fifty eight percent during the period 1980 to 1992. This includes conditions such as pneumonia and septicaemia. Within the United States antibiotics are the second most commonly prescribed category of

drug. (McCaig and Hughes, 1995). This amounts to 160 million prescriptions being written annually in that country (Gums, 2002). There are a number of possible reasons as to why infectious diseases have increased in incidence but changes in human behaviour are contributing factors. These include the rapid expansion in international travel and world trade. Specifically, large quantities of food are transported around the planet thus enabling food related illnesses to spread. The level of concern regarding infectious disease is illustrated by the Central Intelligence Agency in the United States producing a report (Central Intelligence Agency, 1999) focussing on the threat to the country from infectious diseases. This report quotes the case of a multidrug resistant strain of Streptococcus pneumoniae which originated in Spain and which had spread across the world in a matter of weeks during the early 1990's.

The development of resistance to antibiotics has ensured that there is a focus on their judicious use to ensure that their value as a therapeutic option is maintained (Daw and Drah, 2001; Phillips, 2001), The first description of the use of penicillin to treat infectious disease (Chain *et al.*, 1940) was only sixty years ago and interestingly, use was restricted, mainly to the military owing to production and purification difficulties. So, the birth of the antibiotic era was accompanied by a strategy that limited the use of these products to certain groups of patient. The awareness that the misuse of antibiotics could lead to the selection of resistant strains of bacteria is not new and was probably first voiced by Alexander Fleming in a newspaper article in 1945 (New York Times, 1945). The potential at this time for misuse was particularly acute as oral penicillin was available as an over-the-counter medicine in the United States until the middle of

the 1950's (Levy, 1992). Resistance is a particular concern within the hospital environment as increased morbidity (Murray, 1994) can lead to increased length of stay (Holmberg *et al.*, 1987; The Brooklyn Antibiotic Resistance Task Force, 2002). The frequency of use of antibiotics within the hospital environment is much greater than in the community in general and this acts as a powerful driver for the emergence of bacterial resistance in these ecosystems. In addition, the in-patient population may have a compromised ability to challenge infection particularly where it is hospital acquired and this may impact on mortality rates. In a recent study (Garcia-Martin *et al.*, 2001) it was estimated that nosocomial infection may be associated with more than twenty percent of hospital deaths. The adverse effects of antibiotic resistance have a cost to society which has been calculated (Phelps, 1989) in monetary terms to be of the order of $3 billion each year in the United States.

In 1998, the House of Lords Select Committee on Science and Technology published a report (House of Lords, 1998) which detailed the findings of a sub-committee formed to examine antibiotic resistance and the use of antibiotics in medicine in the United Kingdom. The report included descriptions of the use of formularies within hospitals, and the process by which antibiotics are prescribed by junior doctors. The need for Continuing Professional Development and improvements to the undergraduate medical curriculum were highlighted as areas where work was required to improve the level of knowledge of antibiotic prescribing among medical practitioners. The report also covered the use of antibiotics in animals. The importance of infection control was highlighted including the need for improved surveillance. The development of new drugs and

new vaccines was discussed. The report produced fifty-four recommendations. It concluded that there was a lack of data on antimicrobial use in hospitals and that hospitals should install computerised systems for patient specific prescribing. The opening sentence of the conclusions is worth repeating " this enquiry has been an alarming experience, which leaves us convinced that resistance to antibiotics and other infective agents constitutes a major threat to public health, and ought to be recognised as such more widely than it is at present."

The House of Lords Select Committee on Science and Technology published a report (Report of the Select Committee on Science and Technology of the House of Lords, 2001) in March 2001 'Resistance to Antibiotics and other antimicrobial agents' this looked at progress made since the publication of the first report in 1998. Concern was expressed in the report over the time being taken to implement some of the recommendations made in the original report.

The European Society for Clinical Microbiology and Infectious Disease (ESCMID) established a study group on antibiotic policies (ESGAP) which in turn created a number of sub-groups to develop strategy related to the stewardship of antibiotics within European hospitals. ESGAP produced a number of recommendations (Gould, 2001), which include a recommendation that 'measurement of antibiotic consumption should be performed with regular benchmarking of figures and discussion between prescribers, pharmacists and infection specialists.'

In the light of such official concern over the appropriate use of antibiotics, the emergence of resistant strains and the financial impact of the use of antibiotics in secondary care together with the need for improved monitoring, the present study was designed to collect comparative information from a group of hospitals. The intention was to validate an objective measure to compare levels of antibiotic usage within the National Health Service and to determine whether medicines management arrangements within trusts influence antibiotic usage. The antibiotic usage measure was developed by the author in 1998 and has been applied to the usage of quinolone antibiotics in a previous study (Curtis *et al.*, 2001) that was a precursor for this work.

In addition to comparing patterns of use of antibiotics of individual hospitals over time it was planned that specific indicators of bacterial resistance would be applied to these results to establish whether any relationship between them is identifiable. Also, where possible, the influence of the general health status of the study population would be considered using surrogate markers of morbidity. It was anticipated that the benefit of specific medicines management measures within hospitals would be identified as a result of this study and recommendations would be developed would be applicable to hospitals throughout England.

1.2 Regulation, Guidance and Recommendation.

Antibiotics are unique in that their prescription to treat a suspected infection will not only impact upon the responsible pathogen but will also affect the commensal flora present in the individual, potentially resulting in preferential selection for resistant organisms within that host. Additionally, the resistant strains may be disseminated within the community at large through contact between individuals. Such far-reaching consequences are perhaps not at the forefront of the thoughts of the prescriber when confronted with a sick patient either in general practice or on a hospital ward (Metlay *et al.*, 2002). Certainly, issues of inappropriate use and resistance are unlikely to be considered by individuals purchasing antibiotics from a pharmacy without a prescription (in those countries and circumstances where this is permissible). It is estimated (Central Intelligence Agency, 1999) that two thirds of all oral antibiotics used worldwide are obtained without a prescription. Because of the societal consequences a great deal of guidance has been created in an attempt to address issues around the use of antibiotics.

1.2.1 International Guidelines.

The World Health Organisation has produced a strategy (World Health Organization, 2001) which contains proposals to improve access to appropriate antimicrobials, improve the use of antimicrobials, strengthen surveillance, enforce regulation and encourage development of new drugs and vaccines. The strategy sets out recommendations that should be included in individual national chemotherapy guidance in countries around the world.

Usefully, the strategy includes a definition of the appropriate use of antimicrobials as follows "the cost effective use of antimicrobials which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance." This definition succinctly identifies the key issues to be considered when deciding whether or not antibiotics are being used appropriately.

Specific advice is provided for hospitals which addresses the need for effective infection control programmes, monitoring and control of the activities of pharmaceutical companies and empowering Drugs and Therapeutics committees to control antibiotic use. It is recommended that the latter committees produce policies governing the use of antibiotics and include selection of appropriate antibiotics for use within the hospital. A programme of Drug Utilisation Review with feedback to prescribers of the results is needed. This review should include monitoring of both the quantity of antibiotic prescribed together with the indication for antibiotic use. To further this recommendation the use and development of valid indicators of antibiotic use is fundamental, particularly if meaningful comparisons are to be made between hospitals.

As part of the WHO work on antibiotic resistance a great deal of joint work has been carried out with other groups. The Alliance for the Prudent Use of Antibiotics (APUA) has, at the request of WHO, produced a review (Alliance for the Prudent Use of Antibiotics, 2001) of recommendations of various bodies in relation to antibiotic resistance. The review produced a series of recommendations that encompassed the following areas:

- raising awareness of the problems of antibiotic resistance

- improving surveillance of antibiotic resistance
- improved use of antibiotics in humans
- regulation of antibiotic use in animals
- encouragement of new product development
- increased resources to reduce resistance in the developing world
- increased funding for surveillance, education and research

To improve the use of antibiotics in humans a number of recommendations were made which impacted upon hospitals. Of particular interest was the recommendation that each hospital should appoint an antimicrobial resistance monitor. This individual would follow the literature in relation to resistance, analyse local usage data, develop local strategies for control of resistance and work with clinicians in the care of specific patients.

It is proposed additionally, that specific pharmacy usage reports be produced which should express usage as Defined Daily Dose per 1000 beds. The education of hospital staff was also proposed through teaching, problem oriented training sessions and the development of treatment guidelines. The role of the monitor could encompass all of these functions which could in effect be seen as the elements of a job description for a hospital antibiotic pharmacist.

A United States Congressional Advisory Committee report (U.S. Congress, 1995) published in 1995 contained a number of observations relating to the use of antibiotics which included the fact that at any given time in the US twenty-five to thirty-five percent of all hospitalised patients are receiving antibiotics either as

prophylactic or therapeutic treatments. Further, it is stated that up to fifty percent of antibiotic use is inappropriate. The report contains a series of recommendations for US healthcare providers which are pertinent to a wider audience. These include, the establishment of a national surveillance system, co-ordinated infection control, research into antibiotic resistance, control of antibiotic use and empowerment of the Food and Drugs Agency (FDA) to extend market exclusivity to manufacturers who agree to restrictions on the marketing of antibiotics. This report concluded that the effectiveness of currently available antibiotics must be prolonged and that new antibiotics must be developed to treat resistant bacteria. This aim coincided with a period when the development of new antibiotics was at its nadir (Amyes, 2000; Silva and Davies, 2001), though developments in genetics and screening may result in future market launches of new antibiotics. In 2001 in the United States there were 19 antibiotics undergoing clinical trials (Pharmaceutical Researchers and Manufacturers of America, 2000) although with a high rate of attrition only a small proportion are likely to become licensed medicines. There is a growing need for co-operation between governments, the pharmaceutical industry, academics and health care providers to develop innovative antibiotics (Bax, 1997; Turnidge, 1998). Other novel developments include the development of an aminoglycoside molecule which is inactivated by binding in the same way as other aminoglycosides but is capable of detaching the inihibitory molecule and regaining its activity. Also, a cephalosporin molecule is under development which is broken down by sunlight. This ensures that outside the body after excretion the molecule is not found in the environment, particularly the sewage

system where its presence would encourage the development of resistant organisms (Voelker, 2000).

The development of a novel agent ramiplanin has been described (Weissman, 2002). This antibiotic targets a different stage of peptidoglycan construction to established antibiotics such as vancomycin and so there will be no development of cross-resistance between the two agents. It has been anticipated that ramiplanin could be the precursor of a family of analogous antibiotics.

The importance of surveillance of the use of antibiotics and its link with bacterial resistance is included in a number of other major reports (Shlaes *et al.*, 1997; American Society for Microbiology, 1995; Chadwick and Goode, 1997) which highlight the importance of this aspect of monitoring.

The United States Centers for Disease Control (CDC) launched a campaign in 2002 (Stephenson, 2002) to reduce antibiotic resistance in hospitals as their data indicated that each year 2 million patients suffer from nosocomial infections which result in ninety thousand deaths. Seventy percent of bacteria, which cause hospital infections, are resistant to at least one antibiotic. The cycle of infection, use of an antibiotic and emergence of resistance leads to multi-drug resistance. In order to address this the CDC has detailed twelve steps to prevent the development of resistance. The twelve steps are detailed on a laminated card that is being widely distributed throughout hospitals in the United States.

The 'steps' cover the prevention of infection, diagnosis and effective treatment, using antimicrobials wisely, prevention of disease transmission, targeting the

pathogen (using culture and sensitivity results) and treating accordingly. There is also a caution to avoid unnecessary use of vancomycin. Examples of good practice are used, for example, at Cook County Hospital, Chicago, the pharmacy computer prints out a list each day of patients prescribed two or more antibiotics. This enables these patients to be targeted and appropriate treatment prescribed ensuring that there is no duplication in the spectrum of action of the antibiotics prescribed.

1.2.2 European Guidelines.

The Commission of the European Communities has published a strategy document (Commission of the Eurpean Communities, 1.2001) which includes proposals to address collection of data relating to the consumption of antimicrobial agents, prevention of communicable diseases, research and product development and international co-operation. The European Community has supported the European Antimicrobial Resistance Surveillance System (EARSS) that will produce aggregated, comparable data on antimicrobial resistance across Europe. By Summer 2001 eighteen countries had contributed data covering fifty-three percent of their population (range 14-90%). The document includes recognition that antimicrobial consumption must be monitored to enable intervention strategies to be developed and evaluated. It is also recognised that such data is not available in a homogeneous form that may be used to inform policy development.

In a separate document (Commission of the European Communities, 2. 2001) there are proposals concerning the prudent use of antimicrobials in humans. The

document contains a number of proposals that include the collection and analysis of data on antimicrobial usage in hospitals. This would involve pharmacists amongst others in the data collection so that it is possible to link data relating to antimicrobial use with data on the development of resistant pathogens. Recommendations also include the development of guidelines on the prudent use of antimicrobials, the education of healthcare professionals and informing the general public regarding antimicrobials. The European Commission will set up an advisory group to co-ordinate and help member states to address the recommendations in the strategy.

1.2.3 United Kingdom Guidelines.

A Department of Health report (Department of Health UK, 1998) published in 1998 included a series of recommendations for both primary and secondary care in the United Kingdom. These included the development by the National Institute for Clinical Excellence (NICE) of evidence-based national guidelines for the treatment of certain infections, with integration of their use within computerised prescribing decision support systems, as soon as possible. Recommendations were made that studies should be undertaken in selected hospitals to test prototype systems.

Also, it was recommended that local prescribing information should be in accordance with that contained in the British National Formulary (BNF). The report also recommended the formation of a national steering group to develop a national strategy to counter the development of antibiotic resistance.

Subsequently, a national action plan and strategy has been published (Department of Health, 2000) that contains two aims

- to minimise the morbidity and mortality that is due to antimicrobial infection
- to maintain the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections in man and animals

The strategy contains three elements surveillance, prudent antimicrobial use and infection control.

1.2.4 Antibiotic Surveillance

With regard to setting up effective surveillance to monitor antimicrobial use it is acknowledged that data on patterns of use and antimicrobial resistance will need to be collected. In order to address this issue, data collection systems will require development and evaluation. It is suggested that this will be achieved through elements included in the NHS Health Information Strategy (NHS Executive, 1998). The prudent use of antimicrobials will be encouraged by professional education, prescribing support, (such as electronic prescribing in hospitals), and the use of clinical governance infrastructure to support the monitoring and audit of prescribing.

Antibiotic resistance surveillance was described in 1992 (Neu *et al.*, 1992) as follows 'There are no reliable data in this area- simply fragments of information and anecdotes that we use to draw an overall picture'. In the ten years since this paper was published the need for greater activity has been highlighted in all of

the international and national guidance which has been published relating to antimicrobial resistance.

To carry out large-scale surveillance programmes it is important to define and standardise the information that will be collected and to continue with the programme over a number of years so that meaningful trends can be identified and links between resistance and antibiotic use established (Livermore *et al.*, 1998). In order to promote ownership of any surveillance programme it is important that data is fed back to participants so that local decisions can be taken based on the results. It is important to realise at the outset that surveillance data is based on the percentage of patients who have been prescribed an antibiotic that have a pathological specimen investigated by the microbiological culture and sensitivity. It has been reported (MacGowan *et al.*, 1998) that as few as 3% of patients visiting a doctor with a respiratory tract infection have a sample collected. There may also be a sampling bias where specimens are more likely to be submitted for laboratory investigation from patients who have not responded to current therapy.

When results are produced from a surveillance programme it is important to decide what outcomes from the data are expected, since data acquisition without subsequent interpretation with change in practice is a futile exercise. If data from surveillance shows that resistance to specific antibiotics is increasing then this should be used as a trigger to change prescribing habits. As influencing prescribing is the raison-d'etre for carrying out surveillance (Masterton, 2000; Livermore *et al.*, 1988), it should then be possible to demonstrate that any change

in prescribing has produced positive outcomes on local resistance patterns. It is also vital to ensure that results of practice research are communicated to junior doctors in hospitals who are the most prevalent prescribers of medicines in hospitals.

It is assumed that extensive surveillance systems will be expensive to administer but with the development of information technology data collection should be facilitated. There is little comparative data collected at a national level in England. The PHLS (Castle *et al.*, 1977) survey of hospital acquired bacteraemia is one programme which is on-going and the data from this have been extracted for each of the hospitals in this study.

This surveillance programme has collected data from over one million patients in sixty-one hospitals which showed 3,824 episodes of bacteraemia at an incidence of 3.6 patients per 1000 admissions. The incidence of bacteraemia showed great variability between hospitals and even between specialties within hospitals. The commonest cause of hospital-acquired bacteraemia was from central IV catheters. Microbiological isolates demonstrated that almost half of *Staphylococcus aureus* were resistant to methicillin and ten percent of *enterococci* were vancomycin resistant. A trend towards Gram positive organisms causing more bacteraemias than Gram negative species has taken place over the last few decades (Glauser *et al.*, 1997) and this knowledge guides clinicians when making empirical choices of antibiotic in these situations. This work also helps to predict future trends (Johnson *et al.*, 2001). High rates of resistance to ceftazidime and ciprofloxacin were found amongst Gram- negative

organisms. It is only from large-scale surveillance of this type that robust results can be obtained.

The Alexander Project (Adam, 2002) a multinational project was set up in 1992 to collect data on the susceptibility of community acquired lower respiratory tract pathogens to various antibiotics. The results have shown over time increasing resistance of *S.pneumoniae* to penicillins and macrolides particularly in France and Spain.

A related programme (Felmingham, 2002), the PROTEKT study, has also been set up to collect data on the susceptibility of organisms which cause respiratory tract infection. This is a global programme involving centres in twenty-six countries. A novel feature of the PROTEKT study is that local susceptibility data can be downloaded from the Internet onto hand-held computer devices at the bedside, in order to support prescribing decision making.

Surveillance funded by governments can be carried out on a large scale, for example the European Commission funds the European Antimicrobial Resistance Surveillance System (EARSS) which monitors a number of organisms including nosocomial *Staphylococcus aureus* incidence across Europe. The largest and oldest of these schemes is that organised by the Centers for Disease control (CDC) in the United States of America (Emori *et al.*, 1991) which collects data that includes resistance rates in approximately two hundred American hospitals.

Hospital acquired infections have a devastating effect on individuals and also have been estimated to cost the NHS in England nearly £1 Billion per year (Plowman *et al.*, 2000).

The pharmaceutical industry has funded a number of international surveillance programmes. These include MYSTIC (Turner, 2000; Meropenem Yearly Susceptibility Test Information Collection), which includes susceptibility to meropenem and five other antibacterials and is funded by AstraZeneca. Also, the Alexander Project (Felmingham and Gruneberg, 1996), which is funded by GlaxoSmithKline and is following susceptibility trends for twenty-two antibacterials to a number of common respiratory tract isolates. Also, the Antimicrobial Resistance Management (ARM) database (Gums, 2001) developed in conjunction with Roche provides customised resistance data to hospitals. This database was set up in 1990 and covers 103 hospitals in the United States. It allows health care professionals to compare resistance of specific micro-organisms to antibiotics in various regions of the United States. These studies being funded by the pharmaceutical industry bring into focus issues around the ownership of results and how data may be interpreted by these companies.

It is important that good quality surveillance is carried out at a level where the results can be meaningfully applied to local situations yet also inform debate at national and international level relating to patterns of resistance and antibiotic prescribing trends. It is equally important that it needs to be agreed who is to

fund these programmes and ensure that actions are taken when results have been obtained.

1.3. Measures available for quantification of drug usage data.

1.3.1 General properties.

The purpose of any indicator of prescribing is to enable comparisons to be made over time. The comparison may be between individual prescribers, wards, specialties, hospitals or geographical groups of hospitals. Measures are not definitive but act as a focus for the commencement of review and should act as a stimulus for change. They must be based on consensus and be relevant to clinical practice. Any effective measure should be capable of demonstrating changes in practice and be able to discriminate between different prescribing behaviours. The majority of work in this area has been carried out in the primary care sector as a response to the need for measures to support decisions made in budget setting and monitoring of general practitioner prescribing budgets (Leach and Wakeman, 1999; Klepping, 2000; Wilcock, 2001).

The development of qualitative measures of prescribing by general practitioners has been difficult. With the influence of clinical governance on primary care the emphasis on cost-effective prescribing within a framework of clinical effectiveness will continue to grow and highlights the need for more work in this area. A report (Bishop, 2001) on the development of rational prescribing indicators (RPI) illustrates the potential in this field. Using data from the Prescribing Information System for Scotland (PRISMS) a number of measures were trialled. These included data on a category of drugs whose use was 'often presumptive', that is the diagnosis was presumptive and the drug was being used as a therapeutic 'trial' a key example of this type of medicine are antibiotics. High levels of prescribing in this category led to a negative RPI score. Antibiotic

prescribing also featured in three other categories that contributed towards the calculation of the RPI. These included generic prescribing rate, level of adherence to a formulary and cost per item. The study concluded that although the RPI was not robust it did enable the measurement of rational prescribing, and acted as a lever for change.

1.3.2 Cost

The most basic measure to quantify drug usage is cost. The expenditure on medicines can be used as an indicator to compare expenditure per head of population in different countries. This type of data requires careful interpretation as the variation in prices between countries and in the relationship with income levels per head of population must be considered.

1.3.3 The Item.

In the Primary Care sector in the United Kingdom the 'item' has been used as a measure of the volume of drug usage. The use of the item originates from the Prescription Pricing Authority reports on prescribing trends. These prescribing analysis and cost (PACT) data reports use the item as a measure of prescribing volume. This measure may be used to produce an average cost per item for an individual prescriber, practice or Primary Care Group. It can also provide comparative data relating to the number of items prescribed per 1000 patients in a particular period of time. A study (Bogle and Harris, 1994) to evaluate the validity of the item concluded that it was not a consistent measure. This work compared data from a number of selected practices and found a wide variation between practices in the quantity of medicine prescribed per item. It was felt that

this inconsistency is a serious shortcoming of the item as a measure for comparing prescribing volume of medicines.

1.3.4 The Therapeutic Course.

The therapeutic course (TC) has been proposed (Resi *et al.*, 2001) as a complementary measure to the Defined Daily Dose (DDD) for quantifying the use of a particular drug in a given population. It was felt that the DDD may not be an accurate measure, owing to the rapid turnover of patients prescribed antibiotics, as the course length is normally very brief. The therapeutic course could offer additional insight into the prevalence of use of a medicine. The study carried out in Italy surveyed antibiotic prescribing during 1998. Therapy in which antibacterials were prescribed for a period of ten days were considered to be one therapeutic course. The DDD per 1000 inhabitants was compared with the TC per 1000 inhabitants. The TC has deficiencies in that a three-day course of a medicine to treat a urinary tract infection would not be counted as a course and long-term antibiotic treatments are counted as multiple courses. So this measure in its suggested form does not appear to offer any advantages over the accepted ATC/DDD methodology.

1.3.5 Average Daily Quantity (ADQ).

The ADQ was developed in 1994 for use in the United Kingdom. The ADQ is not a proposed dose, but a unit for comparing prescribing volume (Whiteside *et al.*, 2001). The ADQ was calculated from a number of parameters that include the Defined daily Dose (DDD), Prescribed Daily Dose (PDD), recommendations on maintenance dosage in the British National Formulary (BNF) and data from

the Prescription Pricing Authority. These sources were used to determine which dosage should be prescribed and which dosage is currently being prescribed. Data on therapeutic equivalence was consulted to inform decisions made on doses.

The PDD was established by collecting data from 1250 general practices to establish a mean value. Therefore within this parameter there could have been a great deal of variation. The data from the PPA provided the number of items dispensed over time for specific quantities of particular medicines. It was felt that the ADQ would be an aid for primary care Pharmaceutical Advisers and other healthcare professionals when discussing prescribing volume with general practitioners. There are potential limitations in use of the ADQ in that it is not internationally applicable, and it may be that its development is a reflection of a parochial attitude on the part of some United Kingdom practitioners.

1.3.6 Age-sex, temporary resident originated prescribing units (ASTRO-PU).

Prescribing Units (PU) were introduced in 1983 to enable prescribing analysis to take account of age. Each person under 65 years old was counted as one PU and any person older than 65 years was counted as three PU. In 1993 the ASTRO-PU was developed by the prescribing research Unit at Leeds (Roberts and Harris,1993). The ASTRO-PU is made up of ten age-related bands for each sex, for use as a denominator to compare prescribing costs between practices. The measure was revised in 1997 creating the ASTRO97-PU. This was to take account of changes in prescribing habits such as the introduction of new

medicines and the withdrawal of others. The ASTRO-PU is of use because it takes into account the age structure of the population being studied.

1.3.7 The Specific therapeutic group age-sex related prescribing unit (STAR-PU).

The STAR-PU system was developed by the Prescribing Support Unit at Leeds (Lloyd *et al.*, 1995) to enable comparisons to be made between specific therapeutic groups e.g. antibiotics. This measure was reviewed in 1997 to produce STAR97-PU to take account of developments in prescribing. This measure has been developed for most commonly prescribed therapeutic classes of medicines. Work has been completed (Watson *et al.*, 2000) using the number of Defined daily Doses (DDD) per 1000 STAR-PU and also the cost per 1000 STAR-PU in order to compare the effectiveness of various prescribing interventions in Primary Care.

1.3.8 MEMPHIS indicators.

These indicators were published by the Prescription Pricing Authority, and data is supplied to Health Authority Pharmaceutical Advisers. Amongst the indicators, which provide information on prescribing of generic products, inhaled corticosteroids and benzodiazepines, there are two measures relating to the use of antibacterials. These are firstly, the number of items per STAR-PU for antibacterials, and secondly, the Net Ingredient Cost (NIC) per item for antibacterials. These two measures enable comparisons to be made of antibacterial prescribing between General Practitioners.

1.3.9 Low Income Scheme Index (LISI).

The LISI (Lloyd *et al.*, 1995) is a measure of deprivation based on the number of prescription exemption claims made on the grounds of low income. The index is calculated from a sample of 5% of prescriptions submitted to the Prescription Pricing Authority. Use of the index enables a determination to be made of local factors in the population, which may predispose to a greater or lesser use of specific medicines.

1.3.10 The Anatomical Therapeutic Chemical (ATC), and Defined Daily Dose (DDD) system.

The need for an international classification system for drugs has been recognised for many years (Capella, 1993). It is a pre-requisite for drug utilisation review (DUR), particularly where comparisons need to be made between different organisations. The Anatomical Therapeutic Chemical System (ATC), was developed by the Norwegian Medicinal Depot, in Oslo, by modification of an existing system that had been used by pharmaceutical market researchers in Europe. In addition to a robust classification system it was necessary to develop a unit of measurement. The Defined Daily dose (DDD) was developed, also by the Norwegian Medicinal Depot as a unit of measurement for use in drug utilisation studies. The ATC/DDD methodology, was recommended for international drug utilisation studies by the World Health Organisation (WHO) in 1981. In order to ensure that this methodology was widely used the WHO established the WHO Collaborating Centre for Drug Statistics Methodology in 1982, and in 1996 this centre was directly linked to the WHO headquarters in Geneva. The purpose of

the ATC/DDD system is to act as a tool for drug utilisation research so that the quality of drug usage will improve.

The ATC classification system is structured so that drugs are divided into groups according to the system or organ on which they act and their chemical, pharmacological and therapeutic properties. The classification has five levels, level one consists of fourteen main anatomical groups, level two and level three are pharmacological/therapeutic main and sub-groupings. Level four is the pharmacological/therapeutic/chemical sub-group, while level five is the individual chemical entity. The international non-proprietary names (INN) are the preferred nomenclature. New entries to the ATC system can be added by request of manufacturers, researchers or regulatory agencies. Amendments to the classification of a medicine may be made should its principal indication change. At this time the DDD would also be reviewed.

The DDD is defined (United Kingdom Drug Utilisation Research Group, 2000) as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'. A DDD is only assigned when a compound has been given an ATC code. All of the ATC codes and DDD are published in the ATC Index with DDDs (WHO Collaborating Centre for Drug Statistics Methodology, 1999) The DDD is not a reflection of the prescribed or recommended daily dose. It represents a unit of measurement to enable researchers to identify trends in consumption of medicines and to compare the exposure to specific medicines of population groups. The DDD is a compromise in that it is based on a review of doses used in a variety of countries. The DDD for a medicine is normally reviewed after three years, following this it will normally remain unchanged for

at least five years. This is essential if longitudinal studies are to be carried out over a number of years. The DDD when associated will normally be associated with a denominator to correct for workload variations. For hospital in-patients the number of DDD per 100 beddays is normally used (Hekster *et al.*, 1982; Natsch *et al.*, 1998; Ronning *et al.*, 2000; Hutchinson *et al.*, 2004). Whilst for out-patients and populations in general the number of DDD per 1000 patient days or inhabitants is usually calculated.

A review of the DDD system (Wertheimer, 1986) compared the approach of Europeans to drug utilisation review and compared this to the North American approach which has focussed more on review of individual prescribers and individual drug regimens in order to optimise patient treatments. It concluded that the DDD system would serve as a valuable additional tool for drug utilisation studies. A study carried out to evaluate the DDD methodology (Wessling and Boethius, 1990) concluded that it was a valuable first step in measuring total drug use in a population, but that for more precise estimates of drug use, other techniques would also be required.

1.3.11 Minimum Marketed Dose (MMD).

The MMD (Merlo *et al.*, 1996) is the minimum dose that will produce a desired therapeutic effect. This is normally the minimum dose marketed by the manufacturer. The MMD reflects a single dose of the product. A weakness of the MMD is that different manufacturers of the same drug may market different minimum doses, thus causing confusion.

1.3.12 Average Daily Dose (ADD).

The ADD also known as the German Drug Index has been defined by pharmacologists in the German Scientific Institute of General Health Insurance. It is very similar to the DDD but is calculated using parameters based on German healthcare practices.

1.3.13 Qualitative measures of usage.

Qualitative measures of antibiotic use can focus on the appropriateness of a product for a specific indication, cost-effectiveness, measures of resistance locally, or trends reflecting an increase or decrease. The most important measure of clinical outcome is whether the patient recovered from the infection. The development and use of quality indicators enable an objective view to be taken on the appropriateness of antibiotic therapy (Kunkel, 1998). It is possible to integrate monitoring of such indicators into a hospital's clinical governance programme (Scally and Donaldson, 1998). Some possible measures have been suggested (Nathwani *et al.*, 2001) which relate to outcome, safety, appropriateness and competence. For instance, it is possible to monitor the percentage of patients taking antibiotics who require a change in treatment owing to an adverse-effect or clinical failure of treatment. Also, where educational sessions are held, the percentage of medical staff attending may serve as a quality indicator.

In most hospitals actively operating an antibiotic prescribing policy it is relatively easy to audit compliance with its recommendations. Such work requires resource in terms of staff time to carry out the audit and develop

recommendations from the findings. For this reason it may be cost-effective to focus on specific treatments which observation has shown are being used inappropriately.

1.4. Bacterial Resistance.

1.4.1 Background

Bacteria have evolved a variety of strategies (Levy, 1982; Hart, 1998; Hawkey, 1998) to cope with environmental stresses which include encounters with antibiotic molecules. This may act as a stimulus for selection (Levy, 2001) of those organisms that have the genetic makeup to aid them in surviving the assault from the antibiotic. Other variables associated with the use of antibiotics which impact on the selection of resistance include the dose used, the duration of treatment and the penetration of the antibiotic into various parts of the body e.g. skin, cerebro-spinal fluid, kidneys. Individual patient factors may also play a part. These can include an individual's ability to absorb, metabolise and excrete the antibiotic that will impact on concentrations in various body compartments and tissues. The composition of the resident flora may also influence the interaction between the antibiotic and the pathogen which is competing with the patient's flora for a niche.

The importance of infection control measures to reduce cross-infection cannot be overstated and its contribution to improving antimicrobial resistance has been discussed (Struelens, 1998; Levin and Andreasen, 1999; Levin, 2001). Within hospitals the incidence of nosocomial infection is related to intensity of usage of antibiotics together with hygiene factors such as proximity of patients and hand-washing by medical and nursing staff. In fact it is thought that these factors are of equal weight in promoting the development of resistant strains (Lipsitch *et al.*, 2000).

The link between the use of antibiotics and the development of resistance has been demonstrated in a number of studies (McGowan, 1983; Courcol *et al.*, 1989; Conus and Francioli, 1992; Gaynes and Monnet, 1997; Swartz, 1997; Austin *et al.*, 1999; Magee *et al.*, 1999; Lopez-Lozano *et al.*, 2000; Lang *et al.*, 2001; Milatovic and Braveny, 1987) and these findings underpin the efforts to promote rational us of antmicrobials.

There are a number of targets within bacteria and the acquisition of genes which encode for changed molecular structure in the target can lead to resistance to specific antibiotic agents. This can include changes in cell wall structure that reduces permeability to penicillins (Nikaido, 1989). Changes of a single amino acid in a ribosomal protein can produce resistance to streptomycin and over expression of a protein involved in the efflux pump in S.pneumoniae is a component of resistance against fluoroquinolones (Zeller *et al.*,1997).

The genome of bacteria has a number of mobile elements which are not essential to the survival of the bacterium but which are additional elements that enable adaptation to new conditions and these include plasmids and transposons (Hughes and Andersson, 2001).

1.4.2 Plasmids

Bacteria possess a single chromosome but this is not always sufficient to provide the resilience to cope with changes in the environment. The bacterial cell also contains a number of circular pieces of DNA which each carry a number of additional genes. These DNA fragments are termed plasmids and carry genetic

information that may confer traits that can have a beneficial impact on the survival of the cell. These traits may include the ability to accommodate changes in temperature, or the ability to adhere to the cells that line the gastrointestinal tract. They may also confer the ability to resist the action of an antibiotic. Within the host bacterial cell the plasmids interact with each other and are able to exchange pieces of DNA between themselves. Such exchange may involve segments of DNA that confer antibiotic resistance traits. Plasmids are not able to survive independently outside of the host bacterial cell, but may be exchanged when cells come into contact when conjugation occurs. In this dynamic environment where plasmids are combining and exchanging material it is possible for multiple resistance factors to a number of antibiotics to emerge and spread. Plasmids may be exchanged between widely different species of bacteria (Tauxe *et al.*, 1989) therefore this process can act as a driver for dissemination of antibiotic resistance.

The genes that confer resistance to antibiotics have not been created recently as a result of the introduction of penicillin and other antibiotics into clinical use. They have developed as part of the continuing evolutionary process to protect bacteria from antibiotic substances that occur naturally. The widespread use of antibiotics in both agriculture and in medical practice has introduced an additional antibiotic load into the environment on a previously unseen scale and has thus created a selection pressure for the emergence of bacteria which carry resistance genes (so called R factors).

Interestingly, the possession of resistance genes must also confer some disadvantages for the survival of organisms which carry them otherwise those

organisms which don't carry them would not have survived. The spread of resistance genes has been expedited by the change in the environment where antibiotics are more widespread. Our use of antibiotics has introduced an evolutionary driver into what was a finely balanced system.

1.4.3 Transposons.

The transfer of resistance factors may also be accomplished by small pieces of DNA that are smaller than plasmids and are termed transposons. These elements are capable of moving from one larger piece of DNA in a chromosome or a plasmid to another. So they have the ability to be transferred by normal cell division processes or by conjugative processes.

Transfer of resistance genes can occur via bacteriophages when they attach to a bacterial cell and inject their DNA. This DNA can pick up genetic material from transposons that are subsequently able to transfer to further cells via the bacteriophage. So, there are a number of related methods for the transfer of resistance factors to be exchanged and disseminated within the environment.

1.4.4 Mutation

Evolutionary processes can result in the spontaneous mutation of genes which produce a micro-organism that is capable of counteracting the effects of a specific antibiotic. This process produced methicillin-resistant *staphylococci* (Hiramatsu *et al.*, 2001) which has spread around the world. The mutation enables the cell wall binding sites to alter so that binding sites are altered (Hand, 2000) and methicillin is unable to bind to the sites therefore the bacterial cell

becomes resistant to methicillin. It has been proposed (Blazquez *et al.*, 2002) that antibiotics can increase the mutation rate within bacterial populations. This would increase the likelihood of the development of antibiotic resistance through random change.

Resistance to antibiotics acquired by bacteria has a cost to the organism as it is capable of producing a protein that non-resistant bacteria do not produce. This cost may be evidenced in reduced virulence or reduced fitness shown by reduced growth and survival rates or reduced competitive abilities. These complex issues will play a role in the stability of resistance and whether it can be reversed (Hughes and Andersson, 2001).

When confronted with antibiotics bacteria have a range of options for responding to their effects (Levy, 1994). The pressures created from the use of antibiotics encourage the emergence and persistence of resistance and it is extremely difficult to reverse this situation so that bacteria regain their sensitivity to antibiotics (Barbosa and Levy, 2000). A strategy is required where we take a balanced overview of all bacteria so that we recognise that pathogenic species require treatment but that we should endeavour to avoid harming commensal species. This will reduce resistance problems as the commensals are able to out-compete resistant strains in the absence of antibiotics (Levy, 2002). A degree of respect for the microbial world will aid society in controlling the development of bacterial resistance to antibiotics.

1.4.5 Costs of resistance

Some work has been carried out to investigate the pharmaco-economics of bacterial resistance to antibiotics (Coast *et al.*, 1996) and economic appraisal of antimicrobials is recommended. The economic perspective of antibiotic resistance has been examined (Smith and Coast, 1998) and novel concepts proposed. Looking at the issue from an economists viewpoint it can be assumed that reducing antimicrobial resistance will have a benefit to the whole of society. Options to achieve these aims include regulations, charging and the use of permits. The use of permits in primary care is a novel proposal. Permits are already in use in other industries, for example the Fishing industry where fish catch quotas have been allocated. Allocations may be on the basis of land area or population or calculations of sustainable catches. It would be possible to set up a permit system for physicians to prescribe a specific number of antibiotics during a specified time period. The quota could be calculated by reference to practice population and take account of morbidity. Prescribers already work within a fixed prescribing budget and could purchase additional permits from this budget. The decision to do this would be explicit as the funds to purchase the permits would then not be available to purchase other medicines. Such a system could be monitored and enforced by the Prescription Pricing Agency (PPA). Potential drawbacks include the cost associated with maintaining the permit system and also acceptance by primary care physicians.

1.5. Strategies to influence the use of antibiotics.

1.5.1 Educational measures.

The international and national guidance concerning the cost-effective use of antibiotics places great emphasis on the use of education of prescribers and also the public, as a tool to ensure that antibiotics are used in a cost-effective manner. The results of work carried out to evaluate the impact of education have been equivocal as to its long-term impact on prescribing behaviour (Johnston *et al.*, 1992; Hogerzeil, 1995; Rifenburg *et al.*, 1996; Jakrawatana and Yingsaeree, 1997; Belongia and Schwartz, 1998; Davis *et al.*, 1999; Zwar *et al.*, 2002; John and Fishman, 1997; Dartnell and Korman, 2002). The development of clinical governance with its emphasis on Continuing Professional Development (CPD) may act as a stimulus for ensuring that medical staff remain up to date in the rational use of antibiotics and the funding of educational programmes has been recommended by a European study group (Keuleyan and Gould, 2001).

The rapid turnover of junior medical staff in the UK can reduce the impact of educational programmes (Swindell *et al.*, 1983). Results of long-term studies can be confounded owing to external factors. For example the greater awareness of and participation in, continuing education related to prescribing by clinicians can have a supplementary effect on more focussed educational programmes aimed at optimising antibiotic prescription.

A study (Spector and Heller, 1978) carried out over a seven-month period during 1976-77 examined the impact of an education programme on the use of amikacin in a US hospital. The programme consisted of lectures to medical staff given by

specialist physicians that were supplemented by a lead article in an internal pharmacy bulletin. The use of amikacin was evaluated according to agreed criteria, which included appropriateness of use, acceptability of dose, precautions taken regarding toxicity, evaluation of the clinical outcome and whether consultation took place with colleagues from infectious disease or clinical pharmacology departments. During the study period seventeen patients were prescribed amikacin, and the results indicated that it had been prescribed rationally. It was concluded that the education programme had been successful and that this was an effective alternative to antibiotic restriction. Although this conclusion is based on a study of a very small number of patients.

An indication of the prevailing culture at the time of the above study, could be gained from the issues discussed regarding the restriction of the availability of medicines. Specifically, it was perceived that large amounts of professional time and associated cost would be required to administer any restriction system. The limitation of clinical freedom with the potential for denial of life-saving treatment was discussed. In addition, it was argued that lack of restriction was beneficial as physicians would educate themselves and become experienced users of new medicines, subsequently being able to use them appropriately.

The impact of educational outreach has been studied (Avorn and Soumerai,1983) on a population of 435 prescribers. The physicians were divided into three groups. One group acted as a control and received no intervention, a second group received printed educational material by post, while the third group received the printed material and an educational visit from a clinical pharmacist.

Evaluation of the prescribing of the group receiving the educational visit found that their prescribing of the drugs targeted (oral cephalosporin, propoxyphene and vasodilators) had reduced by 14 percent overall compared to the controls. The effect was sustained for an observed period of nine months and importantly there was no compensatory increase in the use of alternative drugs. It was concluded that this type of educational visit might be a cost-effective way to reduce unnecessary expenditure and improve the quality of drug use.

Given the plethora of published guidance available concerning the use of antibiotics it is likely that medical staff are aware of the dangers of overuse. Therefore, providing information alone is likely to be insufficient to change clinical practice. More sophisticated educational strategies are required. These strategies could include the use of evidence based medicine guidelines for treatment (Bisno *et al.*, 1997) which appear particularly influential when produced by professional bodies.

Reviews (Davis et al., 1995; Davis et al., 1999) of the impact of Continuing Medical Education (CME) have been carried out in order to interpret whether this activity changed physician behaviour or outcomes in healthcare. One review identified sixty-four published studies of which fourteen met the criteria for the review. It was concluded that didactic sessions did not change performance but that interactive CME that enhanced participation and provided the opportunity to practice skills could change professional practice. The greater impact of interactive hands-on workshops over didactic lectures has been discussed by other workers (Sbarbaro, 2001). The lessons from these reviews should be noted

when planning educational interventions (such as workshops or conferences) to influence prescribers' use of antibiotics. This contrasts with the views of physicians when surveyed (Brown *et al.*, 2001) as to their preferred method of receiving CME. It was found that 87% preferred to read journal articles. It may be that it is perceived as less taxing to read an article in a journal rather than become involved in an interactive workshop.

The impact of targeting senior members of the medical staff in an institution was demonstrated (Everitt *et al.*, 1990) in a study which used an educational intervention (face to face educational sessions) aimed at this influential group and coupled it with an antibiotic order form which contained reminders of the intended educational message. The results in this study showed a long lasting change in practice from one antibiotic (cefoxitin) to another (cefazolin) when used in prophylaxis during caesarian section. Other workers (Weller, 2002) have shown persistent improvements in the prescribing of intravenous ciprofloxacin over a sustained period, following an educational letter directed at clinical directors, as part of a broader programme to reduce the use of this product. These studies demonstrate the value of careful selection of the target audience when planning an educational programme.

A comparison (Goldwater *et al.*, 2001) of the effectiveness of an educational intervention and a therapeutic interchange over a fourteen month period at four hospitals provided results which show the limitations of education as an agent for change. The therapeutic interchange involved pharmacists changing prescriptions for ciprofloxacin to levofloxacin and was found to have been effective in ninety-

seven percent of patients. The educational strategy consisted of a programme to influence prescribers to use levofloxacin instead of ciprofloxacin. This was found to be successful in forty-three percent of patients. The programme consisted of the use of a newsletter, education sessions presented during ward rounds and at department meetings targeting prescribers. An on-going element of the strategy was the use of "Dear Doctor" letters that were placed in the patients notes whenever ciprofloxacin was prescribed. The letter outlined the benefits of switching to levofloxacin. It was concluded that a therapeutic interchange programme was more successful than an educational programme.

Work in a large University hospital in Holland (Gyssens *et al.*, 1997) evaluated the effectiveness of an education programme together with an antibiotic order form on the quality of antimicrobial drug use. A quality-of-use study was conducted over a four-week period, this was followed by a programme of prescriber education and the introduction of an antibiotic order form. Four years later an identical quality-of-use survey was conducted. The quantity of antibiotic therapy prescribed had increased from 59.8 to 72.6 DDD per 100 beddays. The number of antibiotic prescriptions deemed to be appropriate rose from 40% to 53%, with those definitely inappropriate reducing from 13% to 9%. The use of the antibiotic order forms was felt to be successful as they were used on a voluntary basis for seventy-seven percent of cases. It was felt that the order forms were useful for surveillance of antibiotic usage. The educational strategy had been successful as the quality of prescribing was shown to have improved.

The greater impact of using a control strategy, such as a pre-printed antibiotic order form over a simple educational strategy, such as an antibiotic handbook has been demonstrated in a Canadian study (Girotti *et al.*, 1990) which demonstrated that a handbook changed prescibing conforming to recommended regimens from 11% to 18% whilst the order form increased compliance with recommendations from 17% to 78%.

Measurable changes in antibiotic usage were demonstrated (Jones *et al.*, 1977) in a study carried out to evaluate the effects of an educational programme. The study consisted of two, six-week surveys conducted six months apart. During the interval an education programme, consisting of lectures to medical staff was delivered. The lectures included an analysis of prescribing errors related to antibiotic prescribing, with information on alternative treatments for specific indications. Emphasis was placed on appropriate indications for prophylactic prescribing of antibiotics. It was found that costs arising from the unjustified use of antibiotics decreased and that there was a decrease in the inappropriate use of antibiotic prophylaxis. However, fifty-five percent of the prophylactic antibiotic treatments were still felt to be inappropriate.

It was concluded that the educational strategy had had a minimal effect. In order to improve the impact of such a strategy it should be designed not around cost-reduction but should be focussed on the problems faced by the prescriber in decision-making. This could be linked to a system of peer review of junior medical staff prescribing carried out by consultant staff. However, the use of peer review and quality management for implementing guidelines has been

demonstrated to have minimal effectiveness in another study (Kritchevsky and Simmons, 1994) carried out to evaluate measures that might be used to improve antibiotic prescribing in hospitals.

If education relating to effective prescribing is to be effective it should perhaps commence during the medical undergraduate programme. A study (de Vries *et al.*, 1995) carried out by the World Health Organisation (WHO) evaluated the impact of a training course delivered to medical undergraduates in seven medical schools in various countries of the world. The course involved training based on a WHO manual on the principles of rational prescribing. Students' problem solving skills were evaluated before and after the training, and their retention of the skills was evident six months after the training had been completed. Use of the problem solving skills was developed in association with their development of a personal list of drugs for specific indications. This would enable undergraduates to gain an in-depth knowledge of a small number of medicines. The results demonstrated that teaching of medical students should be re-oriented and that a problem solving approach adopted. In detail the elements of the training involved definition of the patient's problem, specification of the treatment objective, verifying the suitability of a chosen drug and then choosing a treatment for the individual patient. The use of this rational prescribing approach with antibiotics would enhance their use in all sectors of healthcare.

A survey (Kerr *et al.*, 2001) of seventeen undergraduate medical schools in the United Kingdom found that the contact time allocated for the teaching of the rational use of antibiotics varied from half an hour to twenty-two hours. The

teaching was mainly delivered via lectures, in some cases these were supplemented by problem-based learning exercises. There is a need for the development of core curricula for teaching the appropriate use of antibacterials so that undergraduate training on this topic is consistent.

It must be borne in mind that the pharmaceutical industry is a major provider of education concerning the use of medicines to medical staff. Prescribers would be thought to be a sophisticated audience for such training and should be capable of identifying and critically rejecting any bias in content. The pharmaceutical industry has much to gain from being seen as a provider of unbiased education on the appropriate use of its products. Specifically this is true with antibiotics as inappropriate use could render a product less effective in the clinical environment. A reduction in effectiveness of a medicine might potentially leading to a reduction in use. Therefore it is in the industry's interest to encourage informed use of the products that they have spent large sums of money to develop.

The techniques used by the pharmaceutical industry to change prescriber behaviour have been reviewed (Soumerai and Avorn, 1990) and it was observed that as the industry invests a large amount of money in this activity, it must be viewed as something which is cost-effective and which achieves results. A presentation (Armstrong and Kunz, 2001) by an Executive Vice-President of Bayer at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy in 2000 outlined the view that it is in the interest of the pharmaceutical industry that antibiotics are used appropriately to preserve their

benefit for as long as possible so that they have an active product to sell. Methods of ensuring that this goal is met include education of physicians and also patients.

The pharmaceutical industry can also contribute to improved antibiotic use by ensuring that the Summary of Product Characteristics (SPC) contains appropriate information for prescribers (Schlemmer, 2001). The SPC can be viewed as an educative document and should inform prescribers of the licensed indications for the antibiotic together with the recommended dose and duration of treatment and the spectrum of activity. This should promote correct use of the antibiotic.

The role of the pharmaceutical industry in containing development of antimicrobial resistance has been documented in a position paper formulated by the European pharmaceutical industry (European Federation of Pharmaceutical Industries and Associations, 2001). The value of on-going research and development in producing innovative new antibiotics is recognised, as is joint work with regulatory bodies to ensure that product labelling and package information are instructive to users. The weakness of current surveillance activities will require concerted corrective action and the need for a Pan-European surveillance initiative was discussed.

A review (Soumerai and Avorn, 1984) of cost-containment measures in hospitals was carried out to compare the effectiveness of various educational strategies. It was concluded that the use of bulletins and other internal publications had little impact on prescribing habits. There were ambiguous results from group

education, through lectures, ward rounds and discussions of audit results. The use of clinical pharmacists to deliver outreach educational programmes did improve prescribing. This was supported by the benefits shown from face-to-face educational contact. The pharmaceutical industry use this method linked with educational material as the basis for influencing the behaviour of medical staff by their representatives.

Education has benefits in that it can improve prescribers' decision-making skills and ability to select the appropriate antibiotic for a specific indication. In so doing they are ensuring that antibacterials remain effective in the future. Strategies used must be multi-faceted and repeated regularly as the rapid turnover in junior medical staff will ensure that any learning outcomes will be rapidly diluted. So, a single lecture at induction of a medical position would be insufficient: key messages must be augmented by written material and regular educational sessions which are of an interactive nature. To maximise impact, educational process should be delivered by pharmacists, microbiologists, infection control staff or other healthcare professionals, in order that the concept of appropriate use of antibiotic therapy is embedded in the culture of a hospital. It is only when junior doctors and other medical staff are working in an environment where this is practiced that quality of prescribing of antibiotics will become evidence based.

Patient pressure exerted on medical staff to prescribe an antibiotic can lead to unnecessary prescribing and therefore, education of the public has been recommended (Macfarlane *et al.*, 1997; Little *et al.*, 1997; Webb and Lloyd,

1994; Bauchner *et al.*, 1999; Barden *et al.*, 1998). Work has been carried out (Macfarlane *et al.*, 2002) to evaluate the effectiveness of an intervention designed to provide an information leaflet together with verbal advice to patients presenting with acute bronchitis in primary care. This study found that patients receiving the intervention had a 47% rate of taking antibiotics whilst a separate group receiving no intervention had a rate of taking antibiotics of 62%.

Public education is a large undertaking and has been attempted in a number of countries (Watson, 2001; Department of Health, 1999; Bauchner and Philipp, 1998) which have implemented national strategies to educate the public not to expect an antibiotic when they visit a physician with a variety of infections. A review (Shapiro, 2002) of the literature relating to patient satisfaction and how it can influence the prescription of antibiotics found that in some cases (Mangione-Smith *et al.*, 1999) physicians appeared to change their diagnosis in order to justify the prescription of an antibiotic. The review concluded that physicians in their desire to promote patients' satisfaction thought that prescription of an antibiotic was what the patients wanted when in fact the patients wanted improved communication in the form of an explanation of their illness and the appropriate treatment. The miss-match between patient expectations and physicians beliefs of patient expectations has been documented (Cockburn and Pit, 1997).

The patient expectation that the doctor will prescribe an antibiotic is perhaps symptomatic of a society that expects a solution to be instantly available for every problem. This expectation was satirised in a cartoon (New Yorker, 1998)

of a doctor's office that displayed a sign saying 'Don't forget to take a handful of our complimentary antibiotics on your way out', and perhaps leaves little more to be said.

An indication of how much progress is needed to change prescribing patterns was demonstrated in a study (Metlay *et al.*, 2002) of a group of general physicians and infection control specialists when asked to rank in order of importance the factors for selecting an antibiotic for a hypothetical patient with community acquired pneumonia. The general physicians placed the risk of contributing to the problems of antibiotic resistance as lowest of seven factors and the infectious disease specialists placed this factor as sixth of the seven factors. Factors involved in the decision making process that ranked above resistance included, cost to patient, ease of use and previous experience and knowledge about the drug. The study also examined which antibiotic was selected and whether the choice coincided with the national guideline recommendation. The treatment guidelines include a range of antibiotic choices including macrolides, tetracyclines and in some circumstances β-lactams, with newer fluoroquinolones reserved for a sub-group of patients. The study found that both the general physicians and infectious disease specialists recommended levofloxacin and azithromycin more frequently. The results demonstrate that national guidelines may have a limited impact on prescribing patterns. It was concluded from the analysis of the ranking of the choices influencing which antibiotic to prescribe that both groups of prescriber rated antibiotic resistance and its impact on Society below providing the best treatment for individual patients. This might be expected and illustrates that educational programmes

which seek to promote the future public health by improving which antibiotic is prescribed require a raised profile and the backing of opinion leaders and influencers.

The success of an antibiotic guideline is not only dependent on how it is communicated to users. An Australian study (South *et al.*, 2003) used a laminated card which was small enough to be attached to a hospital identification card and was issued to all medical staff. The card contained prescribing advice. The study found that prescribing behaviour was influenced both in the choice and the dose of antibiotic prescribed. A review (Brown 2002) of antibiotic guidelines evaluated their development, dissemination and implementation and also included reasons why clinicians did not adhere to guidelines. Reasons for not following guidelines included lack of representation of particular groups in the development of the guideline (Greco and Eisenberg, 1993; Miller and Petrie, 2000) and distrust of experts creating national guidelines. Guidelines may not be applicable to specific patients or may not be followed because of fear of litigation or due to lack of endorsement by opinion leaders (Hayward *et al.*, 1997; Lee and Cooper, 1997). The implementation of any guideline also requires assessment as to whether it has achieved its aims in changing practice and improving outcomes. The Consensus Group on Resistance and Prescribing in Respiratory Tract Infection is an international group of opinion leaders that produced a review of strategies (Ball *et al.*, 2002) for appropriate antibiotic treatment of community acquired respiratory tract infection. Prescribers should be able to use this information as a guide to improve the quality of their treatment choices.

A study (Branthwaite and Pechere, 1996) of patient's attitudes to antibiotic use involved over 3,600 patients in six European countries. The study population included patients who had taken an antibiotic or had given one to a child in their care within the previous twelve months. Over 50% of patients felt that antibiotics should be prescribed for respiratory tract infections, with 75% judging antibiotics to be effective and to speed their recovery. Most patients waited two to three days before consulting a doctor, with over 80% expecting their symptoms to improve after three days antibiotic treatment. With regard to compliance this concurred with the finding that most non-compliers stopped treatment after three days because they felt better.

The issues around patient compliance with antibiotic treatment have been reviewed (Kardas 2002) and it was found that frequency of dosing (once daily was associated with the highest rates of compliance), length of course, lack of adverse effects, easy to use packaging and patient education were all associated with higher compliance rates.

An example of an educational initiative that combined many of the elements discussed has been carried out in the United States (Axelrod *et al.*,2002). In the USA there is an opportunity to influence antibiotic usage in a multi-factorial manner since patients in specific geographical locations are registered with a healthcare provider in the form of a managed care organisation. An educational initiative with the message 'resistance kills' was launched in 1999 and combined both consumer and medical practitioner education. The programme concentrated on antibiotic overuse and also misuse. What is unique is that the pharmaceutical

industry was involved in the campaign with sixteen companies providing funding in the form of educational grants. Pharmaceutical representatives also helped to distribute educational material to physicians. The physician element of the programme involved the use of report cards which detailed their antibiotic prescribing patterns. Report cards were issued at the beginning and also at the end of the campaign with changes highlighted and including a thank you from the Medical Director of the managed care organisation. Physicians also received posters and pamphlets. The community element was similarly thorough and community pharmacies were included, also over one hundred thousand postcards were posted to local people. In addition, cards were inserted in local newspapers, radio and television advertising was used, even local parent teacher organisations received a lecture. To complete the coverage the staff of the managed care organisation went through an educational programme. The outcome was an immediate reduction in antibiotic prescribing of 10.9% followed by a further 6.2% decrease, and there have been early changes in the sensitivity results for *S. pneumoniae* isolates. A programme of this type could act as a template for similar work in England which might be carried out by a partnership between an Acute Hospital Trust and Primary Care Trust.

1.5.2 Information Technology

The developments in information technology in recent years have transformed the working lives of many people across the world. This is particularly so in healthcare as large amounts of information relating to individual patients are now able to be brought together to aid in decision making regarding appropriate treatment strategies. In fact much information is available on the Internet that can be accessed by the public this enables the public to make informed choices about what treatment they want. The 'educated' patient can in fact possess more up to date knowledge than the clinician who they are consulting. The potential benefits from integrating emergency care services and hospital information systems are described by Bill Gates in a book (Gates, 1999) which devotes a large section to the benefits of information technology to healthcare. In addition, aggregated data can be used by Public Health specialists to facilitate epidemiological studies to monitor the health of populations.

The national strategy for the use of information technology in healthcare (Burns,1998) included targets for the implementation of electronic prescribing and decision support in acute hospitals in England. The development of Electronic Patient Records (EPR) and Electronic Health Records (E.H.R.) will enable clinicians to practice evidence-based medicine as they will have appropriate information available when it is required. The EPR is a record of an episode of care in an institution while the E.H.R. (now known as an Integrated Care Record) is a longitudinal lifetime record of the healthcare of an individual, which may have been provided by a number of institutions in both Primary and Secondary care.

The use of information technology to provide decision support for prescribers has been discussed in a number of studies (Pestotnik *et al.*, 1996; Nightingale *et al.*, 1997; Ford *et al.*, 2000; Ford and Curtis, 2001; Gould and Jappy, 2000) and it is instructive to look at this as it can be a powerful tool to influence prescribing of antibiotics by medical staff. It is possible to set up systems so that medical staff are presented with targeted messages when they making the choice of what product to prescribe. These messages can take the form of a reminder. For instance if an intravenous antibiotic is selected then a reminder to review the route after forty-eight hours could be useful (Grayson *et al.*, 2002). It is also possible, with the agreement of clinicians, to programme automatic stop dates so that courses lengths for antibiotics are fixed at seven days, with a manual override being required to prolong treatment.

Another strategy for influencing antibiotic prescribing is the development of 'rules' that add a degree of 'intelligence' to electronic prescribing software. Rules can be created to aid dose calculation by calculating doses based on body weight or changing dose recommendations when laboratory results are within specific ranges. A rule to calculate gentamicin doses taking into account body weight and creatinine clearance results would ensure that appropriate doses were prescribed. It is possible to design software so that inappropriate medicines or doses are prevented from being prescribed. This can be accomplished by the use of warning messages or in certain circumstances by blocking drug selection. In the majority of cases an override facility may be required, and a full audit trail is essential. It is possible for prescribing systems to check laboratory biochemical results as discussed with gentamicin. This can be extended such that

microbiological sensitivity results are automatically checked, so preventing the prescription of an antibiotic where the particular isolate has shown resistance to that antibiotic.

The impact of decision support for antibiotic prescribing as discussed in these studies has been examined and benefits such as improvements in antibiotic prophylaxis have been demonstrated. These included improvements in commencement and duration of prophylactic treatment. Over time it has been demonstrated that clinicians take greater note of alerts and warning messages and change their original treatment decisions. Examination of microbial resistance patterns showed that over a seven-year period these were unchanged. A reduction in numbers of adverse effects relating to antibiotic usage was also noted. This can be explained by the use of allergy warnings where the computer system alerts the prescriber that the patient has an allergy to the proposed antibiotic. Thus the potential adverse consequences which could ensue can be avoided. This is particularly common in the prescribing of penicillins to patients allergic to this class of antibiotic. During the period of the study the percentage of patients prescribed an antibiotic increased. This may be due to increased morbidity of patients admitted, or improvements in diagnostic techniques to identify when an antibiotic is an appropriate therapeutic option.

To gain the maximum benefit from a decision support system the rules, alerts and content of any warning must be locally agreed with local clinicians in order to gain commitment and ownership. There should be an educational component so that junior medical staff can learn what is appropriate treatment in specific

conditions. The system must act immediately while the prescribing process is taking place. There should, if possible, be a choice of therapy presented to the clinician. Clinical freedom to override the system is necessary so that individual patient circumstances can be taken into account.

A significant area where decision support systems can show benefits is in the empirical prescribing of antibiotic therapy. This by its nature takes place in an urgent situation requiring a rapid decision to be made without the benefit of microbiological information regarding the infecting organism. A study (Evans *et al.*, 1994) comparing the prescribing of physicians either using their clinical judgement or using a clinical decision support system demonstrated impressive results. Using susceptibility of micro-organisms to the chosen antibiotic and rapidity of initiation of treatment as indicators of success, both indicators were improved by use of a decision support system. Clinicians also felt that their patient care was improved by use of the system.

The development of decision support software is labour intensive and programming requires extensive validation. It can only be built on an existing integrated clinical computer network that covers a whole hospital. The system referred to above (Evans *et al.*, 1993) was developed over a period of twenty years. Information is collated from various parts of the patient record including renal function results and allergies, and is linked with information on the 'most likely' pathogen, based on local microbiology data. The prescriber is offered a choice of five antibiotic regimens which are likely to be appropriate. In addition, the system can display product monographs and so has educational potential. Similar systems have been reported (Schentag *et al.*, 1993) which integrate all of

the above data and this is used by pharmacists to individualise patient treatment. The fact that these systems can produce improved prescribing is an indication of how information technology can aid prescribing systems by presenting collated targeted information at the time when it is required. This does not detract from the practice of the art of medicine, but supports clinicians when they make a judgement on what is the most appropriate way to treat a patient. The need for such systems cannot be discounted when studies emerge which indicate that up to fifty percent of antibiotic use is inappropriate (Kurin *et al.*, 1990).

Progress in developing Electronic Patient Records in England has been reported (Dodd and Brennan, 1997). The system in use at Burton on Trent is based on an integrated clinical platform with electronic prescribing (Curtis and Ford, 1997). The prescribing and administration of medicines is carried out via the use of laptop computers with wireless links (Paul *et al.*, 2001). This enables clinicians to carry out their care at the bedside. The use of decision support embedded in the prescribing process is immediate and can occur at the bedside while prescribing decisions are being made.

This decision support system consists of a number of separate elements. The most basic element, being the use of the computer library for all of the hospital policies relating to the use of medicines. In particular the prescriber can readily access the most relevant antibiotic policy during the decision making process. This involves opening discrete files and so requires a conscious effort on the part of the prescriber. Warnings and comments are used relating to both length of treatment and route of administration. The use of external databases on the

hospital intranet includes the 'WeBNF' an intranet version of the British National Formulary.

In addition, development work with First Databank Europe, Ltd.(Exeter, England) has delivered on-line interaction checking and drug monographs, while drug dose checking is under development. It is important that drug monographs are available for health professional (doctors, nurses, pharmacists) and that separate patient information leaflets are available for patients.

The internet will become an important vehicle for disseminating information and guidelines concerning antibiotic use. In accordance with the recommendations in the Standing Medical Advisory Committee (SMAC) report *The Path of Least Resistance* (Standing Medical Advisory Committee 1998) national guidelines should be developed by the National Institute for Clinical Excellence (NICE). The Public Health Laboratory Service (PHLS) has commenced work (McNultie *et al.*, 2002) to produce guidance for primary care and this is available on the internet. The advantages of this approach are that the guideline can be a dynamic document that can be readily updated and reviewed by users across the country.

These developments when implemented across all hospitals will improve the prescribing of antibiotics in hospitals across the United Kingdom and prolong the period when effective antibiotics are available.

1.6. Drug Utilisation Review (DUR)

To determine whether antibiotics are being overused, underused or used inappropriately (Roberts and Visconti, 1972; North, 1993; Lutters *et al.*, 1998; Bell, 2001; Hooi *et al.*, 2001) it is necessary to carry out a thorough, well-organised DUR. Various data can be collected depending on the aims of the study from estimating global antibiotic consumption (Col and O'Connor, 1987; Kunin *et al.*, 1987), and epidemiological issues (Levin *et al.*, 1998) to highly focussed review of the use of antibiotics in the treatment of septicaemia in a group of departments (Leibovici *et al.*, 2001) or as is frequently the case examining the financial impact of antibiotic prescribing (Craig *et al.*, 1978; Garrelts *et al.*, 1994; MacIntyre *et al.*, 2001; Pelletier ,1985; Griffiths *et al.*, 1986; Griffiths *et al.*, 1986; Karki *et al.*, 1990; Capri and Dellamano, 1993; Sasse *et al.*, 1998; Mylotte and Weislo, 2000). There is also value in comparing data for specific situations such Critical Care Units (Archibald *et al.*,1997)

There should be defined aims and objectives to ensure that the DUR meets its objectives (Sloan *et al.*, 1994) and when complete a method to ensure that results are disseminated to participants so that if required, practice can be changed. Apart from quantitative studies there are a number of qualitative parameters which may be measured. Qualitative measures have been previously reviewed (Gyssens, 2001; van der Meer and Gyssens, 2001) and can include audit of the appropriateness of the antimicrobial used for a specific indication, particularly once the results of culture and sensitivity testing are known. Also, the issue of whether or not an alternative agent with a narrow spectrum or improved side-effect profile might have been more appropriate has been considered. The choice

of route of administration together with dose, frequency and length of treatment course can be recorded to assess the quality of antibiotic prescribing. Outcome results such as mortality rates and the presence or absence of multidisciplinary input from microbiology or pharmacy into the therapeutic choice can provide qualitative indicators.

Studies from around the world have examined the appropriateness of antibiotic prescribing according to a variety of assessment parameters (Gaynes and Monnet, 1997; Saizy-Callaert *et al.*, 2003). The increasing use of broad-spectrum agents without evidence that they are required has been demonstrated (Burkett *et al.*, 1991) together with evidence that physicians are poor at making rational choices of antibiotic, duration of treatment, route or dose (Witte *et al.*, 1980; Aswapokee *et al.*, 1990; Misan *et al.*, 1990; Parret *et al.*, 1993; McDonald *et al.*, 2001). A study (Lawrence *et al.*, 2001) which examined changes in antibiotic treatment in patients with suspected serious infections in the first seventy-two hours of treatment found that changes were made without any apparent clinical or microbiological indication in 93% of cases: this led to these patients being unnecessarily exposed to multiple antibiotic agents. Other investigations have shown similar results. A review of hospital patients prescribed vancomycin found that only 35% of prescriptions complied with guidelines owing to a failure to obtain cultures for sensitivity testing (Evans, 1996). Another study carried out in Spain (Escolar *et al.*, 1980) concluded that diagnosis was doubtful or incorrect in 60% of cases examined. It was suggested that supervision of prescribing and also Continuing Medical Education would be valuable.

Reviews of the effectiveness of antibiotic control measures, written request forms, guidelines and interventions from various healthcare professionals has demonstrated that they are all effective in reducing cost and quantity of antibiotics used (Harvey *et al.*, 1983; Fraser *et al.*, 1997; Giamarellou and Antoniadou, 1997; White *et al.*, 1997; Bassetti *et al.*, 2001). This has also been demonstrated on a national level with reductions in the use of erythromycin in Finland during the early 1990's (Seppala *et al.*, 1997).

This type of survey can be carried out to determine the incidence of policies which restrict or guide antibiotic prescribing within hospitals (Godin *et al.*, 1988; Gindre *et al.*, 2000; Medina-Cuevas *et al.*, 2000). Carrying out repeated surveys of antibiotic prescribing may itself improve prescribing standards (Mashford and Robertson, 1979) by raising the profile of the issue while carrying out the studies within an institution. Reviews of the role of antibiotic policies in helping to control antibiotic resistance within hospitals have found that they can be useful in improving prescribing (Sturm, 1990; McGowan,1994; Gould, 1999; Gould, 2002). It is still not possible to describe the optimal antibiotic prescribing control measures (Bonhoeffer *et al.*, 1997; McGowan, 2001) and the hopes that strict control of antibiotic prescribing could reverse high levels of resistance are now considered to be less certain (Schrag and Perrot, 1996). A paper (Quirk, 2002) from the International Forum on Antibiotic Resistance (IFAR) describes plans to audit strategies to control bacterial resistance so that good practice can be promoted.

Drug Utilisation Reviews that examine antibiotic prescribing (and express the results in Defined Daily Doses per 100 in-patient bed-days or per 1000 patient days for Primary Care) within a number of institutions in a single country (Fletcher *et al.,* 1990; Carling, *et al.*, 1999; Gould and Jappy, 2000; Bengoa *et al.*, 2002; Mazzeo *et al.*, 2002) or in a number of countries can assemble powerful data which informs decision makers at all levels of healthcare. A review in The Netherlands found an increasing trend over the years 1991 to 1996 from 37.2 to 42.5 DDD per 100 beddays. This can be compared with the results of a study (Kiivet *et al.*, 1998) of antibiotic usage in 1992, in three University Hospitals in Estonia, Spain and Sweden where a range of 41 to 51 DDD/100 bed-days between the three sites was found. The quantity of antibiotics used varied depending on the particular specialty within hospitals compared but overall usage was similar. The major difference, being in the antibiotic which was prescribed. Use of this methodology has demonstrated differences in antibiotic consumption in Scandinavia (Bergan, 2001), with Denmark and Norway having the lowest total consumption. Such studies raise further questions as it is not the overall level of antibiotic usage that is important but the quality of treatment and patient outcomes, but these are rarely recorded.

Work carried out in Spain (Baquero, 1996), a country with a relatively high per capita consumption of antibiotics (Baquero, 1996) found that there is a higher level of antibiotic resistance. The maximum consumption of antibiotics occurred in the period 1966 to 1976 at 31 DDD per 1,000 persons per day. This reduced over time and by 1993 had fallen to 19 DDD per 1000 persons per day. Factors leading to the high level of antibiotic usage in Spain were patient pressure, lack

of knowledge by physicians, together with illegal supply without a prescription. The solutions proposed included continuous surveillance, education of physicians, patient information, antibiotic policies and also promoting pharmacists as agents of the rational use of antibiotics.

Despite the accepted value of using the DDD in methodologies to evaluate antibiotic prescribing, many studies do not use the DDD and employ a variety of other indicators (Leigh, 1982; McDonald et al., 2001). Studies comparing duration of treatment and the use of the parenteral or oral routes can demonstrate national differences in practice (Halls, 1993; Cooke et al., 2002). Such work has shown that prescribers in the United Kingdom use a shorter duration of treatment, greater use of older therapy, higher levels of oral therapy with the highest rates of initial treatment failure when compared with colleagues in hospitals in France, Germany, Spain and Italy.

An alternative antibiotic prescribing measure proposed as a comparator for use in English hospitals is the DDD per FCE (Curtis *et al.*, 2002) and it is proposed that this measure will enable different hospitals to objectively compare their antibiotic use.

The benefits of abbreviating a course of parenteral antibiotic therapy with early initiation of oral therapy have been demonstrated in a number of studies (Craig and Andes, 1995; Carling *et al.*, 1999; Kuti et al., 2002) and include shorter length of stay (Hendrikson and North, 1995) reduced cost (Gentry and Koshdel, 1989; Khan and Basir, 1989; Janknegt and van der Meer, 1994; Sevinc *et al.*, 1999) with no difference in patient outcome (MacGregor and Graziani, 1997). A

survey (Smyth and Tillotson, 1998) carried out in 1998 to ascertain the extent of the adoption of this strategy across the British Isles found that 44% of a total of 277 hospital pharmacists indicated that facilitated conversion to the oral route been adopted. Studies where pharmacists contact physicians to prompt them to discontinue intravenous therapy found that the treatment costs for these patients was reduced (Przybylski *et al.*, 1997) although in one example the cost of the intervention outweighed the cost reduction (Bailey *et al.*, 1997) whereas a similar study which used a nurse interventionist to make proposals to change therapy to physicians found that this was cost-effective (Ehrenkranz *et al.*, 1992). A simpler approach where pharmacists are authorised to discontinue parenteral antibiotic therapy within specified circumstances has been demonstrated to be cost-effective (Nickman *et al.*, 1984).

The use of printed forms and notes attached to medical notes and prescription charts to act as reminders to review the route of patients antibiotic therapy have been demonstrated to be effective in enabling the conversion of IV to oral forms (Frighetto *et al.*, 1992; Mandell *et al.*, 1995; Bui and Quintiliani, 1998; Lowy *et al.*, 2001). The use of parenteral fluoroquinolones in particular ciprofloxacin and conversion to the oral route has been studied extensively (Chrysanthopoulos *et al.*, 1989; Gangji *et al.*, 1989; Paladino *et al.*, 1991; Amodio-Groton *et al.*, 1996; Jensen and Paladino, 1997; Conort *et al.*, 2002). One study demonstrated that conversion from the parenteral route, to the oral route could be effectively carried out by pharmacists (Marvin and Dowdall, 1998).

A three-component strategy implemented in Canada (Salama *et al.*, 1996) used

pharmacist generated reminders to change from parenteral to oral therapy, therapeutic interchange and restriction of a number of antibiotics. After two years both the therapeutic interchange and the restriction strategies had been highly effective and had reduced the study hospital's expenditure on antibiotics from 41.6% to 28.2% of total spend on medicines. The impact of restricting the availability of specific antibiotics by requiring the physician to justify their request has been demonstrated elsewhere (Gleckman and Gantz, 1983).

1.7 Aims and Objectives of the study

1.7.1 Aims

- To collect antibiotic usage data and activity data from a group of hospitals over a period of three consecutive years.
- To apply a number of prescribing indicators to the usage data in order to validate a measure which is independent of workload.
- To use the results of the analysis to determine whether there is a relationship with the medicines management strategy in place at each hospital.
- To produce qualitative and quantitative measures which may be used to compare antibiotic prescribing between hospitals.
- To collect deprivation data relating to individual hospital referral populations in order to determine whether any relationship can be identified between deprivation and hospital antibiotic prescribing.

1.7.3 Objectives

- To select twelve hospitals, based on their medicines management self-assessment scores (high, medium and low scoring) (Department of Health, 2000). To include one cohort of three hospitals with electronic prescribing systems to determine whether the impact of the additional controls afforded by such systems could be identified.
- To create a dataset containing antibiotic use data (using the ATC classification system) as Defined Daily Doses (DDD) for all twelve hospitals for three financial years commencing April 2001 to March 2004.

- To compare hospital use of clavulanate-potentiated amoxicillin with amoxicillin in order to establish a benchmark for initiation of audit of practice.
- To identify a ratio of first/second generation cephalosporin to third generation cephalosporin use which may indicate a need for further investigation.
- To examine the variation in individual hospital uptake of long-acting macrolides.
- To determine the percentage of total quinolone use represented by parenteral doses to enable comparison between hospitals.
- To establish the validity of using the Medicines Management self-assessment scores (MMAS) as an indicator of control of antibiotic prescribing by use of an Antibiotic Medicines Management (AMS) survey instrument.
- To examine whether a relationship can be established between the MMAS and the identified qualitative indicators of antibiotic use.
- To examine the relationship between antibiotic use when quantified as the DDD/100beddays and the DDD/FCE for each hospital over the study period.
- To identify any trend in total antibiotic use during the study period.
- To identify trends within each antibiotic ATC category during the study period.

- To examine the relationship between glycopeptide use per FCE and the reported incidence of MRSA.

- To determine whether there is a relationship between medicines management scoring (MMAS) and quantitative measures of antibiotic use.
- To create a dataset containing the Primary Care Trust (PCT) or origin of patients treated at each hospital during 2001/2, the Index of Multiple deprivation (IMD 2000) and the Primary Care antibiotic prescribing rate (number of items per 1000 patients) 2001/2.
- To use the dataset to create a mean IMD 2000 for the referred population.
- To use the dataset to create a mean Primary Care antibiotic prescribing rate for the referral population for each hospital.
- To compare the mean IMD 2000 with the Primary care antibiotic prescribing rate (items per 1000 patients).
- To compare the mean IMD 2000 with the Secondary care antibiotic prescribing rate (DDD/FCE).
- To establish whether there is a relationship between the Primary care antibiotic prescribing rate (items per 1000 patients) and the Secondary care antibiotic prescribing rate (DDD/FCE).

2. Methods.

2.1 Sample selection.

Four cohorts of three hospitals were used as data collection sites. Hospitals were selected at random on the basis of their Medicines Management Self-Assessment Scores (Department of Health, 2000) from the scores for West Midlands hospitals. They were then sub-grouped according to pre-determined differing inter-group characteristics, in terms of size and case-mix (see Table 2.1). Three hospitals, representing a single cohort, had fully operational electronic prescribing systems (Table 2.1A) and represented all of the hospitals operating electronic prescribing systems in England at the time (2001/2), two of these hospitals were located outside the West Midlands.

The total sample consisted of twelve hospital trusts which carried out 6.7% of total hospital activity in England based on the total number of FCE's completed in the year 2001/2 [822,445 FCE's of a total of 12,357,360 (Department of Health, 2004).

A finished consultant episode (FCE) was defined as 'a period of healthcare under one consultant, in one hospital provider' (Department of Health 2004).

A request to participate in the study was mailed to the Chief Pharmacist of each hospital to explain the background to the study and that data would be requested at the end of each financial year for each of three consecutive years commencing April 2001/2. All twelve hospitals approached agreed to participate.

Table 2.1 Details of the Hospital sites included in the study.

Hospital	*Comment*	*Number of beds*	*Cohort*
1	Urban acute trust	1347	A
2	Urban acute trust	1330	A
3	Urban acute trust	811	A
4	Small town, electronic prescribing	465	B
5	County town, electronic prescribing	569	B
6	Suburban, electronic prescribing	1279	B
7	Urban acute trust	956	C
8	Urban trust	634	C
9	Urban trust (inc infectious disease unit)	1320	C
10	Suburban trust	503	D
11	Specialist trust	227	D
12	County town	630	D

Key : Cohort A – Medicines Management score >19
Cohort B – Electronic Prescribing system (average score 18)
Cohort C – Medicines Management score >15 and <19
Cohort D – Medicines Management score <15

The Medicines Management scores are explained in section 2.3.3

Diversity in workload was reflected in the large hospitals (in terms of bed numbers) (1,2,3,6,7,9) which possessed individual tertiary referral specialties, whilst hospital eleven was a specialist hospital receiving referrals from across the country. Hospital nine contained an infectious diseases unit and therefore treated patients with a wide-range of conditions requiring antibiotic therapy. The remainder of the hospitals (4,5,8,10,12) provided the full range of acute care specialties for their local communities.

2.2 Literature review.

An electronic search was carried out using MEDLINE. The search period was from 1966 onwards, and the search terms used included 'antibiotics', 'hospitals', 'administration', 'therapeutic use' and 'dosage'. These terms were combined with the term 'measure'. The terms were mapped to Medical Subject Headings (MeSH) terms used in each database. The search terms were developed following discussion with Dr J.Paton and Dr T. Weller, Consultant Microbiologists at Queen's Hospital, Burton and City Hospital, Birmingham respectively. All relevant original papers identified by the search were obtained and evaluated. These papers were manually searched and relevant references from them were obtained and added to a database.

An electronic search as above using PHARMLINE was carried out using the period 1980 onwards using the same set of terms. An electronic search of the Department of Health website was carried out also using the same strategy.

To ensure that current publications were identified, an electronic table of contents alert service provided by the British Library (Zetoc) was used. This searched selected pharmaceutical, microbiological and medical journals for the key terms 'antibiotic' and 'drug utilisation review' in the titles of published articles. Results from the electronic search were validated as being complete by carrying out a manual search of the Science Citation Index for correlation of results with the Medline/Pharmline results.

A database of publications was set up and maintained using Endnote version 5 software (ISI Researchsoft, Berkeley, CA, USA) to organise references.

2.3 Data collection.

2.3.1 Antibiotic usage data

Antibiotic usage data was collected for systemic antibacterials (ATC category J01). Each financial year-end (end March) from 2002 for three consecutive years, the Chief Pharmacists at each study site were sent a written request to provide the antibiotic issue data for their hospital. An e-mail reminder was sent after four weeks and if required telephone reminders were delivered. The data were provided as flat field data files (Microsoft Excel) and in one case as a hardcopy. The data fields required were the name, form and strength of the antibiotic together with the issue unit and the number of units issued during the year.

The data for all sites were transcribed onto a Master Excel spreadsheet in a format where the data for each dose form and strength was summed and this enabled a single 'grand' total number of grams dispensed to be recorded for each antibiotic. The spreadsheet was also designed to calculate the total number of DDD issued for each antibiotic by each hospital each year. Antibiotics were grouped together using the ATC classification system, so that sub-totals for each class (e.g. J01C Penicillins) were calculated. The grand total for all classes of antibiotics was then calculated.

Anatomical Therapeutic Chemical (ATC) classification.

The ATC classification system uses a five level categorisation to define individual drug entities. This is illustrated with the example of Amoxicillin as follows :

J	Anti-infectives for systemic use	1st level, anatomical main group
J01	Antibacterials for systemic use	2nd level, therapeutic sub-group
J01C	Beta-lactam antibacterials, penicillins	3rd level, pharmacological sub-group
J01C A	Penicillins with extended spectrum	4th level, chemical subgroup
J01C A04	Amoxicillin	5th level, chemical substance

The data in table 2.2 details the Defined Daily Dose for the antibiotics used in the hospitals in the study and is taken from the ATC Index 1999 (WHOCollaborating Centre for Drug Statistics Methodology, 1999). Values for DDD's are reviewed as new editions of the Index are published. The DDD values used in the study were those listed in the table.

Table 2.2 Table of the Anatomical Therapeutic Chemical (ATC) classification with Defined Daily Doses (DDD) for Antibacterials for systemic use. (Only those products used in the study sites are included).

ATC code	Antibiotic	DDD
J01A A	**Tetracyclines**	
01	Demeclocycline	0.6g
02	Doxycycline	0.1g
04	Lymecycline	0.6g
06	Oxytetracycline	1g
07	Tetracycline	1g
08	Minocycline	0.2g
J01B A	**Amphenicols**	
01	Chloramphenicol	3g
J01C A	**Penicillins with extended spectrum**	
01	Ampicillin	2g
04	Amoxycillin	1g
09	Azlocillin	12g
12	Pipericillin	14g
J01C E	**Beta-lactamase Penicillins**	
01	Benzylpenicillin	3.6g
02	Phenoxymethylpenicillin	2g
J01C F	**Beta-lactamase resistant Penicillins**	
05	Flucloxacillin	2g
J01C R	**Combinations of Penicillins, incl. Beta-lactamase inhibitors**	
02	Amoxycillin & enzyme inhibitor	1g
03	Ticarcillin & enzyme inhibitor	15g
05	Piperacillin & enzyme inhibitor	14g
J01D A	**Cephalosporins & related substances**	
01	Cephalexin	2g (O)
04	Cefazolin	3g (P)
06	Cefuroxime	0.5g (O) 3g (P)
08	Cefaclor	1g (O)
09	Cefadroxil	2g (O)
10	Cefotaxime	4g (P)
11	Ceftazidime	4g (P)
13	Ceftriaxone	2g (P)
23	Cefixime	0.4g (O)
31	Cefradine	2g (O,P)
33	Cefpodoxime	0.4g (O)
J01D F	**Monobactams**	
01 0	Aztreonam	4g (P)

ATC code	Antibiotic	DDD
J01D H	**Carbapenems**	
02	Meropenem	2g (P)
51	Imipenem & enzyme inhibitor	2g (P)
J01E A	**Sulphonamides & Trimethoprim**	
01	Trimethoprim	0.4g (O,P)
ATC code	**Antibiotic**	**DDD**
J01F A	**Macrolides**	
01	Erythromycin	1g (O,P)
09	Clarithromycin	0.5g (O)
10	Azithromycin	0.3g (O)
J01F F	**Lincosamides**	
01	Clindamycin	1.2g
J01F G	**Streptogramins**	
02	Quinupristin/Dalfopristin	1.5g (P)
J01G B	**Other Aminoglycosides**	
01	Tobramycin	0.24g (P)
03	Gentamicin	0.24g (P)
05	Neomycin	1g (O)
06	Amikacin	1g (P)
07	Netilmicin	0.35g (O,P)
J01M A	**Fluoroquinolones**	
01	Ofloxacin	0.4g (O,P)
02	Ciprofloxacin	1g (O), 0.5g (P)
06	Norfloxacin	0.8g (O)
12	Levofloxacin	0.25g (O,P)
J01M B	**Other Quinolones**	
02	Nalidixic Acid	4g (O)
J01X A	**Glycopeptide antibacterials**	
01	Vancomycin	2g (P)
02	Teicoplanin	0.4g (P)
J01X B	**Polymyxins**	
01	Colistin	3MU (P)
J01X C	**Steroid antibacterials**	
01	Fusidic acid	1.5g (O,P)
J01X D	**Imidazole derivatives**	
01	Metronidazole	1.5g (P)
J01X E	**Nitrofuran derivatives**	
01	Nitrofurantoin	0.2g (O)
J01X X	**Oxazolidinones**	
08	Linezolid	1.2g (O,P)

2.3.2 Hospital Activity data

Hospital activity data recorded as both the number of occupied beddays and Finished Consultant Episodes were recorded for each year of the study. This data was obtained from the Department of Health Hospital Episode Statistics site for each study hospital.

2.3.3 Medicines Management Self-Assessment scores

The twelve study sites were selected on the basis of their Medicines Management Self-Assessment scores arising from a nationally sponsored self-assessment exercise carried out in 2001 (Department of Health, 2000). The self-assessment consisted of six equally weighted domains of activity related to medicines management, with a high score being indicative of a high degree of control of medicines usage. The maximum possible aggregate score was 23. The six domains of activity were as follows:

(i) Senior management awareness and involvement

(ii) Information and financial issues

(iii) Medicines policy management, including the introduction of new drugs

(iv) Procurement of medicines

(v) The primary and secondary care interface

(vi) Influencing prescribers

Scores from this exercise are likely be indicative of the degree of control and influence over the general use of medicines and more specifically, antibiotics,

and that a high scores in this measure would be linked to low levels of antibiotic usage (divergent validity).

Reviewing the scores for the hospitals of the West Midlands it was possible to select three high-scoring sites (score >19), together with three medium-scoring hospitals (score >15 but <19) and a third group with lower scores (score <15). In addition to these nine hospitals, it was felt that the three English hospitals which have fully implemented electronic prescribing systems would be used as a discrete comparator, for the reasons previously stated. The characteristics of the sites are listed in table 2.1.

2.3.4 Antibiotic medicines management scores

In order to validate the Medicines Management Self-Assessment scores, which relate to general control systems in place for all medicines, a postal questionnaire was designed containing eleven questions covering eleven aspects of medicines management relating specifically to control of the use of antibiotics. The questionnaire (Appendix 1)was mailed to the Chief Pharmacist at each study site together with an explanatory letter.The content of the questionnaire was validated by a Delphi group consisting of three Microbiologists and a Pharmacist. The members were Dr T. Weller, Consultant Microbiologist, City Hospital, Birmingham; Dr J. Paton, Consultant Microbiologist, Queen's Hospital, Burton on Trent; Dr I. Gould, Consultant Microbiologist, Aberdeen Royal Infirmary; Mr C. Curtis, Chief Pharmacist, Queen's Hospital, Burton on Trent. A draft version of the questionnaire was e-mailed to the group and all comments received were incorporated in to the final version.

The data generated from the questionnaire were also used to support and cross-reference the results from the medicines management self-assessment tool. The eleven questions covered areas of recognised good practice in control of antibiotic usage and included: audit of usage, data sharing between pharmacy and microbiology departments, liaison with infection control services, pharmacy led educational initiatives, pharmacist empowerment to convert from intravenous (iv) to oral routes, pharmacist discontinuation of therapy and rationalisation of formulary choices of antibiotics. The maximum possible score for this assessment was 22.

2.3.5 MRSA data

The individual hospital data for the incidence of MRSA (cases per 1000 beddays) was taken from the Health protection Agency published surveillence results (Health Protection Agency, 2005).

2.3.6 Referral data

A written request was submitted to the Department of Health for a HES tabulation to be provided from the Health Episode Statistics database detailing the PCT of origin of every patient treated at each of the twelve study hospitals for the year 2001/2. The data was provided as an Excel spreadsheet listing each PCT with the number of patients treated in each of the twelve study hospitals for the year requested.

2.3.7 Deprivation data

An electronic search (Microsoft MSN Search) was carried out using the term 'Public Health Observatory' to locate each of the Regional Public Health Observatory websites. These sites were then examined for reports listing the deprivation scores for the PCT's within that Region. Where this data was not found then electronic searches (Microsoft MSN Search) for individual PCT websites were carried out using the name of the PCT as the search term, and the IMD (Index of Multiple Deprivation) (Noble *et al.*, 2000) data was extracted from the individual Public Health Annual Reports. This methodology enabled the IMD 2000 to be collected for each PCT that referred patients to the twelve study hospitals during 2001/2. It was then possible to calculate a mean IMD 2000 for the referral population for each hospital.

2.3.8 Primary care antibiotic prescribing data

A data set was obtained from the Prescription Pricing Authority that listed the number of antibiotic items prescribed per 1000 residents by GPs in each PCT in England and Wales for the year 2001/2. This data is a standard prescribing indicator provided to PCTs to enable monitoring of GP antibiotic prescribing trends. The data for the relevant PCTs in which patients treated in each of the study hospitals were resident was then extracted and tabulated. The tabulated data for the mean number of antibiotic items prescribed in general practice for patients from each PCT which referred to each sample hospital was multiplied by the proportion of patients which they represented and these values were summed to produce a mean value.

Using a hypothetical hospital (A) as an example;

Hospital A, completed 2000 FCEs in a year and the FCE contribution by PCT could be broken down as follows:

PCT	Number of FCEs	Proportion of total FCEs	Number antibiotic items prescribed	Weighted number of antibiotic items
A	500	0.25	500	500 x 0.25=125
B	1000	0.50	750	375
C	500	0.25	400	100

Total weighted number of antibiotic items = 125 + 375 + 100 = 600.

In this example the weighted Primary care antibiotic prescribing rate for Hospital A would be 600 items per 1000 patients.

The mean primary care antibiotic prescribing rate was then calculated for the referral population for each hospital in the study.

2.3.9 Statistical methodology

All data was analysed using SPSS software version 11 and values tested for correlation using Pearsons bi-variate correlation. The software also calculated the significance of any correlation. P values of < 0.05 were considered significant, P values of < 0.01 were considered very significant and P values of < 0.001 were considered highly significant in the present study.

3. Antibiotic Use and Medicines Management.

3.1 Introduction

3.1.1 Background

The collection and collation of antibiotic usage data over a number of years is the crucial first stage in enabling objective comparison of antibiotic utilisation between hospitals. Qualititative data relating to patient care may then be collected and related to antibiotic use profiles. Specifically, the impact of the application of evidence-based practice may be assessed. Evidence-based concepts relating to the use of medicines were originally described as 'pharmaceutical care' (Hepler and Strand 1990). This was defined as 'the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patients quality of life.' This was developed into the concept of 'medicines management' (Fitzpatrick *et al.* 2001), that described systems to control medicines procurement, managed entry of new drugs onto a hospital formulary through to prescribing review and the use of clinical guidelines.

3.1.2 Prudent use of antibiotics.

In order to compare antibiotic use across the full spectrum of secondary care settings a robust measure is needed that is independent of workload. The UK Department of Health has recently allocated funding for each English hospital in order to promote the 'prudent use of antibiotics' (Department of Health 2003). The funding is to be used to employ pharmacy resources to enable work to commence to improve targeted clinical pharmacy initiatives and also to begin to address the collection of data from hospitals.

In order to demonstrate that this initiative has had a positive impact, measurable outcomes will have to be demonstrated. Potential indicators of change are included in a report published by the Chief Medical Officer (Chief Medical Officer 2003) and include use of appropriate course length and dose, use of narrow spectrum groups in preference to broad spectrum antibiotics and use of local information concerning resistance to guide antibiotic choice. Resistance in three strains of bacteria is highlighted as creating patient risk – MRSA, vancomycin resistant enterococci and penicillin resistant S. *pneumoniae.* Changes over time in ratios of IV to oral antibiotic usage, reduction in use of broad-spectrum antibiotics and decrease in incidence of *C.difficile* are also possible qualitative indicators of an impact.

Potential activities for antibiotic pharmacists have been discussed previously and examples have been reported (Barriere *et al.* 1989; Berman *et al.* 1992; Dickerson *et al.* 2000; Cooke 2003; Lawson *et al.* 2000). The benefits include providing education, audit, monitoring of antibiotic use and formulary development. Specifically, these activities may include ensuring that therapeutic guidelines are followed (Dranitsaris *et al.* 2001), providing educational literature for physicians (Hickman *et al.* 2003), promoting responsible prescribing (Knox K et al. 2003), therapeutic substitution (Pasquale *et al.* 2004) early switching from parenteral to oral therapy (von Gunten *et al.* 2003; Florea *et al.* 2004) and reduction in medication errors (Strong *et al.* 1990).

In order to maximise the opportunity for change to occur, antibiotic pharmacists will need to work closely with microbiologists to influence prescribing habits.

Multidisciplinary antibiotic working groups can produce demonstrable outcomes (Cooke *et al.* 2004) and they may provide a model for use in acute hospitals.

3.1.3 Medicines Management Scoring.

The Medicines Management Self-Assessment score (MMAS) (Department of Health 2000) provided a method of quantifying a range of activities carried out by hospital pharmacists to influence medication usage. It was assumed that the scores from this exercise would be indicative of the degree of control over the general use of medicines and more specifically, antibiotic usage. The activity domains quantified cover information and financial issues (internal reporting to clinicians of drug usage trends), medicines policy management (antibiotic policies), and influencing prescribers. High scores in this measure would be expected to be associated with low levels of antibiotic usage (divergent validity).

In order to validate that the medicines management scores that relate to general control systems in place for all medicines are indicative of the degree of control over antibiotic prescribing, a questionnaire (see Methods) was designed containing questions covering eleven aspects of medicines management relating specifically to control of the use of antibiotics. This enabled an Antibiotic Medicines Management (AMS) score to be generated for each hospital and it was intended to determine whether there was any correlation between the MMAS and the AMS scores.

3.2 Results

3.2.1 Tabulated Antibiotic uage data calculated as DDD, grouped by ATC classification.

The data presented in tables 3.1, 3.2 and 3.3 show the calculated number of DDDs for each antibiotic, grouped by ATC class (eg Tetracyclines J01 A) used in each hospital for 2001/2, 2002/3 and 2003/4 respectively. There is also a grand total number of DDDs for total antibiotic use.

Table 3.1 Antibiotic use for each hospital site for 2001/2 expressed as DDDs with antibiotics listed by ATC category.

ATC Code	Antibiotic	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8	Hospital 9	Hosptial 10	Hospital 11	Hospital 12
	Tetracyclines												
J01A A01	Demeclocycline			101.7	233.8	658	204	763	384	570.8	329		
J01A A02	Doxycycline	33067	23146	35482	9915.6	10468	29372	21590	8089.5	94966.5	1608	289	14421
J01A A04	Lymecycline				1472		171		219.6	104		7	102
J01A A06	Oxytetracycline	1561	6558.5	2799	2411	658	607	3549	658.5	1651	4200	120.3	936.5
J01A A07	Tetracycline	23	256	14	398	39.5	27	40	200	533	43	1432	80
J01A A08	Minocycline	1008	74.5	679.25	590	868	133	2142	35.5	977.5		19	330.5
	Sub-total	**35659**	**30035**	**39076**	**15020.8**	**12691.5**	**30514**	**28084**	**9587.3**	**98803**	**6180**	**1867.3**	**15870**
	Amphenicols												
J01B A01	Chloramphenicol	132.2	33.5	20.6	1	20.3	21.3	11.3	26.6	450			44.6
	Penicillins												
J01C A01	Ampicillin		1323		364.75	931.75				1082		9	507
J01C A04	Amoxycillin	56136	33397	54875	10582	14828	13085	37157	15688	206130	18214	5421	13851
J01C A09	Azlocillin		8.7			0.8			10				11
J01C A12	Piperacillin		91.3	6.3	11.7	291	18		192	830	18		
J01C E01	Benzylpenicillin	7487	8270	4444	1302	2025	1583	3454	5299	14627	4991	375.8	3530
J01C E02	Phenoxymethylpenicillin	12468	13476	8655	3404	3626	4920	8916	5500	7630	6750	897	5529
J01C F05	Flucloxacillin	44747	47575	40926	16759	13725	23253	33147	17162	46602	19200	11546	18030
J01C R02	Amoxycillin + enzyme inhibitor	58784	75770	17157	32978	22905	56162	34155	17065	53971	31168	5613	50165
J01C R03	Ticarcillin + enzyme inhibitor			43				140	10	555			
J01C R05	Piperacillin + enzyme inhibitor	2256	903	21.7		256	549		22	2063		23.2	293
	Sub-total	**181878**	**180814**	**126128**	**65401.4**	**58588.5**	**99570**	**116969**	**60948**	**333490**	**80341**	**23885**	**91916**
	Cephalosporins												
J01D A01	Cefalexin	13523	14618	6190	1539		7244.7	8886.2	2712	5852.6	5752	471.7	6848.5
J01D A04	Cefazolin		2		18								

J01D A06	Cefuroxime oral			94.5	5586			125		861.5			25
J01D A06	Cefuroxime parenteral	13862	22214	11425	5566	5930.7	6765.6	12422	5016	17029.8	416.5	3367.5	5905
J01D A08	Cefaclor	13			2469	1966.5	557.5			46.5	271.5	62.5	47
J01D A09	Cefadroxil				46						5		
J01D A10	Cefotaxime	257	915.8	588.5	2109	132.7	46.8	1288.5	3346.5	2085.2	830.6	46.7	1854.8
J01D A11	Ceftazidime	2560	3974.6	1768.5	2575	684.3	2546.6	1396.3	418	9727.5	1105		816
J01D A13	Ceftriaxone	1548	1861.6	8.5	75.5	1530	5222.8	1	75	90	748.8		195.7
J01D A23	Cefixime		11	79									
J01D A31	Cefradine		7.8	34	386.5	8926	5284	50	2906.5	22.5		12.5	946
J01D A33	Cefpodoxime			8007									
	Sub-total	**31763**	**43605**	**28195**	**20370**	**19170.2**	**27668**	**24169**	**14474**	**35715.6**	**9129.4**	**3960.9**	**16638**
	Monobactams												
J01D F01	Aztreonam	57.2	365			31.5		1.5	9	1677.7			5
	Carbapenems												
J01D H02	Meropenem	825	295	106.5	109	135	45	262	14	4256	412.5		159
J01D H51	Imipenem + enzyme inhibitor	662.7	427		334		141	164.5	78.5	266.5		34.7	
	Sub-total	**1487.7**	**722**	**106.5**	**443**	**135**	**186**	**426.5**	**92.5**	**4522.5**	**412.5**	**34.7**	**159**
	Trimethoprim												
J01E A01	Trimethoprim	21269	24925	15495	7911	7100	14022	23351	10873	17014	14774	2356	13551
	Macrolides												
J01F A01	Erythromycin	49989	34897	35276	9616.8	8830.5	16369	8280	25470	141443	9443	2898	20515
J01F A09	Clarithromycin	1451	6477	5038.5	23614	8902	6997	12334	1918.5	13343	2411	170	5400
J01F A10	Azithromycin	368	935	253.5	1196.2	1323.3	616	780	674.8	1888	100		1031
	Sub-total	**51801**	**42309**	**40568**	**34427**	**19055.8**	**23982**	**21394**	**28063**	**156674**	**11954**	**3068**	**26946**
	Lincosamides												
J01F F01	Clindamycin	2145.8	665.7	502	393.5	1571.8	356	236.5	84.5	3768.4	435		1478
	Streptogramins												
J01F G02	Quinupristin/Dalfopristin									31	72		
	Aminoglycosides												
J01G A01	Streptomycin	60	21	32				120	58	75			38

J01G B01	Tobramycin	1343	2389	1266	106	579.6	1827.6	225	90	15342	1.6		265
J01G B03	Gentamicin	9748.7	5879	2374	1517.8	2519.8	4588.7	2111.6	1993.9	4219.9	1650.4	707.3	1564.5
J01G B05	Neomycin	100	140	133	547		2365	200	34.5	105	100		275.5
J01G B06	Amikacin	102.5	33.5	21				7.5	22.5	56.5			10
J01G B07	Netilmycin	2.8				0.8	74	2.8	2.8			40	4
	Sub-total	**11357**	**8462.5**	**3826**	**2170.8**	**3099.4**	**8855.3**	**2666.9**	**2201.7**	**19798.4**	**1752**	**747.3**	**2157**
	Fluoroquinolones												
J01M A01	Ofloxacin	450	14082	56	2254	15	39937	450	735	26770	170	10	9370
J01M A02	Ciprofloxacin oral	33325	18581	15742	14171	9690	5411	15178	19052	23662	10113	1788.5	8629
J01M A02	Ciprofloxacin iv	3496	2852.2	597	3482.6	518	399	1329	1471	542	1078	59.6	1997
J01M A06	Norfloxacin		7			3208				95		1569	40
J01M A07	Levofloxacin	50	226			30	52736	2854	120	994	7200		
J01M B02	Nalidixic Acid	47	0.8	23						12			57
	Sub-total	**37368**	**35748**	**16418**	**19907**	**13461**	**98483**	**19811**	**21378**	**52075**	**18561**	**3427.1**	**20093**
	Glycopeptides												
J01X A01	Vancomycin	3020.5	2124.7	1137	1016.6	112	2740.5	1644	627.4	3783	1007.6	1619	621
J01X A02	Teicoplanin	1121	508	151	2358	1038	1168	742.5	2423.5	478.5	228.5	417.5	547
	Sub-total	**4141.5**	**2632.7**	**1288**	**3374.6**	**1150**	**3908.5**	**2386.5**	**3050.9**	**4261.5**	**1236.1**	**2036.5**	**1168**
	Polymyxins												
J01X B01	Colistin	420	1092.6	4.2		248.3	738.4	226.6	130.5	4464.6	1.3	5.3	153.6
	Steroids												
J01X C01	Fusidic Acid	3004.6	1993	339.7	1577.9	2331.7	2408.5	1618.2	3143	4848.7	600.7	198	1142.8
	Imidazoles												
J01X D01	Metronidazole	29957	29486	57134	13234	12085	16534	25773	18645	31483	12574	1227	14424
	Nitrofurans												
J01X E01	Nitrofurantoin	555	880	440	1279	724	1363	1407	590	539.8	368	87.7	797
	Oxazolidinones												
J01X X08	Linezolid	15	38	774		260	241	75	71	44	30	131	
	TOTAL DDDs	**413011**	**403807**	**330315**	**185511**	**151724**	**328851**	**268607**	**173368**	**769661**	**158421**	**43032**	**206543**

Table 3.2 Antibiotic use for each hospital site for 2002/3 expressed as DDDs with antibiotics listed by ATC category.

ATC Code	Antibiotic	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8	Hospital 9	Hospital 10	Hospital 11	Hospital 12
	Tetracyclines												
J01A A01	Demeclocycline			347	153	308	413	896	297	434			
J01A A02	Doxycycline	38694	25569	34478	11493	11652	24464	21464	5696	42582	2674	619	19963
J01A A04	Lymecycline		19		1313		162	19	132	333		17.5	313
J01A A06	Oxytetracycline	960.5	5550	2244	1323	539	583	3311	647	1528	3836	258	1206
J01A A07	Tetracycline	244	185	7	207	48	5	84	225	851	5	1147.5	95
J01A A08	Minocycline	1196.5	213	490	409	812	315	3514	28	1655		35	180
	Sub-total	**41095**	**31536**	**37566**	**14898**	**13359**	**25942**	**29288**	**7025**	**47383**	**6515**	**1819**	**21757**
	Amphenicols												
J01B A01	Chloramphenicol	50	77	2.7		28	16	42.6	7		738.7		12.6
	Penicillins												
J01C A01	Ampicillin	1192.2		209	1297.5				909		68.5	68.5	181.7
J01C A04	Amoxycillin	60819	34097	60052	11644	17675	7163.5	38289	14867	37950	16942	5357	15118
J01C A09	Azlocillin									28.5			
J01C A12	Piperacillin	1.7				10	1.4		6	18.5	18.2	6.5	
J01C E01	Benzylpenicillin	6871.5	6814	4243	1777.8	2076.5	2229.3	169.3	6082.8	13747	7245.8	332.4	2820.3
J01C E02	Phenoxymethylpenicillin	14347	14291	11138	3706.8	4436.2	4903	10342	5695	12966	8091.5	789.6	5922
J01C F05	Flucloxacillin	51519	48651	45603	18181	14635	13423	28583	18166	47051	19323	10733	25859
J01C R02	Amoxycillin + enzyme inhibitor	28012	73815	23570	29077	32714	46008	65950	12117	39415	21321	4048	52729
J01C R03	Ticarcillin + enzyme inhibitor			44	5.9			418.4		83			
J01C R05	Piperacillin + enzyme inhibitor	2053.6	1014	5		479.3	72.8	22.3	37.2	2372	125		250
	Sub-total	**164816**	**178682**	**144864**	**65690**	**72026**	**73801**	**143774**	**57880**	**153631**	**73135**	**21335**	**102880**
	Cephalosporins												
J01D A01	Cefalexin	14643	15892	7077	6444	39.5	4246.5	10166	3555	10145	7471	637	6982
J01D A04	Cefazolin				18								

J01D A06	Cefuroxime oral		3		1493	28		109	7	163.5			25
J01D A06	Cefuroxime iv	15643	24832	11808	4917.5	5488	1840	11434	4744	19801	498.3	3969	5647
J01D A08	Cefaclor	8			460	1677.5	466		21	86	97.5	72.5	32
J01D A09	Cefadroxil				25.5								5
J01D A10	Cefotaxime	268	938	672	369	143	38	1143	3165	2108	985	17.5	1169
J01D A11	Ceftazidime	2858	4269	1414	826	824	2404	1629	939	9426	888	100	665
J01D A13	Ceftriaxone	1458	1602	8	65.5	1863	5263		105	143.5	65.2	13.5	512
J01D A23	Cefixime			31	12.5							3.5	
J01D A31	Cefradine		5	47	79	8154	316.5	125	2126				671
J01D A33	Cefpodoxime		15807										
	Sub-total	**34878**	**63348**	**21057**	**14710**	**18217**	**14574**	**24606**	**14662**	**41873**	**10005**	**4813**	**15708**
	Monobactams												
J01D F01	Aztreonam	64	1008					1.5	5	2235			44
	Carbapenems												
J01D H02	Meropenem	631.5	789.5	77	86	168	20	306	14	5951	412.5		301
J01D H51	Imipenem + enzyme inhibitor	733	590	228.5	128				51.5	2064		165	
	Sub-total	**1364.5**	**1379.5**	**305.5**	**214**	**168**	**20**	**306**	**65.5**	**8015**	**412.5**	**165**	**301**
	Trimethoprim												
J01E A01	Trimethoprim	22591	26571	15220	9834	10058	4606	22553	12378	23609	16694	2357	11967
	Macrolides												
J01F A01	Erythromycin	50379	37334	34907	11685	9149	10993	50256	27454	20239	9823	2403	16275
J01F A09	Clarithromycin	6073	10116	5395	12928	9566	4225	14464	1536.5	16405	3272	175	16087
J01F A10	Azithromycin	2620	1275	331	1179	2702	1325	1173	1127.5	3367	136		1565
	Sub-total	**59072**	**48725**	**40633**	**25792**	**21417**	**16543**	**65893**	**42496**	**63623**	**29925**	**4935**	**45894**
	Lincosamides												
J01F F01	Clindamycin	2302	607	1002.8	58	186.6	395	1234	276.7	5216	344	8.6	1619.9
	Streptogramins												
J01F G02	Quinupristin/Dalfopristin									18		1	
	Aminoglycosides												
J01G A01	Streptomycin	40	17	25				250	30	66			

J01G B01	Tobramycin	1537	2505	821	255.5	244	1715	240	178	15157	38		57.5
J01G B03	Gentamicin	9271	5074	2328	648.5	2657	4796	2100.8	2115	5482	1625	783	1556
J01G B05	Neomycin	175	77	324	65	50	3415	300	100	111.5			174.5
J01G B06	Amikacin	148	99	28	5		85	2.2	2.5	464.5			5
J01G B07	Netilmycin	4					15		5.5	1		20	
	Sub-total	**11175**	**7772**	**3526**	**974**	**2951**	**10026**	**2893**	**2431**	**21282**	**2007**	**803**	**1793**
	Fluoroquinolones												
J01M A01	Ofloxacin		11557	261	1067		66	1300	825.5	5384	390	7386	
J01M A02	Ciprofloxacin oral	36880	21432	18832	10067	6704	1327	18993	21254	25261	9922	2313	18230
J01M A02	Ciprofloxacin iv	2169	2799	483	1090	547	10	1439	1143.5	759.5	1156	49	1520
J01M A06	Norfloxacin		3.5	117.5		2872				275.5		1603	
J01M A07	Levofloxacin	200	56	184			95573	6492	60	93358	38968		10
J01M B02	Nalidixic Acid	20	9.5	10.5			14	7	6	12			42
	Sub-total	**39269**	**35857**	**19888**	**12224**	**10123**	**96990**	**28231**	**23289**	**125050**	**50436**	**11351**	**19802**
	Glycopeptides												
J01X A01	Vancomycin	3110	3765	1545	229.5	145	1535	1375	1548	3907	1537	2471	813.5
J01X A02	Teicoplanin	1817	700	1191	854.5	590	426	389	671	801	360	301	216.5
	Sub-total	**4927**	**4465**	**2736**	**1084**	**735**	**1961**	**1764**	**2219**	**4708**	**1897**	**2772**	**1030**
	Polymyxins												
J01X B01	Colistin	409.5	1190	133.5	198.5			166.9	99	5634.5	1.3		101.3
	Steroids												
J01X C01	Fusidic Acid	3438	1606	273.5	876.5	2138.4	2271	1477	3036.8	265.5	149.5	273.5	457
	Imidazoles												
J01X D01	Metronidazole	34913	33326	22491	11153	10389	17939	26510	19022	33521	16033	1349	16270
	Nitrofurans												
J01X E01	Nitrofurantoin	1613	1197.5	321	997	351	968	1076	780	199		76.9	606.2
	Oxazolidinones												
J01X X08	Linezolid	188	112	641	35	70	540	30	46	1202	44	302	
	TOTAL DDDs	**422165**	**437459**	**310661**	**158738**	**162217**	**266592**	**349848**	**185718**	**513856**	**208337**	**52361**	**240243**

Table 3.3 Antibiotic use for each hospital site for 2003/4 expressed as DDDs with antibiotics listed by ATC category.

ATC Code	Antibiotic	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8	Hospital 9	Hospital 10	Hospital 11	Hospital 12
	Tetracyclines												
J01A A01	Demeclocycline				568	371	511	693	228	861			
J01A A02	Doxycycline	16752	39494	33288	14398	14020	31352	18882	9768	90861	2999	677	20369
J01A A04	Lymecycline	38	19		1334		37		7	873			480
J01A A06	Oxytetracycline	1400	3344	2231	1321	759	903	5422	1186.5	1463	3862	231	890
J01A A07	Tetracycline	10	225	15	140.5	44	1	64	277.5	546	7	1155	20
J01A A08	Minocycline	1232	319	389	617.5	42	322	2520	51	1043		60	182
	Sub-total	**19432**	**4301**	**35923**	**18379**	**15236**	**33126**	**27581**	**11518**	**95647**	**6868**	**2123**	**21941**
	Amphenicols												
J01B A01	Chloramphenicol	228	59	11	5	66	25	15	34	718			10
	Penicillins												
J01C A01	Ampicillin		1205		234.7	929		2	10	629		56	80.5
J01C A04	Amoxycillin	61476	39000	61001	13062	17454	6257	27768	16322	218937	20438	4896	15961
J01C A09	Azlocillin												
J01C A12	Piperacillin						1						
J01C E01	Benzylpenicillin	7250	7682	3870	2148	2573	1856	4467	7203	15349	7911	334	3355.5
J01C E02	Phenoxymethylpenicillin	16757	13015	7942	5519.3	4934	5719	13446	5962	16877	7727	702	6280
J01C F05	Flucloxacillin	60731	48978	47217	20471	13895	13340	40476	19532	52078	12587	10095	20703
J01C R02	Amoxycillin + enzyme inhibitor	69203	75450	20226	37930	40077	53654	81703	14376	41823	17736	3987	59242
J01C R03	Ticarcillin + enzyme inhibitor	9		7	6			532		39			
J01C R05	Piperacillin + enzyme inhibitor	2836	1200	163	23	989	456	32	538	4815	1377	792	
	Sub-total	**218262**	**186530**	**140426**	**79394**	**80851**	**81283**	**168426**	**63943**	**350547**	**67776**	**20862**	**105622**
	Cephalosporins												
J01D A01	Cefalexin	16850	18639	7884.5	8592.5	3.5	8455	10698	4162	8810	8139	593	5688
J01D A04	Cefazolin												

J01D A06	Cefuroxime oral	7	23	51	1876.5	200		154	9	127			23
J01D A06	Cefuroxime iv	13697	24710	10947	7419	6118	4363	12682	5782	19149	5610	3452	6239
J01D A08	Cefaclor	16	5		444	1748	751		7	39	99	102	575
J01D A09	Cefadroxil				19.5						24		
J01D A10	Cefotaxime	384	767.5	759.5	236	126	59	1082	2626	2280	874	40	969
J01D A11	Ceftazidime	2145.5	5955	1504	823.5	652	1980.5	1571	406	12303	153	145	704
J01D A13	Ceftriaxone	2037.5	1933	26	107	1694.5	5215	61	81	387	227	30	1090
J01D A23	Cefixime				29.5				3				
J01D A31	Cefradine		9.5	44	31.5	7836	387.5		3797	7			327
J01D A33	Cefpodoxime			5749									
	Sub-total	**35137**	**52042**	**26965**	**19579**	**18378**	**21211**	**26248**	**16873**	**43102**	**15126**	**4362**	**15615**
	Monobactams												
J01D F01	Aztreonam	1	1517							2471			13
	Carbapenems												
J01D H02	Meropenem	1512.5	288.5	62	120.5	199	97	746	21.5	9580	855		176
J01D H51	Imipenem + enzyme inhibitor	732.5	786.5	158	212.5		159		118.5	59		149	
	Sub-total	**2245**	**1075**	**220**	**333**	**199**	**256**	**746**	**140**	**9639**	**855**	**149**	**176**
	Trimethoprim												
J01E A01	Trimethoprim	23997	24298	13931	15704	12118	12655	21855	10975	7092	17952	2022	14678
	Macrolides												
J01F A01	Erythromycin	52591	39272	104573	10881	7635	10969	30421	20764	152060	11076	2389	10182
J01F A09	Clarithromycin	6076	12156	19632	16053	10915	5920	14595	17812	20295	3570	122	22760
J01F A10	Azithromycin	3180	2147	332	41	2967	762	2700	688	5397	114	7	1790
	Sub-total	**61847**	**53575**	**124537**	**26975**	**21517**	**17651**	**47716**	**39264**	**177752**	**14760**	**2518**	**34732**
	Lincosamides												
J01F F01	Clindamycin	3568	1157	1151	435	1437	83	224	74	7590	500		1410
	Streptogramins												
J01F G02	Quinupristin/Dalfopristin												
	Aminoglycosides												
J01G A01	Streptomycin			39				120	21	68	10		

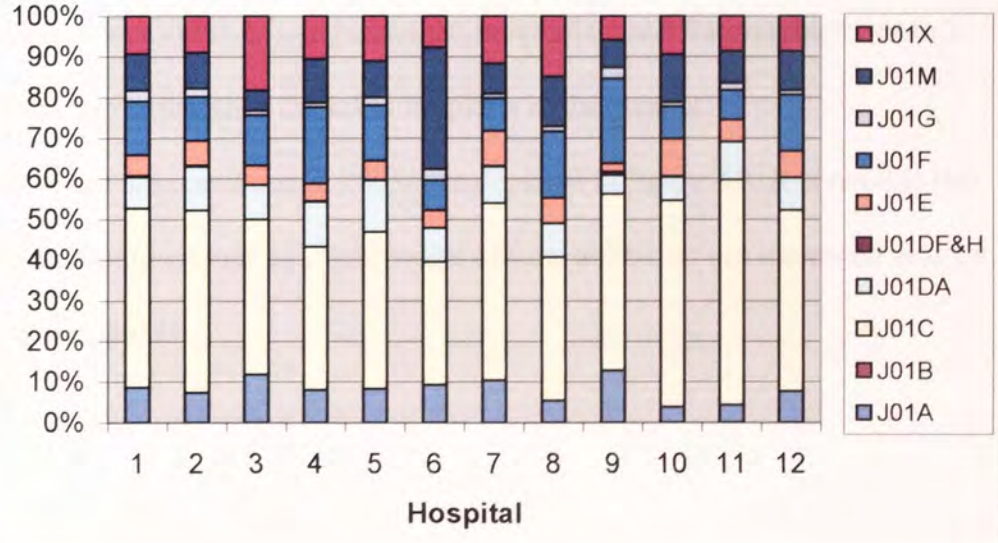
J01G B01	Tobramycin	896	2816	804	70	311	1578	198	65.5	18026	25		10
J01G B03	Gentamicin	10693	5039	2743	1719	2945	4911	2628	2660	6223	2391	638	1957
J01G B05	Neomycin		148	153	185		4099	50	50	133	110		123
J01G B06	Amikacin	1250	37	98	1		4		1	342	197		5
J01G B07	Netilmycin								2.5				
	Sub-total	**12839**	**8040**	**3837**	**1975**	**3256**	**10592**	**2996**	**2800**	**24792**	**2733**	**638**	**2095**
	Fluoroquinolones												
J01M A01	Ofloxacin	2055	10175	939	1080		11	1680	900	4090	1099		6093
J01M A02	Ciprofloxacin oral	39125	25663	24498	12094	9372	1430	22856	19578	36860	13602	1679	13544
J01M A02	Ciprofloxacin iv	2136	3145	575	1278	488	11	1780	1933	843	736.4	76	2349
J01M A06	Norfloxacin	14	79			1806				554		851	
J01M A07	Levofloxacin	120	214	64	66	10	85778	4528	40	56807	45144	5	
J01M B02	Nalidixic Acid				7		7	28	10				39
	Sub-total	**43450**	**39276**	**26076**	**14525**	**11676**	**87237**	**30872**	**22461**	**99154**	**60581**	**2611**	**22025**
	Glycopeptides												
J01X A01	Vancomycin	3925	4077	1945	234	274	1595	1481	1704	4954	1023	1836	864
J01X A02	Teicoplanin	3330	875	94	989	1202	504	383	355	717	578	183	327
	Sub-total	**7255**	**4952**	**2039**	**1223**	**1476**	**2099**	**1864**	**2059**	**5671**	**1601**	**2019**	**1191**
	Polymyxins												
J01X B01	Colistin	515	1449	296	113	130	631	313	30	8524	37	15	218
	Steroids												
J01X C01	Fusidic Acid	2686	2229	488	748	2559	2137	1277	2769	2573	842	385	634
	Imidazoles												
J01X D01	Metronidazole	35606	39272	26114	13810	11420	17756	29357	19719	30466	17139	1118	18592
	Nitrofurans												
J01X E01	Nitrofurantoin	1042	1163	1031	1206	1297	1275	1397	525	767	1104	410	606
	Oxazolidinones												
J01X X08	Linezolid	60	239	556		81	974	245	110	5338	56	215	75
	TOTAL DDDs	**468170**	**421174**	**403601**	**194404**	**181697**	**288991**	**361132**	**193294**	**871843**	**207930**	**39447**	**239633**

Figures 3.1, 3.2 and 3.3 show the percentage of total antibiotic use by ATC category for each hospital for 2001/2, 2002/3 and 2003/4 respectively.

The ATC categories are:

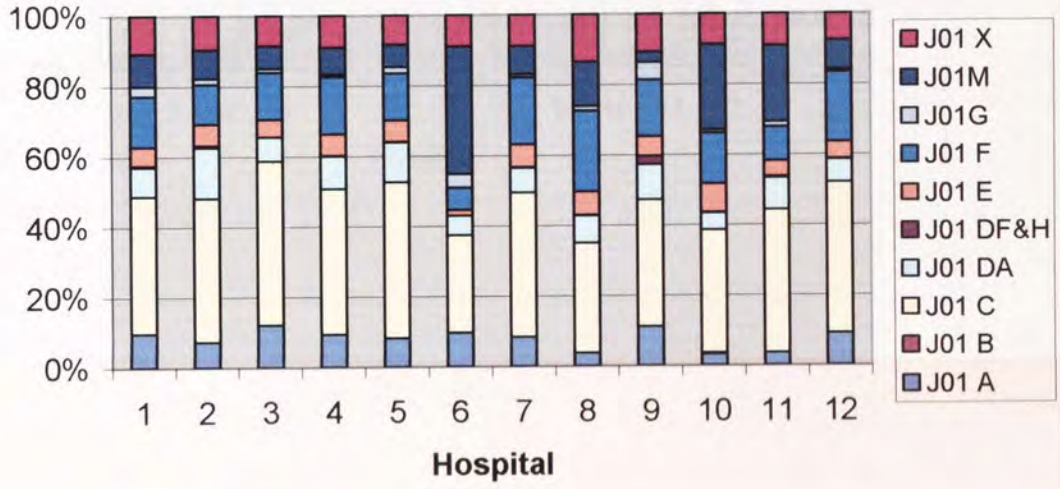
J01 A	Tetracyclines
J01 B	Amphenicols
J01 C	Penicillins
J01 DA	Cephalosporins
J01 DF & H	Monobactams & Carbapenems
J01 E	Trimethoprim
J01 F	Macrolides, Lincosamides & Streptogramins
J01 G	Aminoglycosides
J01 M	Fluoroquinolones
J01 X	Glycopeptides, Polymyxins, Steroids, Imidazoles, Nitrofurans & Oxazolidinones

Figure 3.1 Percentage of antibiotic usage by ATC Classification for each hospital 2001/2



The Penicillins make up the group that is used most commonly. It is notable that there is variation within the sample in the percentage of total use represented by cephalosporins (J01 DA), macrolides (J01 F) and fluoroquinolones (J01 M).

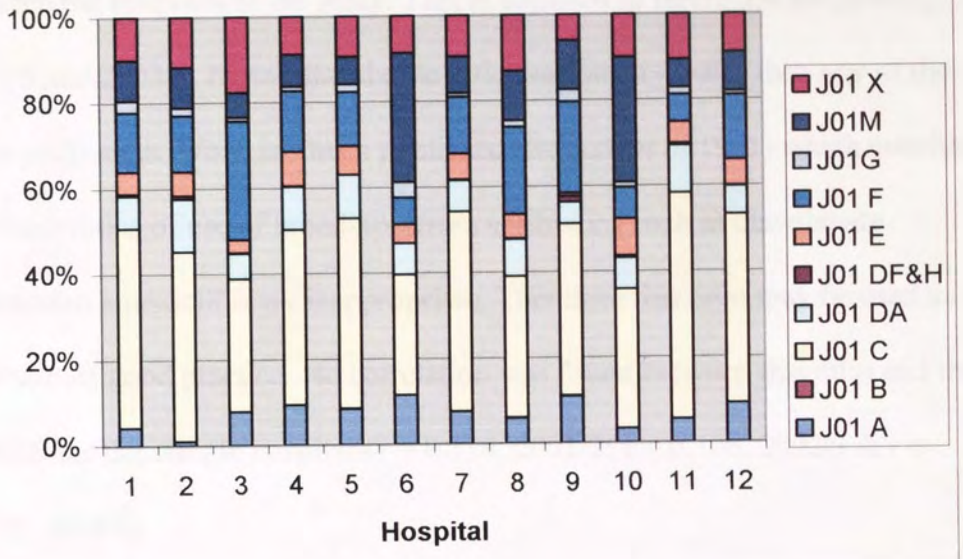
Figure 3.2 Percentage of antibiotic usage by ATC Classification for each hospital 2002/3



The use of antibiotics depicted in figure 3.2 for 2002/3 shows continued variability in use of cephalosporins (J01 DA), macrolides (J01F) and also fluoroquinolones (J01 M). In particular, hospital 6 used fluoroquinolones to a much greater extent than the other hospitals in the sample.

These trends are continued in 2003/4 as depicted in figure 3.3. It is notable that use of fluoroquinolones as a percentage of total antibiotic use increased year on year at hospital 10

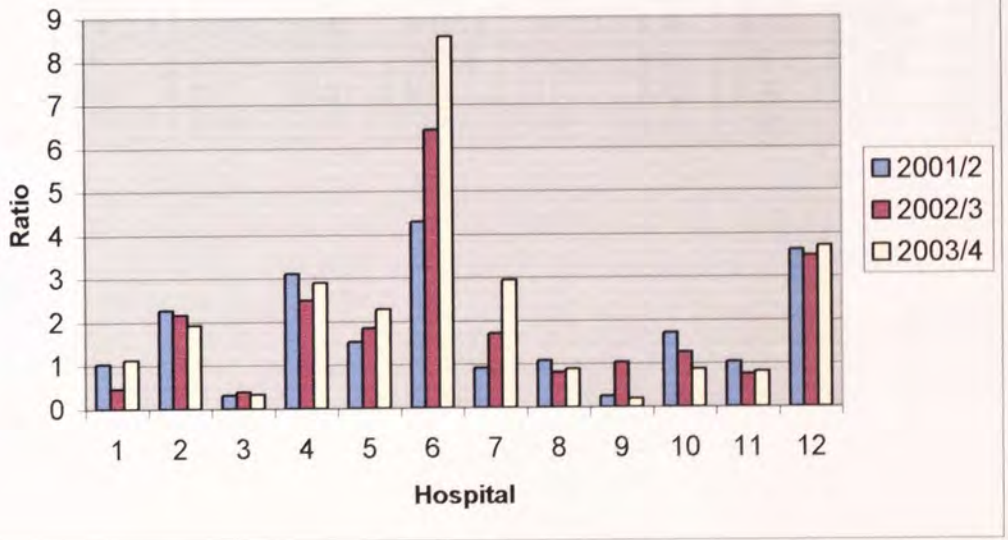
Figure 3.3 Percentage of antibiotic use by ATC Classification for each hospital 2003/4



3.2.2 Use of amoxicillin and clavulanate potentiated amoxicillin.

The ratio of use of clavulanate potentiated amoxicillin to amoxicillin varied between the hospitals in the study. This is depicted in figure 3.4 for 2001/2, 2002/3 and 2003/4. In hospital six the ratio was much greater than any of the other study sites. Work has been published (Burkett *et al* 1991) which concluded that high ratios of use of broad-spectrum antibiotics such as clavulanate potentiated amoxicillin are inappropriate. Therefore this ratio may be used as an indicator of good practice. No correlation was found between this ratio and the MMAS for the sample hospitals($r = 0.136$, 2001/2; $r = 0.306$, 2002/3 & $r = 0.375$, 2003/4).

Figure 3.4 Ratio of Clavulanate potentiated Amoxicillin DDD to Amoxicillin DDD for 2001/2, 2002/2 & 2003/4.

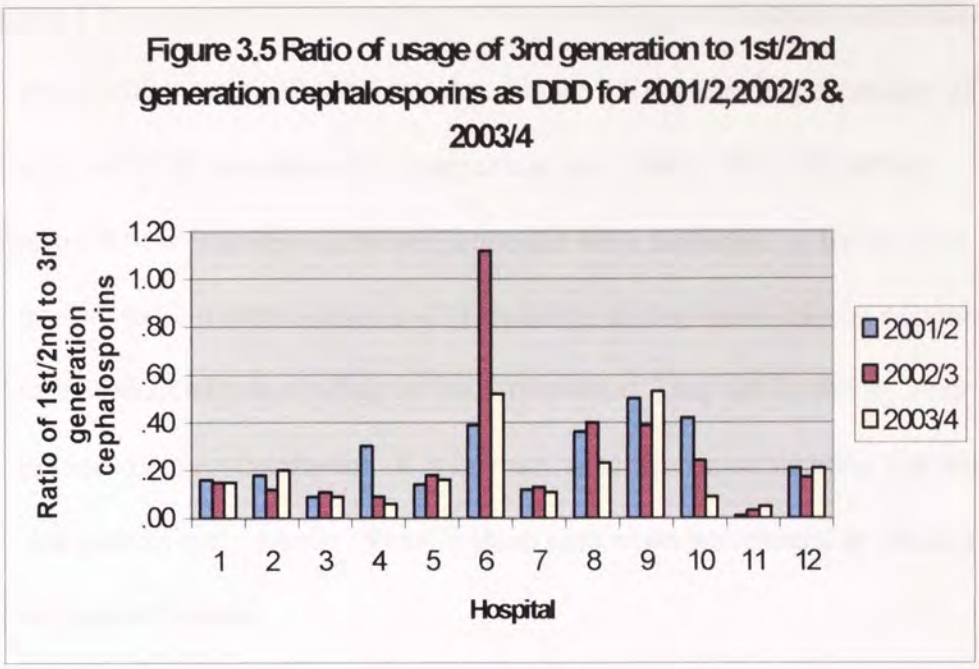


3.2.3 The use of first/second and third generation cephalosporins.

The use of third generation cephalosporin antibiotics is controlled in hospitals in order to control treatment costs and also the emergence of resistance (Godin *et al.*1988; Guglielmo *et al.* 1994; Lang *et al.* 2001). The ratio of use of first and second generation to third generation cephalosporins may be an indicator of the influence of medicines management on the precribing of this class of antibiotics. The data is shown in table 3.4 and in figure 3.5.

Table 3.4. Ratio of number of DDDs of 1st/2nd Generation Cephalosporin use to 3rd Generation Cephalosporin use in 2001/2, 2002/3 & 2003/4.

	2001/2			2002/3			2003/4		
Hospital	1st/2nd	3rd	Ratio	1st/2nd	3rd	Ratio	1st/2nd	3rd	Ratio
1	27398	4365	**0.16**	30294	4584	**0.15**	30570	4567	**0.15**
2	36853	6572	**0.18**	56539	6809	**0.12**	43386.5	8655.5	**0.20**
3	25829.5	2365.5	**0.09**	18963	2094	**0.11**	24675.5	2289.5	**0.09**
4	15610.5	4759.5	**0.30**	13449.5	1260.5	**0.09**	18412.5	1166.5	**0.06**
5	16823.2	2347	**0.14**	15387	2830	**0.18**	15905.5	2472.5	**0.16**
6	19581.8	7816.2	**0.39**	6869	7705	**1.12**	13956.5	7254.5	**0.52**
7	21483.2	2685.8	**0.12**	21834	2772	**0.13**	23534	2714	**0.11**
8	10634.5	3839.5	**0.36**	10453	4209	**0.40**	13760	3113	**0.23**
9	23812.9	11902.7	**0.50**	30195.5	11677.5	**0.39**	28132	14970	**0.543**
10	6445	2684.4	**0.42**	8066.8	1938.2	**0.24**	13872	1254	**0.09**
11	3914.2	46.7	**0.01**	4682	131	**0.03**	4147	215	**0.05**
12	13771.5	2866.5	**0.21**	13362	2346	**0.17**	12852	2763	**0.21**



Hospital six had a high proportion of use of 3rd generation cephalosporins (as cefotaxime) in 2002/3, when compared with the rest of the sample.Use at hospitals' two, nine and twelve decreased in the second year of the study when compared to the first year and returned to the same or to an increased (2,9) level of useage in the third year of the study. Two hospitals (4 & 10) had a year on year reduction in the ratio of 3rd generation cephalosporin and 1st/2nd generation cephalosporin use. No correlation was found between this indicator and the MMAS (r = 0.185 2001/2, r = 0.478 2002/3 & r = 0.380 2003/4) for all hospitals in the sample.

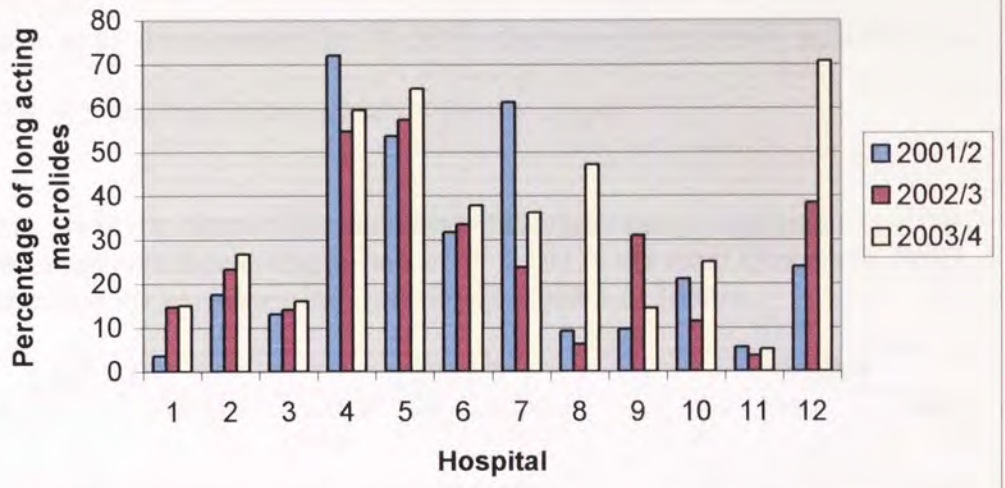
3.2.4 The use of macrolides and long-acting macrolides.

Table 3.5 contains the data relating to the percentage of the total macrolide use represented by long acting macrolides. Figure 3.6 depicts the percentage of macrolide DDD represented by long acting macrolides. The long acting macrolides clarithromycin and azithromycin were marketed on the basis of improved patient convenience and compliance as they need only be administered once or twice daily depending on the formulation. They are however, more expensive than erythromycin. It is instructive to determine whether any pattern of use such as early uptake of use of these medicines was related to Medicines Management scores.

Table 3.5 Percentage of total macrolide DDD represented by long acting macrolides for each hospital in 2001/2, 2002/3 and 2003/4

	Percentage of total macrolide DDD represented by long acting macrolides		
Hospital	2001/2	2002/3	2003/4
1	3.5	14.7	14.9
2	17.5	23.3	26.7
3	13	14.1	16
4	72	54.7	59.6
5	53.6	57.3	64.5
6	31.7	33.5	37.8
7	61.3	23.7	36.2
8	9.2	6.2	47.1
9	9.7	31.0	14.4
10	21	11.4	24.9
11	5.5	3.5	5.1
12	23.8	38.4	70.6

Figure 3.6 Percentage of macrolide DDD represented by long-acting macrolides for 2001/2, 2002/3 & 2003/4



There was variation between hospitals in particular sites 4,5,6 and 7 were early adopters of the use of long acting macrolides while hospital 12 showed a rapid increase in uptake year on year. No correlation between levels of use of long acting macrolides and Medicines Management scores was found ($r = 0.060$ 2001/2, $r = 0.106$ 2002/3 & $r = 0.030$ 2003/4) across all hospitals.

3.2.5 Percentage of total quinolone use represented by intravenous quinolone administration.

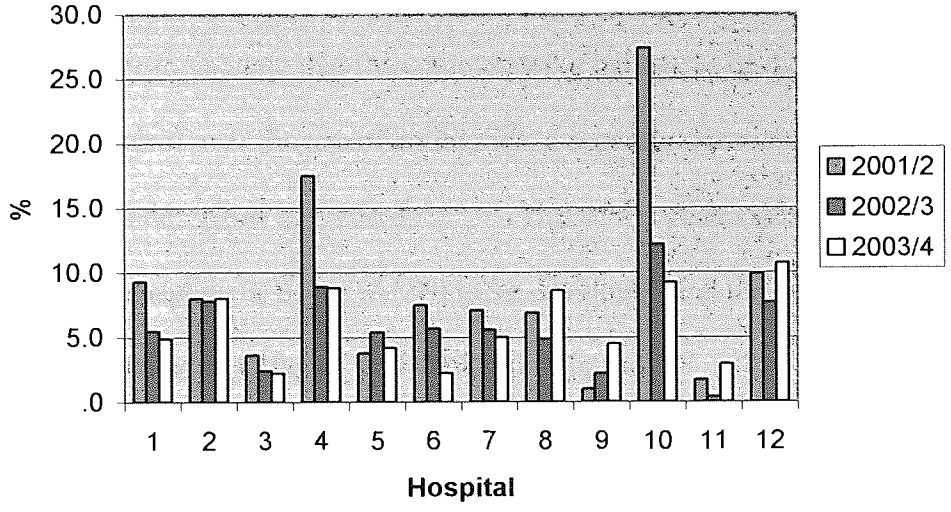
Another indicator of effective control of prescribing is the percentage of total quinolone DDDs which are prescribed by the oral route. When quinolones are prescribed, use of the oral route is more cost-effective and has equal efficacy to the parenteral route (Jensen and Paladino, 1997; Paladino *et al.*,1991). Table 3.6 and figure 3.7 show the trends in use of IV and oral quinolones in each hospital. Hospitals 4 and 10 can be seen as exhibiting very high % of IV Quinolone use in 2001/2 when compared with the rest of the hospitals. There is a reduction in variation between the hospitals over time (2001/2 SD = 7.35, 2002/3 SD = 3.20,

2003/4 SD = 2.97) in the use of the IV route of administration of quinolones. No correlation was found between this indicator and MMAS (r = 0.073 2001/2, r = 0.103 2002/3 and r = 0.254 2003/4) globally. The mean percentage of total quinolone used represented by IV DDDs decreased from 8.64% in 2001/2, to 5.72% in 2002/3 to 5.93% in 2003/4 for the sample.

Table 3.6 Intravenous (IV) and Oral Quinolone usage expressed as DDD with the percentage contribution of IV DDD to the total Quinolone DDD prescribed for each hospital, for 2001/2, 2002/3 & 2003/4.

	2001/2			**2002/3**			**2003/4**		
Hospital	IV	Oral	%IV of total	IV	Oral	%IV of total	IV	Oral	% IV of total
1	3496	33872	**9.3**	2168	37100	**5.5**	2136	41314	**4.9**
2	2852.2	32895.8	**8.0**	2799	33058	**7.8**	3145	36131	**8.0**
3	597	15821	**3.6**	483	19405	**2.4**	575	25501	**2.2**
4	3482.6	16424.4	**17.5**	1090	11134	**8.9**	1278	13247	**8.8**
5	518	12943	**3.8**	547	9576	**5.4**	488	11188	**4.2**
6	7397	91086	**7.5**	5493	91497	**5.7**	1888	85349	**2.2**
7	1405	18406	**7.1**	1582	26649	**5.6**	1568.5	29323.5	**5.0**
8	1471	19907	**6.9**	1143.4	22145.6	**4.9**	1933	20528	**8.6**
9	542	51533	**1.0**	2793.5	122256.5	**2.2**	4507	94647	**4.5**
10	5080	13481	**27.4**	6014	43266	**12.2**	5550.4	55030.6	**9.2**
11	59.6	3367.5	**1.7**	49	11302	**0.4**	76	2535	**2.9**
12	1997	18096	**9.9**	1520	18282	**7.7**	2349	19676	**10.7**

Figure 3.7 Percentage of total Quinolone DDD prescribed as parenteral formulation in 2001/2, 2002/3 and 2003/4



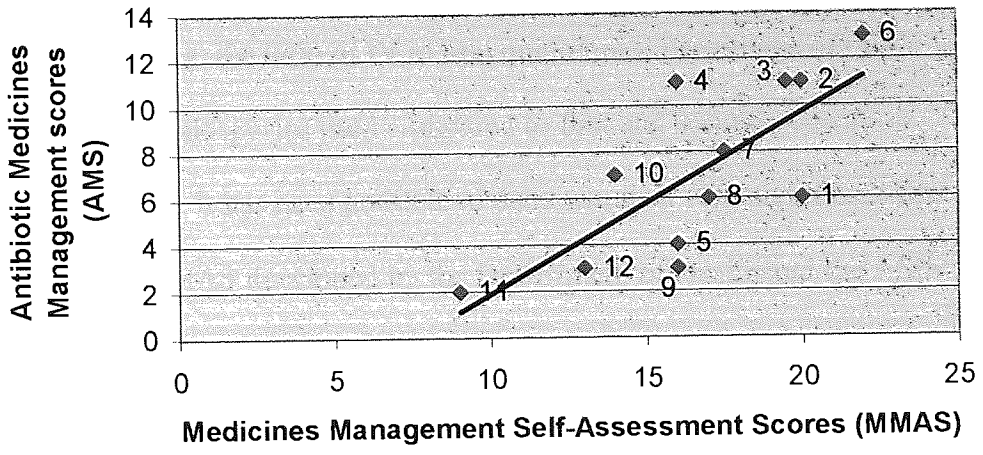
3.2.6 Medicines Management self-assessment scores (MMAS) and Antibiotic Medicines Management scores (AMS).

The Medicines Management Self-Assessment Scores (MMAS) for each of the twelve hospitals were used as a criterion for selection of the hospitals in the study. In order to validate that these scores were indicative of the influence of pharmacy control over the use of antibiotics, a separate questionnaire was developed (as described in methods 2.3.4). Use of the questionnaire enabled an Antibiotic Management Score (AMS) to be developed and the values for both scores are detailed in table 3.7 and depicted in figure 3.8.

Table 3.7 Medicines Management Score (MMS) and Antibiotic Management Score (AMS) for each hospital.

Hospital (cohort)	Medicines Management score (max 23)	Antibiotic management score (max 22)
1 (A)	20	6
2 (A)	20	11
3 (A)	19.5	11
4 (B)	16	11
5 (B)	16	4
6 (B)	22	13
7 (C)	17.5	8
8 (C)	17	6
9 (C)	16	3
10 (D)	14	7
11 (D)	9	2
12 (D)	13	3

Figure 3.8 Comparison of Medicines Management self-assessment scores (MMAS) with Antibiotic Medicines Management scores (AMS)



There was a very significant correlation ($r = 0.74$, $p < 0.01$) between the Medicines Management Self-Assessment Score (MMAS) and the Antibiotic Medicines Management Score (AMS).

3.3 Discussion

3.3.1 Introduction to the discussion.

The data collected in this chapter relate to measures of quality in the prescribing of antibiotics (e.g. the ratio of IV to oral quinolones, percentage of third generation cephalosporins used compared to first and second generation cephalosporins). It has been possible to demonstrate a very significant correlation between the MMAS developed by the Department of Health and the AMS introduced in this study and therefore supports the MMAS, which is widely utilized and adopted, as indicative of the degree of medicines management infrastructure that is operational within a hospital. From the findings from the present study it was also possible to compare some of the various indicators of quality of antibiotic prescribing to establish whether it can be demonstrated that medicines management measures can be shown to influence antibiotic prescribing quality.

3.3.2 Penicillins (J01B)

The most extensively used antibiotic class was the penicillins (J01B) and within this group amoxicillin and clavulanate potentiated amoxicillin (co-amoxiclav) were the most widely used antibiotics. These antibiotics are widely used in surgical and accident and emergency departments, as they have a broad spectrum of activity and they are used in circumstances where the identity of the infecting organism may be unknown. Figure 3.4 illustrates that there was a year on year consistency of choice of prescribing clavulanate potentiated amoxicillin (co-amoxiclav), except at hospitals six and seven. Hospital six exhibited ratios of 4.29, 6.42 and 8.5:1 in 2001/2, 2002/3 and 2003/4 respectively of DDDs of co-amoxiclav to amoxicillin which was higher than the rest of the group. Hospital

seven exhibited a similar trend but at much lower ratios, 0.8, 1.7 amd 2.9:1 for 2001/2, 2002/3 and 2003/4 respectively. There is a view amongst microbiologists that widespread use of broad-spectrum penicillins should be discouraged in favour of use of narrow-spectrum penicillins (such as flucloxacillin) when the sensitivity of the infecting organism has been established (Burkett *et al*, 1991; Yu *et al*, 1991; Lutters *et al* 1998). This will reduce the development of resistance and reduce antibiotic related toxicity. It is suggested that indications of clavulanate potentiated amoxicillin use of a ratio exceeding 2:1 compared with amoxicillin use should be adopted as a benchmark for initiation of audit of practice.

3.3.3 Cephalosporin use (J01D).

In eight of the twelve hospitals the proportion of 3rd generation cephalosporins (ceftazidime, ceftriaxone & cefotaxime) to 1st/2nd generation cephalosporin use was relatively constant year on year (mean 0.24, 0.26 & 0.20 respectively). At two hospitals there was a year on year trend to a reduced proportion of 3rd generation cephalosporin usage, whilst at two hospitals usage was variable. At hospital six the data for 2002/3 showed that more 3rd generation cephalosporins were used than 1st/2nd generation variants. As this is an electronic prescribing site these findings are likely to result from a specific prescribing policy within the hospital, as the prescribing system will be able to ensure that antibiotics are prescribed according to approved policies. The use of narrow spectrum first and second generation cephalosporin might be deemed desirable as many hospitals restrict the use of third generation cephalosporins (Godin *et al.*, 1988; Watson, 2002) as they are broad-spectrum antibiotics which can promote development of

resistance (Lang *et al.*, 2001; Norrby, 1996). They also have a high acquisition cost and therefore low usage of third generation cephalosporins might be seen as an indicator of good practice. The use of third generation cephalosporins has been identified as being associated with the development of MRSA (Wilcox, 2005). In particular high rates of resistance to ceftazidime amongst some Gram negative organisms are thought to reflect its clinical use (Public Health Laboratory Service, 2002). In instances where the ratio of first and second to third generation cephalosporin use was greater than 0.24 may indicate a need for further medicines management intervention.

3.3.4 Macrolides (J01F)

The pattern of use across the hospitals in the sample showed a variation in uptake of use of the longer acting and better tolerated agents clarithromycin and to a lesser extent azithromycin compared to erythromycin. The mean percentage of total macrolide DDD accounted for by these long acting entities changed year on year from 21.1% in 2001/2 to 39.6% in 2002/3 to 27.3% in 2003/4 respectively. It was however noticeable in figure 3.4 that there was variability between individual hospitals with usage of long acting macrolides varying in 2001/2 from 3.5% to 72.0% of macrolide use being accounted for by long acting macrolides. Similar, variability persisted for the three year period with three hospitals having long-acting macrolide use greater than 50% of the total, six hospitals had usage between 20 – 50% of total and three hospitals used less than 20% of their macrolide prescribed as long acting agents.

The case for using long-acting macrolides centres around improved tolerability (mainly reduced gastro-intestinal side-effects), improved patient compliance

owing to the reduced frequency of dosing and reduced nursing costs arising from less frequent medication administration in the ward setting compared to older variants. The major factor against their use is the additional acquisition cost of the medication. The finding that there was great variability in use of long-acting macrolides suggests that individual hospitals have reached different conclusions when making cost-effectiveness decisions. This is also indicative that there may be a potential role for centralised guidance relating to antibiotic selection.

3.3.5 Patterns of use of Quinolones (J01M).

Use of quinolones increased year on year and the ratio of intravenous (IV) to oral (O) use (table 3.6 and figure 3.7) varied. In six of the twelve hospitals studied there was a trend to a reduction in the % of IV quinolone DDDs used compared to oral use over the three year study period. Three hospitals (2, 5,12) showed little change over the three year period and three hospitals experienced an increase in the percentage of doses given by the parenteral route. There was a change in the group mean percentage for all twelve hospitals of IV doses from 8.6% in 2001/2, with a reduction to 5.7% in 2003/3 and then a small increase to 5.9% in 2003/4. In addition, there was a reduction in standard deviation in the results obtained for the percentage of total quinolone DDDs prescribed by the parenteral routefrom 2001/2 to 2002/3 and this was maintained in 2003/4 which was suggestive of a standardisation of practice.

The benefits of early switching from IV to the oral route of administration have been widely documented (Bui and Quintiliani, 1998; Marvin and Dowdall, 1998; Przybylski *et al.*, 1997). However, there is a residual need for IV dosing in patients who are unconscious or unable to take medication by the oral route and

that present results indicate that this will be of the order the total of five percent of quinolone doses administered. This may be used as an indicator of acceptable prescribing and provides a benchmark for comparison between hospitals. Within the sample, use of this benchmark would highlight sites, two, four, eight, ten and twelve for further study.

No correlation was found between the Medicines Management Self-Assessment Score (MMAS) and the % of quinolone doses prescribed and administered intravenously. So, the existence of a well developed infrastructure to influence and control medicines use was not demonstrated to impact on the route of quinolone prescribed. There have been a number of studies published (Przybylski *et al.*, 1997; Pasquale *et al.*, 2004; Marvin and Dowdall, 1998; Kuti *et al.*, 2002; Florea *et al.*, 2004) which demonstrate the impact of pharmacists in changing prescribing habits yet the results from this study did not corroborate this impact. It may be that the proportion of quinolone prescribed by the IV route can only be influenced by specifically targeted programmes a prospective study would be required to demonstrate this. This work would enable an evidence-based approach to be taken in directing funding to appropriate departments to ensure that desired prescribing outcomes are achieved.

3.3.6 Medicines Management Self-Assessment Scores (MMAS) and Antibiotic Medicines Management Scores (AMS).

A strong correlation ($r = 0.74$) was found between MMAS and the AMS (figure 3.8) which supports the use of the MMAS as an indicator of the degree of medicines management control applied to prescribing of antibiotics. It was not possible to demonstrate a link between having a high MMAS and the quality of antibiotic prescribing, using the measures highlighted in this chapter. It is disturbing that the presence of a developed medicines management infrastructure, as demonstrated by a high score in the self-assessment exercise, cannot be demonstrated to impact upon any of the qualitative antibiotic prescribing measures examined. Further work to examine this relationship is urgently required. It may be that a larger sample may provide sufficient data to demonstrate such a link or that other variables such as casemix, characteristics of the referral population or individual hospital's service profiles confound the analysis.

4. Indicators of antibiotic prescribing

4.1 Introduction

The use of the Defined Daily Dose (DDD) as the recognised unit for quantification of antibiotic use is well established (Bergman *et al.* 1980; Wessling and Boethius 1990) and it must be made clear that this is not a dose but a unit of measurement to enable researchers to identify trends in consumption of medicines and also to compare the exposure to specific medicines of population groups (Cosentino *et al.* 2000) (Janknegt *et al.* 2000; Poretta *et al.* 2003; Patrick *et al.* 2004). In order to have value when making quantitative judgements with regard to medicines usage the DDD must be associated with a denominator to correct for workload variations such as numbers of patients treated or number of occupied bed-days of antibiotic treatment dispensed. For hospital in-patients, the number of DDDs per 100 bed-days is normally used. There is an inherent weakness associated with the use of the 100 bed-days measure as a denominator when comparing different hospitals, in that the casemix of the hospital will affect the length of patient stay. In a hospital with a large number of elderly care, orthopaedic or mental health beds, then a small number of patients may be represented by the 100 bed-days. Conversely, hospitals with a large number of ophthalmology, gynaecology and ENT beds will have a tendency to a shorter length of patient stay, which will mean that the 100 bed-days will represent a large number of patients. Therefore, the 100 bed-days does not inherently reflect the numbers of patients exposed to the medicine.

The use of the Finished Consultant Episode (FCE) as a measure of workload in the NHS means that this data is easily obtained and that the FCE may be used as a denominator to compare antibiotic use between hospitals. A comparison of the results obtained for each of the twelve hospitals using both the 100 bed-days and the FCE enables the utility of the FCE to be established.

Trends in the DDD/100 bed-days and DDD/FCE over time may be used to identify changes in prescribing patterns of specific classes of antibiotic and also compare antibiotic use between hospitals at a quantitative level. The use of these prescribing indicators can then be related to other variables to determine their impact on individual hospital antibiotic use without the confounding influence of workload variations.

4.2 Results

4.2.1 Hospital activity data.

The data presented in tables 4.1, 4.2 and 4.3 details the activity of each hospital in terms of FCE's and bed-days, together with the total number of DDDs of antibiotic used together with the derived DDD/100 beddays and DDD/FCE for 2001/2, 2002/3 and 2003/4 respectively.

Table 4.1 Summary FCE, Bed-day and DDD data plus derived DDD/100bedday and DDD/FCE indicators for 2001/2 for each hospital.

Hospital (cohort)	FCEs	Beddays	DDDs	DDD/ 100beddays	DDD/ FCE
1 (A)	93626	376259	413011	109.76	4.41
2 (A)	124357	339618	403806	118.9	3.24
3 (A)	72193	203178	330315	162.57	4.57
4 (B)	48047	142560	185511	130.1	3.86
5 (B)	45225	166047	151724	91.57	3.35
6 (B)	97215	373051	328851	88.14	3.38
7 (C)	66845	263099	268607	102.09	4.01
8 (C)	49856	186924	173368	92.74	3.47
9 (C)	103607	406430	769661	189.37	7.43
10 (D)	54963	176542	158421	89.73	2.88
11 (D)	8984	52906	43032	81.33	4.79
12 (D)	53192	173265	206543	119.2	3.88

Hospitals 3 and 9 have a calculated DDD/100beddays that is greater than the rest of the sample (162.57 DDD/100bedday and 189.37 DDD/100bedday respectively). However, when the DDD/FCE measure is examined hospital 9 remains as a site that has a much greater level of use of antibiotics in comparison to the other sites (7.43 DDD/FCE).

Table 4.2 Summary FCE, Bed-day and DDD data plus derived DDD/100bed-day and DDD/FCE indicators for 2002/3 for each hospital.

Hospital (cohort)	FCEs	Beddays	DDDs	DDD/ 100beddays	DDD/ FCE
1 (A)	97029	387115	422165	109.05	4.35
2 (A)	138676	321075	437459	136.25	3.15
3 (A)	73292	233951	310661	132.79	4.23
4 (B)	49918	141225	158738	112.4	3.18
5 (B)	46836	167478	162217	96.85	3.46
6 (B)	92916	379370	266592	70.27	2.87
7 (C)	69810	261314	349848	133.88	5.01
8 (C)	54736	183917	185718	100.98	3.39
9 (C)	107962	386742	513856	132.87	4.76
10 (D)	57238	191261	208337	108.93	3.64
11 (D)	9430	54533	52361	96.02	5.55
12 (D)	55514	162774	240243	147.59	4.33

The data presented in table 4.2 for 2002/3 shows that there was year on year change when compared with antibiotic usage in table 4.1 2001/2. In particular, hospital 9 had reduced use of antibiotics as measured by DDD/100beddays by 29.8% (35.9% measured by DDD/FCE) from 2001/2 to 2002/3. The use of antibiotics in hospital 12 increased from 2001/2 to 2002/3 by 23.8% as measured by DDD/100beddays (11.59% measured as DDD/FCE).

Table 4.3 Summary FCE, Bed-day and DDD data plus derived DDD/100bed-day and DDD/FCE indicators for 2003/4 for each hospital.

Hospital (cohort)	FCEs	Beddays	DDDs	DDD/ 100beddays	DDD/ FCE
1 (A)	95356	410622	468170	114.01	4.9
2 (A)	146479	333106	421174	126.44	2.87
3 (A)	74986	238951	403601	168.91	5.38
4 (B)	52972	150957	194404	128.78	3.67
5 (B)	44340	181322	181697	100.20	4.09
6 (B)	100199	392495	288991	73.63	2.88
7 (C)	69813	272197	361132	132.67	5.17
8 (C)	56664	193030	193294	100.13	3.41
9 (C)	118433	402086	871843	216.83	7.36
10 (D)	60988	203229	207930	102.31	3.41
11 (D)	9600	54716	39447	72.09	4.11
12 (D)	57244	174581	239633	137.26	4.18

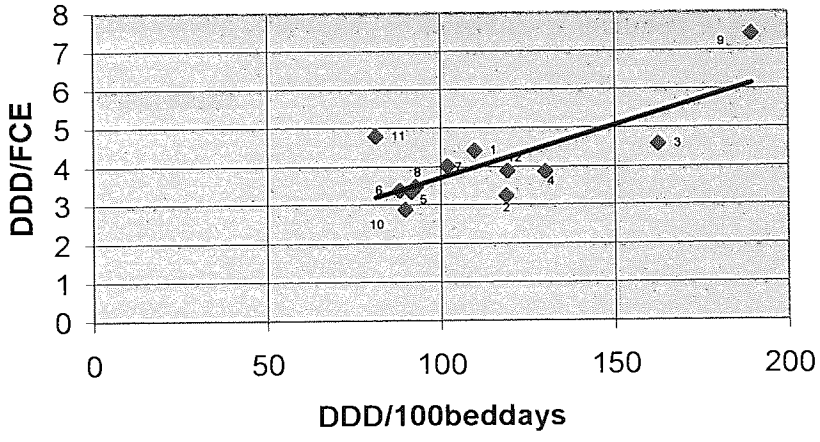
The data in table 4.3 relates to antibiotic use in 2003/4 showed continued variability when compared to the use of antibiotics in 2001/2 and 2002/3. In particular, at hospital 9 the use of antibiotics increased from 2002/3 to 2003/4 by 63.1% DDD/100beddays (54% increase in DDD/FCE).

There was a lower year on year change in the use of antibiotics seen at hospitals 1, 5, 6 and 8 when the DDD/100bedday was used, and at hospitals 2, 6, 8 when the DDD/FCE was used.

4.2.2 The relationship between the DDD/100beddays and the DDD/FCE.

Figure 4.1 shows the relationship between the DDD/100beddays and the DDD/FCE for each hospital in 2001/2.

Figure 4.1 Comparison of DDD/100beddays and DDD/FCE for each hospital for 2001/2.



This figure shows that the DDD/FCE indicator of hospital antibiotic usage correlates with the DDD/100 beddays (Pearson correlation $r = 0.74$ $p < 0.01$). The Pearson correlation for 2002/3 data showed $r = 0.34$ and for 2003/4 $r = 0.804$ ($p<0.01$). This indicates that the DDD/FCE may be used to compare the use of antibiotics in different hospitals (Curtis *et al.*, 2004).

4.2.3 Comparison of the use of antibiotics by ATC class using the prescribing indicators DDD/100beddays and DDD/FCE.

Table 4.4 contains summary data that shows the use of antibiotics expressed as both DDD/100beddays and also DDD/FCE for 2001/2, 2002/3 and 2003/4. The use of antibiotics is presented using the ATC antibiotic classification to enable comparison of antibiotic use to be made by therapeutic class. Data relating to the electronic prescribing cohort (B) of hospitals is included in parentheses for comparative purposes.

Table 4.4 Summary of antibiotic prescribing indicator values by ATC group in sample hospitals (data in parentheses apply to cohort B the electronic prescribing group).

ATC Group	DDD/100bedday			DDD/FCE		
	2001/2	**2002/3**	**2003/4**	**2001/2**	**2002/3**	**2003/4**
J01A Tetracyclines	11.30 (8.54)	9.69 (7.87)	9.71 (9.20)	0.39 (0.30)	0.32 (0.28)	0.33 (0.33)
J01B Amphenicols	0.02 (0.006)	0.03 (0.006)	0.03 (0.013)	0.0009 (0.0002)	0.001 (0.0002)	0.001 (0.0004)
J01C Beta-lactam antibacterials, penicillins	49.64 (32.8)	43.63 (30.74)	52.00 (33.32)	1.73 (1.17)	1.46 (1.11)	1.76 (1.22)
J01D Other beta-lactam antibacterials	9.99 (9.97)	10.26 (6.96)	10.33 (8.27)	0.35 (0.36)	0.34 (0.25)	0.35 (0.30)
J01E Sulfonamides & trimethoprim	6.03 (4.26)	6.21 (3.56)	5.89 (5.58)	0.21 (0.15)	0.20 (0.13)	0.20 (0.20)
J01F Macrolides, lincosamides & streptogramins	16.50 (11.70)	16.65 (9.36)	21.2 (9.39)	0.57 (0.42)	0.56 (0.34)	0.72 (0.34)
J01G Aminoglycosides	2.34 (2.07)	2.35 (2.02)	2.54 (2.18)	0.07 (0.07)	0.07 (0.07)	0.08 (0.08)
J01M Quinolones	12.47 (19.34)	16.45 (17.34)	15.29 (15.65)	0.43 (0.69)	0.55 (0.63)	0.52 (0.57)
J01X Other antibacterials	11.69 (8.87)	10.75 (7.51)	11.47 (8.13)	0.40 (0.32)	0.36 (0.27)	0.39 (0.30)
Total	**119.98 (97.55)**	**116.02 (85.36)**	**128.46 (91.73)**	**4.159 (3.48)**	**3.861 (3.08)**	**4.351 (3.34)**

Total antibiotic usage at the end of the three year period was at a higher level than at the start, 119.98 DDD/100beddays (4.159 DDD/FCE) in 2001/2, 116.02 DDD/100beddays (3.861 DDD/FCE) in 2002/3 and 128.46 DDD/100beddays (4.351 DDD/FCE) in 2003/4. Within the overall prescribing data, usage of 'other beta-lactam' (J01D), macrolides (J01F) and aminoglycosides (J01G) show a year on year increase in usage. The use of penicillins (J01C) and quinolones (J01M) was at a higher level at the end of the three year period than at the beginning. The results for cohort B (electronic prescribing, hospitals 4,5, & 6) show a lower level of antibiotic prescribing than the rest of the sample and which was particularly evident for penicillins (J01C) and macrolides (J01F).

Figure 4.2 Total antibiotic use DDD/100beddays for each hospital in 2001/2, 2002/3 & 2003/4.

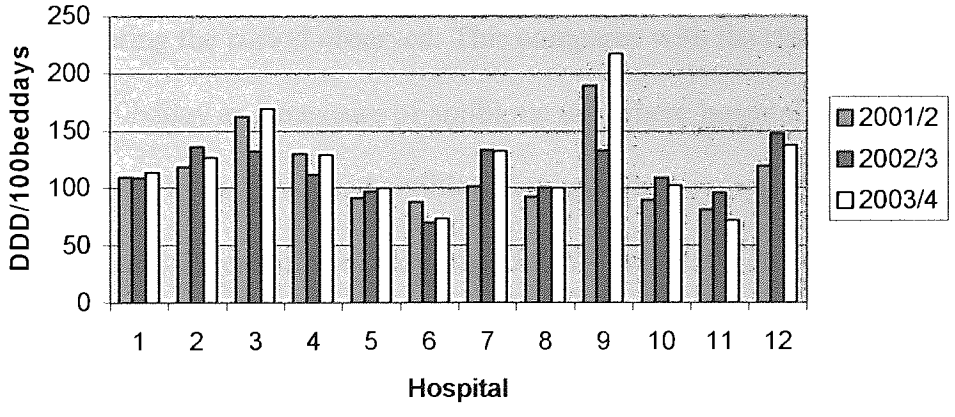


Figure 4.2 shows the trend in total antibiotic usage over time. There are no clear trends with five hospitals showing an increase, three hospitals a decrease and four hospitals no change over the three-year period.

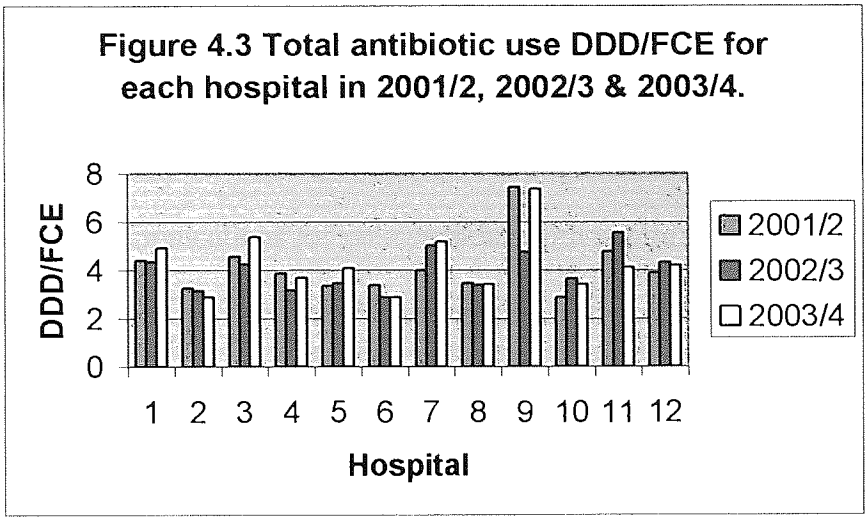


Figure 4.3 shows the total antibiotic usage by hospital over the three-year period expressed as DDD/FCE. Individually, hospitals one, three, five and seven had a higher level of use of antibiotics at the end of the three-year period than at the beginning. Only two hospitals (two and six) had reduced their prescribing of antibiotic during the period observed. This compares with the results when using the DDD/100bdday as a measure of antibiotic use where hospitals six and eleven could be shown to have reduced antibiotic useage when comparing the begininning and the end of the study period. Only hospital 6 demonstrated a reduction in use of antibiotics when using both measures.

Comparatively, within the group, there were four hospitals which had prescribing rates above 4.25 DDD/FCE in 2003/4 (hospitals one, three, seven and nine).

The bivariate correlation between Medicines Management scores and the DDD/100bedday data or the DDD/FCE data was calculated for each year and no correlation was found. For the DDD/100beddays r = 0.183 in 2001/2, r = -0.094

in 2002/3 and r = 0.121 in 2003/4, while for DDD/FCE r = -0.081 in 2001/2, r = -0.158 in 2002/3 and r = -0.550 in 2003/4. The finding that it is not possible to demonstrate that Medicines Management activities have impacted on the quantity of antibiotic prescribed in the twelve hospitals studied is important and may have implications for policymaking with regard to initiatives to reduce the prescribing of antibiotics within hospitals.

4.2.4 Analysis of trends in the prescribing of tetracyclines.

Figures 4.4, 4.5 and 4.6 depict the profile of use of tetracycline antibiotics for the years 2001/2, 2002/3 and 2003/4 respectively. Tetracycline (ATC Group J01A) use in 2003/4 varied by a factor of 7.3 between the hospital with the lowest (0.11 DDD/FCE at site 10) and the hospital with the highest (0.81DDD/FCE at site 9) use. At ten of the twelve hospitals doxycycline was the predominant tetracycline used. At hospital ten, oxytetracycline was used to a larger extent and at site eleven (a specialist orthopaedic hospital) tetracycline was prescribed most frequently compared to other sites.

Figure 4.4 Tetracycline use (DDD/FCE) by hospital for 2001/2

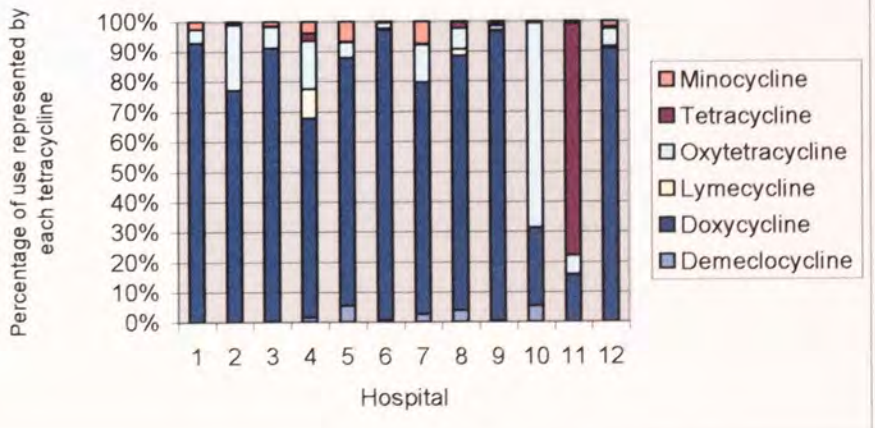


Figure 4.5 Tetracycline use (DDD/FCE) by hospital for 2002/3

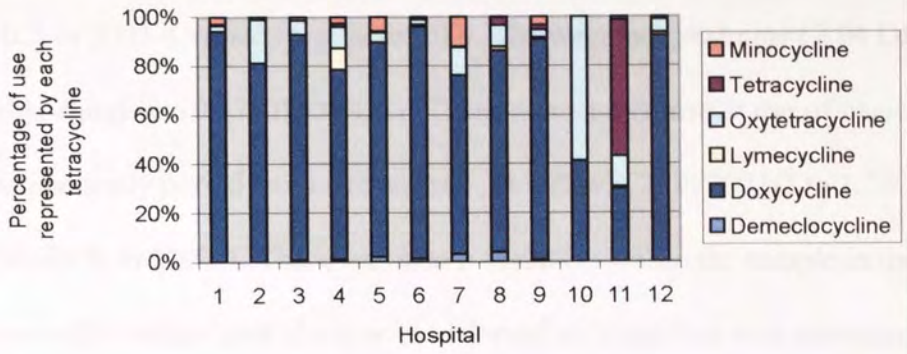
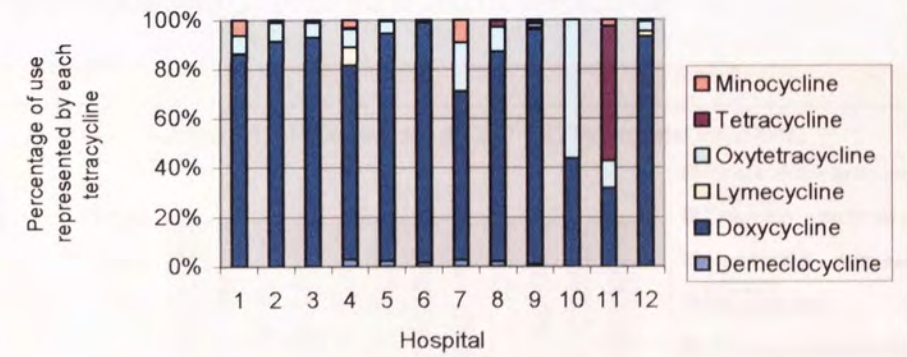


Figure 4.6 Tetracycline use (DDD/FCE) by hospital for 2003/4



4.2.5 Analysis of trends in the prescibing of penicillins.

Figures 4.7, 4.8 and 4.9 show the trends in use of penicillin antibiotics over the three years 2001/2, 2002/3 and 2003/4 respectively. Penicillin use (ATC Group J01C) in 2003/4 varied by a factor of 4.3 between hospital nine (2.94 DDD/FCE) and hospital six (0.67 DDD/FCE). There was an increase in use of penicillins over the study period from a mean of 1.73 DDD/FCE in 2001/2 to 1.76 DDD/FCE in 2003/4. There was also a variation within the sample in the use of amoxycillin either used alone or used formulated together with clavulanic acid. Mean use of amoxicillin over the three years was 0.561, 0.389 and 0.504 DDD/FCE for 2001/2, 2002/3 and 2003/4 respectively, whilst mean use of amoxicillin plus clavulanic acid over the three years was 0.561, 0.515 and 0.595 DDD/FCE for 2001/2, 2002/3 and 2003/4 respectively.

Figure 4.7 Penicillin use (DDD/FCE) by hospital for 2001/2

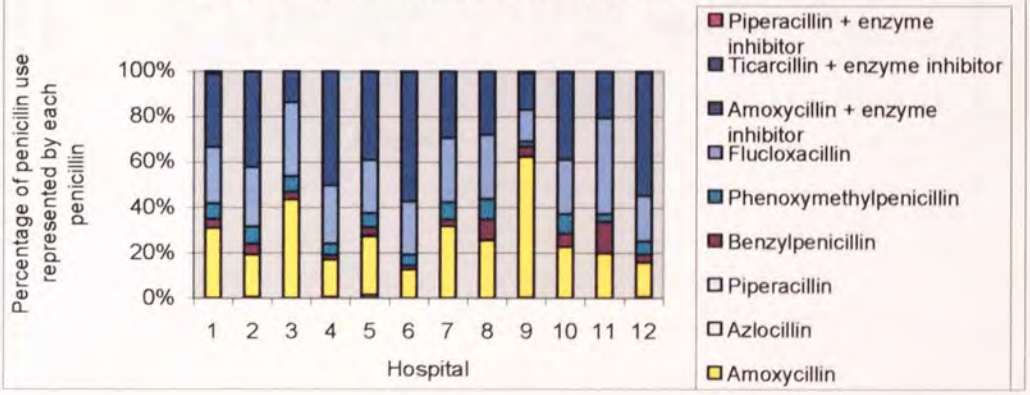


Figure 4.8 Penicillin use (DDD/FCE) by hospital for 2002/3

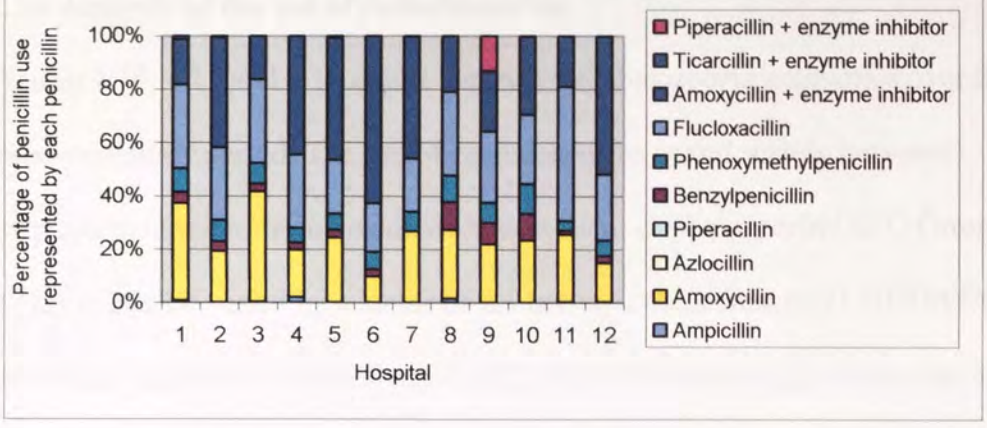
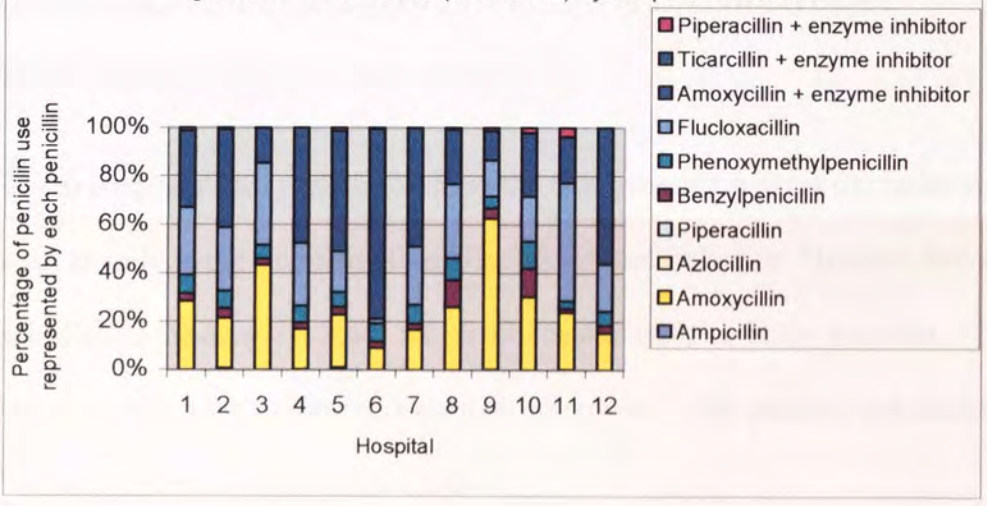


Figure 4.9 Penicillin use (DDD/FCE) by hospital for 2003/4

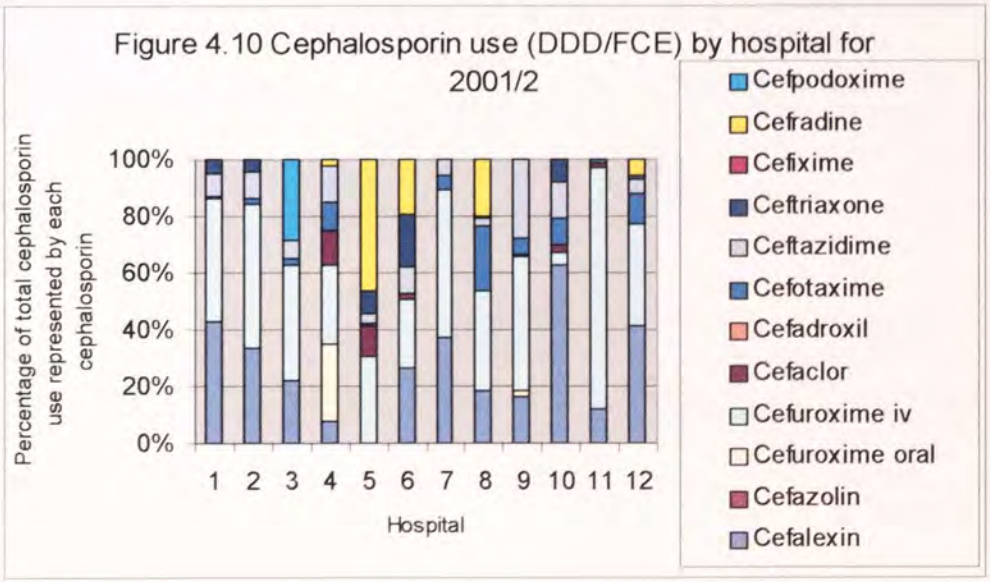


4.2.6 Analysis of the use of cephalosporins.

Figures 4.10, 4.11 and 4.12 depict the use of cephalosporin antibiotics over the three-year study period. The use of cephalosporins varied widely between hospitals in terms of which medicines were used. Cephalosporin (ATC Group J01D) in 2003/4 varied by a factor of 2.1 between the lowest (0.21 DDD/FCE at site 6) and the highest level of use (0.452 DDD/FCE at site 11). Within the sample it is noteworthy that hospital three was the only site to use cefpodoxime. Hospital four was the only site to use significant quantities of oral cefuroxime and this use reduced over time (from 0.116 to 0.029 to 0.035 DDD/FCE for 2001/2, 2002/3 and 2003/4 respectively).

Eleven hospitals used oral cefalexin as the first generation agent of choice with hospital eight using a combination of cefalexin and cefradine. Hospital five used cefradine as the drug of choice for an oral cephalosporin. There was also variation within the group and from year to year as to the quantity and choice of the third generation cephalosporin used.

Figure 4.10 Cephalosporin use (DDD/FCE) by hospital for 2001/2



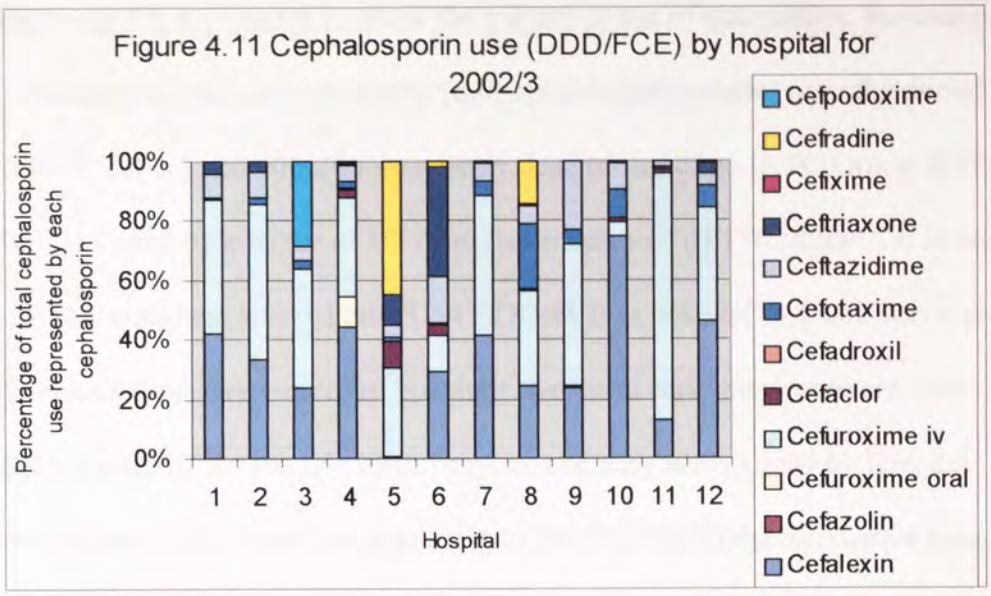


Figure 4.11 Cephalosporin use (DDD/FCE) by hospital for 2002/3
Percentage of total cephalosporin use represented by each cephalosporin
100%
80%
60%
40%
20%
0%
1 2 3 4 5 6 7 8 9 10 11 12
Hospital
Cefpodoxime
Cefradine
Cefixime
Ceftriaxone
Ceftazidime
Cefotaxime
Cefadroxil
Cefaclor
Cefuroxime iv
Cefuroxime oral
Cefazolin
Cefalexin

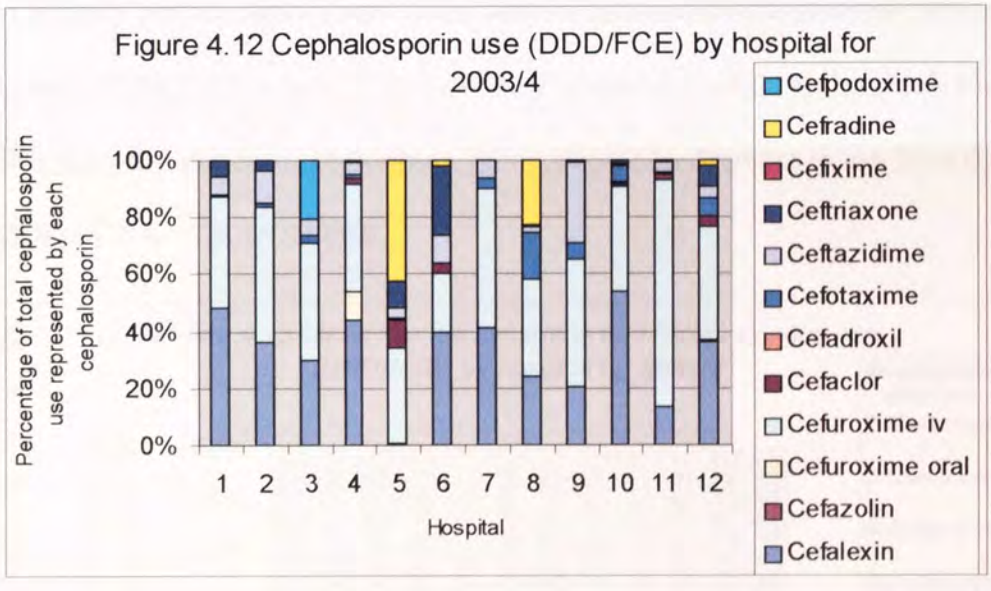


Figure 4.12 Cephalosporin use (DDD/FCE) by hospital for 2003/4
Percentage of total cephalosporin use represented by each cephalosporin
100%
80%
60%
40%
20%
0%
1 2 3 4 5 6 7 8 9 10 11 12
Hospital
Cefpodoxime
Cefradine
Cefixime
Ceftriaxone
Ceftazidime
Cefotaxime
Cefadroxil
Cefaclor
Cefuroxime iv
Cefuroxime oral
Cefazolin
Cefalexin

4.2.7 Analysis of use of macrolides, lincosamides and streptogramins.

Figures 4.13, 4.14 and 4.15 show the pattern of use of macrolides, lincosamides (clindamycin) and streptogramins (quinupristin/dalfopristin) over the period 2001/2, 2002/3 and 2003/4 respectively. Use of this class (ATC Group J01F) in 2003/4 varied by a factor of 8.8 from the lowest rate (0.176 DDD/FCE at hospital six) to the highest level of use (1.56 DDD/FCE at hospital 9).There was a group (hospitals four, five, seven) of hospitals that were early implementers (see 2001/2 data) of the use of clarithromycin, and they were joined by hospital twelve from 2002/3 and hospital eight in 2003/4. Use of the alternative long acting macrolide azithromycin was minimal within the sample. Over the three-year study period, use of macrolides, lincosamide and streptogramins increased from 0.57 DDD/FCE to 0.72 DDD/FCE. The data for cohort B (hospitals four, five, six), the electronic prescribing group, showed a decrease in use from 0.42 DDD/FCE to 0.34 DDD/FCE.

Figure 4.13 Macrolide, Lincosamide and Streptogramin use (DDD/FCE) by hospital for 2001/2

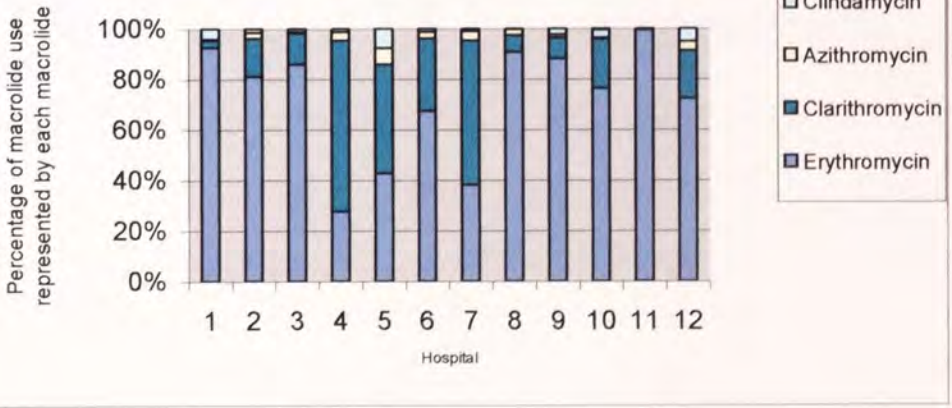


Figure 4.14 Macrolide,Lincosamide and Streptogramin use (DDD/FCE) by hospital for 2002/3

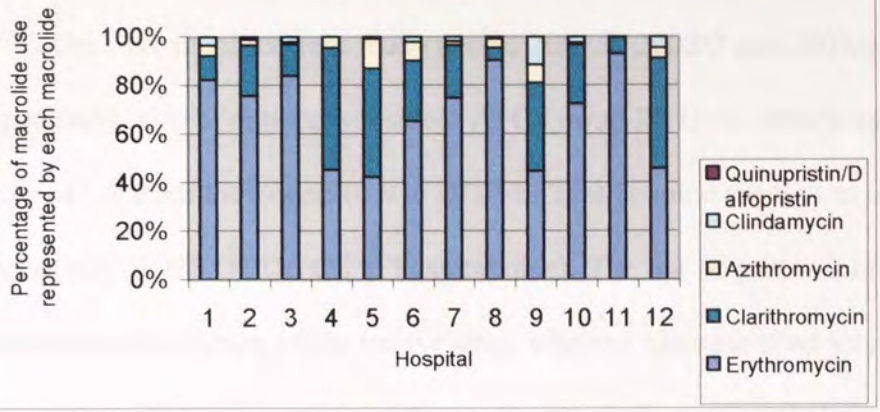
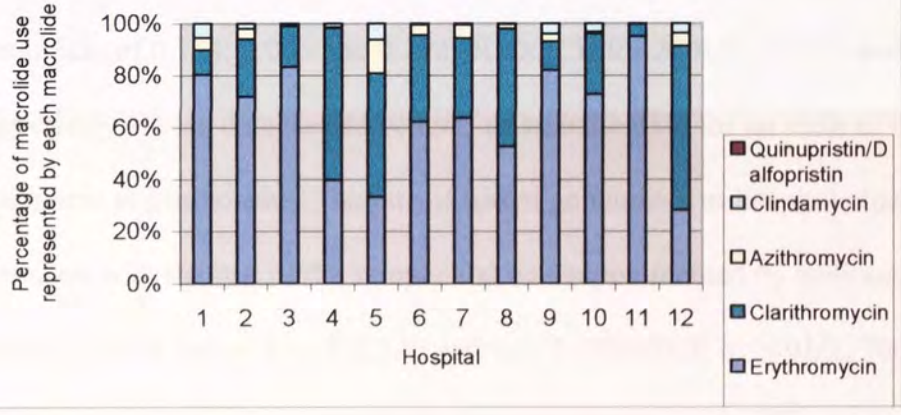


Figure 4.15 Macrolide, Lincosamide and Streptogramin use (DDD/FCE) by hospital for 2003/4



4.2.8 Analysis of use of aminoglycosides.

Figures 4.16, 4.17 and 4.18 show the trend in prescribing of aminoglycoside antibiotics over the three year study period 2001/2, 2002/3 and 2003/4 respectively. Use of aminoglycosides (ATC Group J01G) in 2003/4 varied by a factor of 5.7 from the lowest (0.036 DDD/FCE at hospital twelve) to the highest level of use (0.208 DDD/FCE at hospital nine). The use of gentamicin predominated in eleven of the twelve sites, whereas site nine used tobramycin more widely. Mean annual rates of use of gentamicin remained relatively constant at 0.047, 0.045 and 0.050 DDD/FCE for years 2001/2, 2002/3 and 2003/4 respectively with only small variations within the sample. This was not found at hospital one which had consistantly higher rates of use of gentamicin of 0.104, 0.095 and 0.112 DDD/FCE for 2001/2, 2002/3 and 2003/4 respectively. These data should be used as an indication for an audit of the use of gentamicin at this hospital.The rate of use of gentamicin at hospital nine was consistent with the rest of the sample and was supplemented by additional use of tobramycin at a rate of 0.148, 0.140 and 0.152 DDD/FCE in 2001/2, 2002/3 and 2003/4 respectively. Hospital six was the only site to use significant quantities of Neomycin 0.024, 0.036 and 0.040 DDD/FCE in 2001/2, 2002/3 and 2003/4 respectively.

Figure 4.16 Aminoglycoside use (DDD/FCE) by hospital for 2001/2

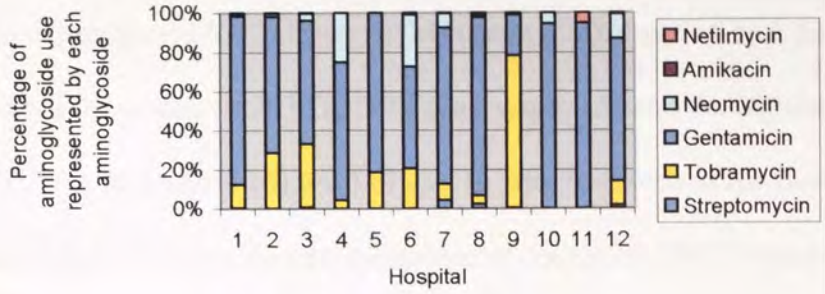


Figure 4.17 Aminoglycoside use (DDD/FCE) by hospital for 2002/3

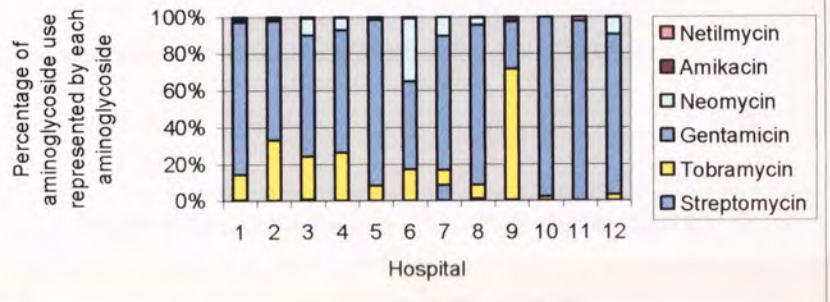
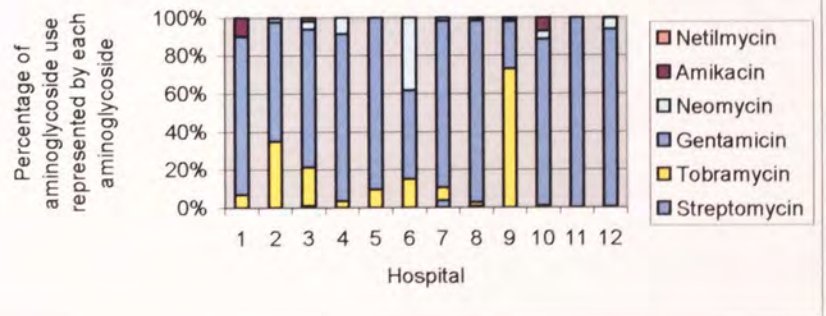


Figure 4.18 Aminoglycoside use (DDD/FCE) by hospital for 2003/4



4.2.9 Analysis of use of quinolones.

Figures 4.19, 4.20 and 4.21 show the use of quinolones for the three years of the study. Quinolone (ATC Group J01M) use in 2003/4 varied by a factor of 3.7 between the lowest (0.263 DDD/FCE at hospital 5) and the highest (0.993 DDD/FCE at hospital 10) level of use. In 2001/2 eleven of the twelve hospitals used ciprofloxacin as the oral quinolone of choice, in 2002/3 eight of the twelve hospitals used oral ciprofloxacin with three hospitals using levofloxacin and one hospital choosing ofloxacin as the oral quinolone of choice. In 2003/4 hospital eleven had stopped using ofloxacin and hospital 12 had changed policy such that 25% of quinolone use was accounted for by ofloxacin.

Figure 4.19 Quinolone use (DDD/FCE) by hospital for 2001/2

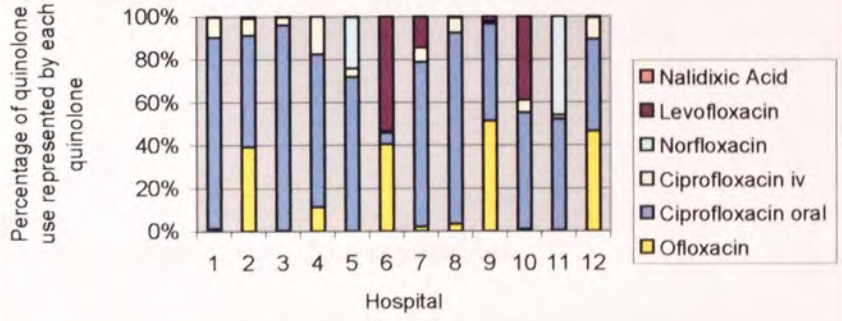


Figure 4.20 Quinolone use (DDD/FCE) by hospital for 2002/3

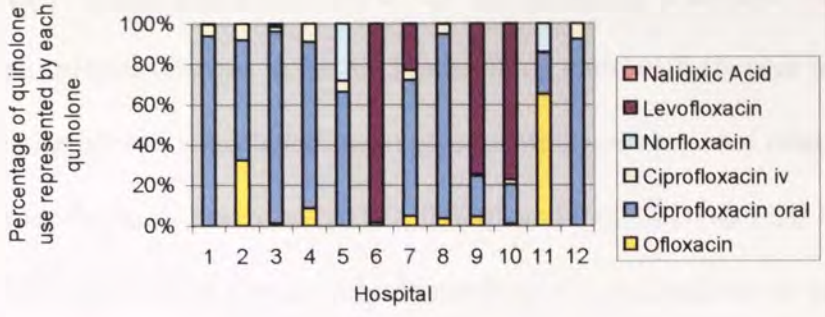
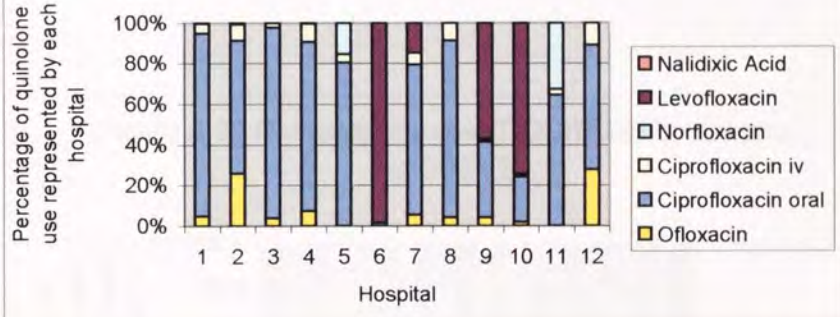


Figure 4.21 Quinolone use (DDD/FCE) by hospital for 2003/4



4.2.10 Analysis of use of glycopeptides.

Figures 4.22, 4.23 and 4.24 show the variation in the use of glycopeptides for the years 2001/2, 2002/3 and 2003/4 respectively. Glycopeptide (ATC Group J01XA) usage in 2003/4 varied by a factor of 10.5 between the lowest (0.02 DDD/FCE at hospital 11) and the highest (0.21 DDD/FCE at hospitals 6 & 12). Hospital eleven, which is a specialist orthopaedic hospital used proportionately larger quantities of vancomycin than the rest of the sample.

The relative quantities used of teicoplanin and vancomycin varied between sites and in 2001/2 hospitals four and eight used more teicoplanin than the other sites.

In 2002/3 hospitals four and five used more proportionately teicoplanin than the other hospitals and this pattern of use was sustained in 2003/4. This data demonstrates changes in hospital prescribing patterns from year to year If hospital eleven is excluded mean glycopeptide use remained relatively constant during the study period at 0.0367, 0.0307 and 0.0337 DDD/FCE for 2001/2, 2002/3 and 2003/4 respectively. Prescribing of glycopeptides at hospital eleven (a specialist orthopaedic hospital) was at a higher level than at the other hospitals.

Figure 4.22 Glycopeptide use (DDD/FCE) by hospital for 2001/2

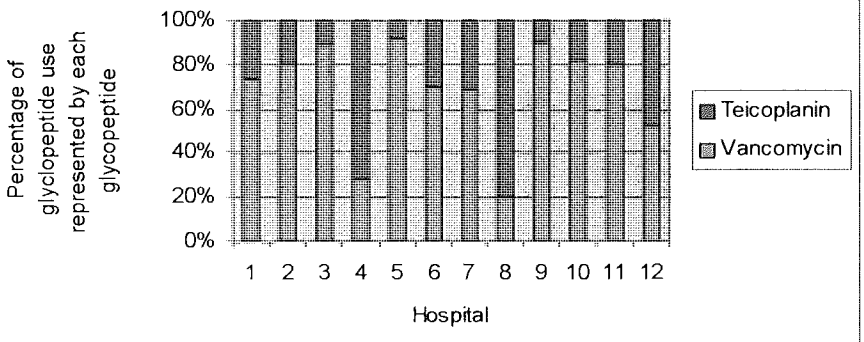


Figure 4.23 Glycopeptide use (DDD/FCE) by hospital for 2002/3

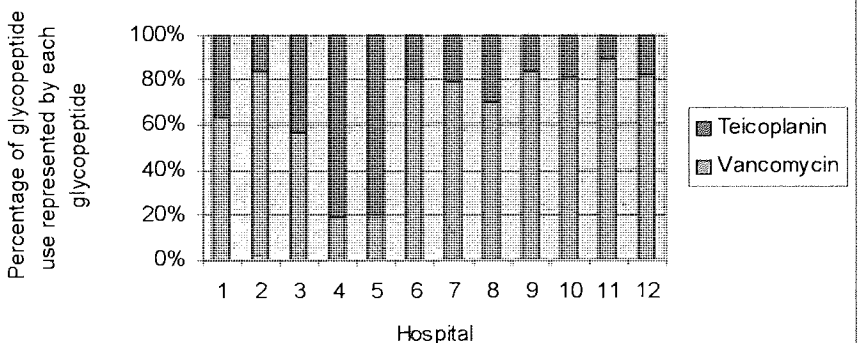
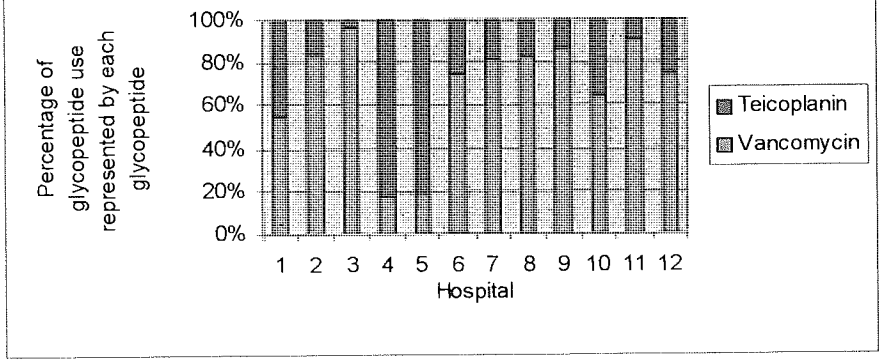


Figure 4.24 Glycopeptide use (DDD/FCE) by hospital for 2003/4



4.2.11 Prescribing rates of glycopeptides and the reported incidence of MRSA.

Table 4.5 contains the calculated DDD/FCE for each hospital for each of the three years of the present study together with the reported incidence of cases of MRSA per 1000 beddays for the sample. The MRSA data was obtained from information published by the Health Protection Agency which is used to monitor MRSA rates in acute hospitals in England (Health Protection Agency, 2005). It can be seen that glycopeptide prescribing rates at hospital eleven were an order of magnitude greater than the other hospitals in the sample.

There was no correlation established between prescribing rates of glycopeptides as quantified using the DDD/FCE and the reported incidence of MRSA per 1000 beddays using bi-variate Pearson correlation ($r = -0.473$ 2001/2, $r = -0.478$ 2002/3, $r = -0.097$ 2003/4). In addition, using the same technique no correlation was found between the Medicines Management scores and the MRSA incidence ($r = 0.541$ 2001/2, $r = 0.338$ 2002/3, $r = 0.319$ 2003/4).

Table 4.5 Total number of Glycopeptide DDD per FCE together with MRSA incidence (number of cases per 1000 beddays) for 2001/2, 2002/3 & 2003/4.

Hospital	2001/2		2002/3		2003/4	
	DDD/FCE	MRSA cases	DDD/FCE	MRSA cases	DDD/FCE	MRSA cases
1	0.0441	0.19	0.0507	0.21	0.076	0.20
2	0.021	0.21	0.0315	0.22	0.0337	0.35
3	0.0177	0.20	0.0372	0.20	0.0271	0.20
4	0.0739	0.22	0.0216	0.18	0.023	0.11
5	0.0253	0.13	0.0158	0.08	0.0332	0.11
6	0.0401	0.08	0.021	0.07	0.0209	0.10
7	0.0356	0.10	0.0251	0.06	0.0266	0.12
8	0.0611	0.20	0.0404	0.20	0.0362	0.20
9	0.0411	0.18	0.0435	0.23	0.0478	0.26
10	0.0224	0.11	0.033	0.16	0.0261	0.14
11	0.2266	0.02	0.2939	0.02	0.210	0.12
12	0.0218	0.08	0.0184	0.17	0.0207	0.15

4.3 Discussion

4.3.1 Introduction to the discussion

The data presented in this chapter highlighted the relationship between the DDD/100beddays and the DDD/FCE prescribing measures and demonstrated a stong correlation between the two indicators. Tabulated data was presented which detailed the use of antibiotics for 2001/2, 2002/3 and 2003/4 in each of the twelve sample hospitals using the ATC classification. This was presented to demonstrate trends in total antibiotic use over time and also to demonstrate trends in the use of individual therapeutics classes of antibiotic over time.

Figures have been used to depict trends in prescribing of individual ATC classes of antibiotic over time and to highlight intra-group differences between individual hospitals in their use of specific classes of antibiotic.

Tabulated data was presented which compared glycopeptide use with reported MRSA incidence to determine whether any correlation could be demonstrated. It was not possible to demonstrate a relationship between these measures.

The quantitative data presented was also examined to determine whether it was possible to correlate this with the Medicines Management self-assessment scores (MMAS) and demonstrate that medicines management activities reduce antibiotic prescribing rates.

4.3.2 The DDD/FCE and the DDD/100beddays in the quantification of antibiotic use.

It was possible to demonstrate a highly significant correlation between the DDD/100beddays and the DDD/FCE prescribing measure (r = 0.74 for 2001/2 data and r = 0.804 for 2003/4 data). This supports the hypothesis that the DDD/FCE is of value as an indicator of antibiotic use when antibiotic drug utilization studies are being carried out (Curtis *et al.* 2004). In particular, when changes in length of patient stay are occurring over time, the DDD/FCE is likely to be of greater value as it reflects changes in the numbers of patients prescribed antibiotics. The DDD/FCE and DDD/100bedday measures may together be used to highlight hospitals where further in-depth analysis of antibiotic prescribing is required i.e. as an audit tool and predictor of inappropriate practice.

When the data relating to cohort B (hospitals 4, 5 and 6), the electronic prescribing group, was isolated, this cohort was shown to have the lowest mean total usage of antibiotics, 3.53 DDD/FCE in 2001/2 versus 4.29 DDD/FCE for the rest of the sample. This trend was maintained in 2002/3 at 3.17 DDD/FCE vs. 4.26 DDD/FCE and in 2003/4 at 3.54 DDD/FCE vs. 4.53 DDD/FCE respectively. The use of antibiotics by both the total sample and also cohort B, showed the same pattern. The total quantity of antibiotics prescribed reduced from 2001/2 to 2002/3 and then increased between 2002/3 and 2003/4, so that by the end of the three-year period the quantity of antibiotic prescribed was at a higher level than at the beginning of the period.

Computerized prescribing systems enable good practice in antibiotic prescribing to be implemented effectively. For example, pre-agreed 'stop dates' may be programmed together with reminders about review of treatment and enforcement of the use of specific formulations so enabling a high degree of formulary control. These measures are all possible using manual systems with clinical pharmacists carrying out prescription review but they can be diminished in effectiveness by staff shortages and this can lead to a reduction in formulary control. However, computerized systems are not affected by staff shortages which is a major benefit of their use. In addition, the existence of a formulary is not proof that the formulary is being applied in a hospital where manual systems are in use. It is likely that the on-going trend for the electronic prescribing cohort to use less antibiotics than hospitals without computerised prescribing systems is related to these facts. This may explain why there was no correlation between antibiotic usage and medicines management scores for the entire sample but does not account for the lack of correlation for the hospitals which had electronic prescribing systems.

The year on year trend in antibiotic use showed a reduction from 2001/2 to 2002/3 and then in 2003/4 the increase to a higher rate of prescribing previously discussed was unexpected. It would be expected that year on year reductions in antibiotic prescribing rates would be observed. This would reflect the continued awareness amongst pharmacists, medical staff and microbiologists of the importance of appropriate antibiotic prescribing. In addition, resource is further directed at ensuring that antibiotic use is evidence-based and guided by sensitivity data. It may be that some hospitals have not implemented such

practices owing to staff shortages or the ability to recruit staff with the expertise to implement such initiatives. That the expected trend has not been identified is an important finding. It is apparent that additional factors influence the increasing use of antibiotics and these may include development of antibiotic resistant organisms and antibiotic use in primary care together with year on year changes in the incidence of infectious diseases. Also an increase in the numbers of patients admitted to hospitals for emergency treatment, which may include empirical antibiotic therapy. Shortages of skilled staff (medical and pharmaceutical) to monitor and ensure adherence to 'good' practice amongst junior medical staff. It is likely that work to identify levels of unfilled posts in key areas of pharmacy, infection control and microbiology would provide insights into the dynamics of how good practice is implemented. The use of prescribing indicators would provide normalized data to aid the interpretation of the impact of these influences on antibiotic use in hospitals.

4.3.3 Trends in antibiotic prescribing (grouped by ATC classification).

4.3.3.1 Tetracyclines (J01A)

The use of tetracyclines reduced over the three-year sample period from 0.39 to 0.33 DDD/FCE (11.3 to 9.91 DDD/100beddays). Analysis of the product mix of tetracyclines prescribed (figures 4.4, 4.5 & 4.6) showed that in ten of the twelve hospitals examined doxycycline was the agent used most widely. Oxytetracycline use was more prevalent at hospital ten. Within hospital eleven (specialist orthopaedic hospital), tetracycline use was more prevalent. The value of tetracyclines in treating infectious disease has decreased owing to increased bacterial resistance. However, tetracyclines remain the treatment of choice for a number of infections such as chlamydia and are used to treat respiratory infections and acne (Royal Pharmaceutical Society of Great Britain, 2005). There has been a renewed interest in the use of doxycycline and minocycline as they are active against methicillin-resistant *Staphylococcus aureus* (Pasquale and Tan, 2005), are well absorbed by the oral route and as they are available generically tend to have a low cost (Klein and Cunha, 2001). There is little to choose between the tetracyclines microbiologically when comparing spectrum of activity, potency and side-efffect profile (Royal Pharmaceutical Society of Great Britain, 2005) and therefore individual hospitals may decide upon the treatment of choice based on other factors such as dosing frequency. Doxycycline is administered once daily and this can improve patient compliance. This may be a reason why it was the tetracycline used most prevalently in ten of the twelve hospitals in this study.

4.3.3.2 Penicillins (J01C)

The use of penicillins varied over the sampling period from 1.73 DDD/FCE in 2001/2 to 1.43 DDD/FCE in 2002/3 to 1.76 DDD/FCE in 2003/4. Eight different penicillins were used and three penicillins were prescribed as combination products with the penicillinase inhibitor clavulanic acid. A general observation shows that two antibiotics plus one combination product accounted for the majority of use, these being amoxicillin, amoxicillin plus clavulanic acid and flucloxacillin. The use of amoxicillin at hospital six reduced markedly in 2003/4 when compared with the previous two years and this was the result of a deliberate change in antibiotic policy where the formulation including clavulanic acid was included more widely in the hospital formulary. It can also be seen that use of flucloxacillin was greatest at hospital eleven, which was a specialist orthopaedic hospital. This would be expected as flucloxacillin is widely used in orthopaedic practice owing to its ability to penetrate into bone and also its broad spectrum of antibacterial activity, which includes beta-lactamase producing *staphylococci* and *streptococci.*

The widespread use of amoxicillin, co-amoxiclav and flucloxacillin results from their activity against a broad range of pathogens. In particular, amoxicillin has antibacterial activity against a range of Gram-positive and Gram-negative organisms and co-amoxiclav may additionally be used when beta-lactamase producing organisms are present. The small quantities of other penicillins used are indicated in specific clinical situations, for example, piperacillin has activity against *Pseudomonas aeruginosa* and is used as part of the treatment of pyrexia

for patients with neutropenia. The profile of use of penicillins in a hospital should relate to the casemix and reflect the service profile of the hospital.

4.3.3.3 Other Beta-lactam antibacterials (J01D)

The use of cephalosporin antibiotics was varied across the sample both by individual drugs used and also showed changes over time. Hospital three was the only hospital to use cefpodoxime and this accounted for between twenty and thirty percent of the total cephalosporin use. Hospital four used oral cefuroxime to a greater degree than all of the other sites and even if this was a conscious policy decision it may be questioned as cost-effective alternatives are available.

The use of oral cefalexin was widespread and in hospital five was replaced by use of cefradine. Parenteral cefuroxime was the most widely used injectable drug and is a standard element of most hospitals surgical prophylaxis regimens (in combination with metronidazole). The use of the third generation drugs ceftazidime, ceftriaxone and cefotaxime varied between hospitals with individual hospitals choosing specific agents to meet local requirements. Third generation cephalosporins have greater activity against a range of Gram-negative bacteria than 'second generation' cephalosporins (e.g. cefuroxime). Hospital six and hospital nine used more of these third generation cephalosporins than the other sites and the reason for this may be formulary inclusion of this class of antibiotic, rather than choice of an equivalent broad-spectrum antibiotic from another class with a similar spectrum of action eg quinolones. This would be agreed locally and informed by local microbiological sensitivity profiles.

Total use of cephalosporins was unchanged from the beginning of the study period to the end remaining at 0.35 DDD/FCE. Within the sample use of cephalosporin antibiotics varied from 0.21 DDD/FCE at hospital six to 0.452 DDD/FCE at hospital eleven. The reason for this is related to choices made by hospitals as part of their antibiotic policies in the same way that individual parenteral cephalosporins are selected and also by casemix, which will influence the spectrum of illness treated and therefore which pathogens are likely to encountered. Two deviations from the general pattern of use have been highlighted and these are the use of cefpodoxime at hospital three, which was the only hospital to use this cephalosporin and the use at hospital six of a greater percentage of ceftazidime than any of the other hospitals. In general, eleven of the hospitals used cefalexin as their oral cephalosporin of choice and this is likely to be a result of it being a cost-effective option.

4.3.3.4 Macrolides, Lincosamides and Streptogramins (J01F)

The use of this category of antibiotics varied over the three-year period (0.57 DDD/FCE in 2001/2, 0.56 DDD/FCE in 2002/3 and 0.72 DDD/FCE in 2003/4). Within the electronic prescribing sub-group, cohort B, there was a reduction in use (0.42 DDD/FCE in 2001/2, 0.34 DDD/FCE 2002/3 and 0.34 DDD/FCE 2003/4). It is likely that this reduction in use within cohort B was the result of change in antibiotic policy supported by effective action to ensure that the change was implemented.

The use of long acting macrolides, specifically clarithromycin showed a trend in that some hospitals (four, five, six and seven) were using significant quantities of

this medicine in 2001/2. Other hospitals changed their macrolide use to accommodate clarithromycin over time (hospitals eight and twelve). There were fluctuating patterns of use of clarithromycin, at hospital nine, when studied longitudinally. There has been debate about the whether or not to use long acting macrolides such as clarithromycin in preference to erythromycin or other broad-spectrum antibiotics (Riffer *et al.*, 2005; Galvez-Mugica *et al.*, 2003; Skrepnek *et al.*, 2005). The area of debate centres around the additional cost of the long acting product and whether this is offset by the benefits in nursing time saved by it only being administered once daily as opposed to four times a day together with improved patient compliance when patients have been discharged.

4.3.3.5 Aminoglycosides (J01G).

The use of gentamicin predominated in eleven of the twelve hospitals and in the other hospital tobramycin was the aminoglycoside used most frequently. Mean annual rates of prescribing of gentamicin remained relatively constant at 0.0472 DDD/FCE in 2001/2, 0.0451 DDD/FCE 2002/3 and 0.0505 DDD/FCE in 2003/4 with a small variation within the sample. The use of gentamicin at hospital one was far higher than the other sites (0.104 DDD/FCE 2001/2, 0.0955 DDD/FCE 2002/3and 0.112 DDD/FCE 2003/4) and this may require further investigation. The rate of use of gentamicin at hospital nine was consistent with the rest of the sample but this was supplemented with extensive use of tobramycin. These findings were consistent with hospital nine being the regional location for the treatment of patients with cystic fibrosis.

4.3.3.6 Quinolones (J01M)

The use of quinolones over the three-year period varied from a mean 0.43 DDD/FCE in 2001/2 to 0.55 DDD/FCE in 2002/3 to 0.52 DDD/FCE in 2003/4. Within the electronic prescribing cohort (hospitals four, five and six) a different trend was observed with usage decreasing from 0.69 DDD/FCE in 2001/2 to 0.63 DDD/FCE in 2002/3 to 0.57 DDD/FCE in 2003/4. The increased us of quinolones in the general hospital sample indicates a more widespread rcommendation of this class reflecting their broad spectrum of activity against both Gram-positive and Gram-negative pathogens. The broad activity spectrum of the quinolones makes them well suited to situations where an empirical approach is required, such as in treatment of fever in patients at risk of neutropenia. However, their use in empirical situations can lead to their inappropriate use which may promote the development of resistance and lead to treatment failure (Zaidi *et al.*, 2001; Gomez *et al.*, 2003; Oosterheert *et al.*, 2003).

In the first year of the study eleven of the twelve hospitals used ciprofloxacin as their oral quinolone of choice. However, in 2002/3 levofloxacin had taken on this role in three hospitals and ofloxacin in a fourth. In the 2003/4 data it can be seen that this trend was maintained. It is likely that as additional quinolones are marketed that this diversity of use will increase and individual agents will be niche marketed (eg moxifloxacin for its high level of activity as a second line treatment in acute exacerbations of chronic bronchitis or community-acquired pneumonia. These newer quinolones will all be more costly than those currently available some of which (ciprofloxacin) are available generically and are

therefore of lower cost. This increase in availability of individual quinolones may also present problems as more widespread use of this class of antibiotics will lead to increased development of resistance (Richard *et al.,* 1994; Carlavilla *et al.*, 2005).

4.3.3.7 Glycopeptides (J01X A)

The relative quantities used of teicoplanin and vancomycin varied between hospitals and during 2001/2 hospitals four and eight used more teicoplanin (71.3 % and 80 % respectively) than the other hospitals in the study (mean 31.2%). This high percentage of use of teicoplanin was maintained at hospital four for all three years of the study. Hospital five was found to use similar quantities of teicoplanin to hospital four in 2002/3 and 2003/4 (80% and 81.3% respectively). This finding indicates a need for further audit of the use of teicoplanin at these two hospitals in which electronic prescribing is used order to determine whether the use is driven by agreed protocols.

The use of vancomycin at hospital eleven, a specialist orthopaedic hospital, was higher than that found at the rest of the hospitals (0.17 DDD/FCE in 2001/2, 0.26 DDD/FCE in 2002/3 and 0.19 DDD/FCE in 2003/4). Glycopeptides are indicated in orthopaedic surgery where there is a risk of MRSA (Hunfeld et al., 2003) and this may explain this finding.The mean use of glycopeptide for the total sample remained relatively constant during the study period at 0.02 DDD/FCE in 2001/2, 0.02 DDD/FCE in 2002/3 and 0.02 DDD/FCE in 2003/4.

There were longitudinal fluctuations in glycopeptide usage at various sites within the sample and it was felt that it might be possible to link MRSA rates within

each hospital with this usage. However, upon further examination (table 4.5) no such relationship was demonstrated. There was also no correlation between Medicines Management scores and glycopeptide usage or correlation between Medicines Management scores and MRSA incidence. Glycopeptide usage is an indicator of treatment of Gram-positive infection found within each hospital and it is of interest that this could not be linked to MRSA rates. It is therefore likely that other influences related to infection control are more strongly related to incidence of MRSA. It may be that glycopeptides are prescribed when there is a high risk of MRSA infection and that patients treated are subsequently found not to have an MRSA infection.

4.3.3.8 Linezolid (J01X X08)

Linezolid was developed to treat Gram-positive pathogens such as MRSA and also Vancomycin-Resistant Enterococci (VRE) and it was expected that use of this agent would increase over time owing to the increasing incidence of serious Gram positive infections. From the data obtained in the present study it was apparent that the total use within the sample increase from 1679 DDD to 7949 DDD between 2001/2 and 2003/4 and that the majority of use was at one hospital. The hospital where the majority of the linezolid was prescribed was hospital nine which possessed an infectious diseases unit and it might be expected that resistant strains of gram-positive pathogens would be encountered. This would occur as patients were transferred here from elsewhere for treatment. Prescribing of this antibiotic remained at very low levels and this may be indicative that a degree of control and or caution has been exercised in relation to its use, although there is no evidence to support this other than the prescribing

data.

4.3.4 Total antibiotic use

The mean total quantity of antibiotic used by the hospitals in the study showed a decrease from 2001/2 to 2002/3 and then increased during 2003/4 to a level greater than that found in the first year of the study period. The data show a mean usage that varied year by year from 119.98 DDD/100 beddays in 2001/2 to 116.02 DDD/100beddays in 2002/3 to 128.46 DDD/100beddays in 2003/4 or 4.15 DDD/FCE in 2001/2 to 3.86 DDD/FCE in 2002/3 to 4.35 DDD/FCE in 2003/4. It is suggested that an antibiotic prescribing rate of greater than 4.25 DDD/FCE should be adopted as a benchmark for initiation of audit of practice. There was variability found in the use of antibiotics from year to year. From 2001/2 to 2002/3 antibiotic use dipped by 3.4 percent when estimated as DDD/100 beddays and by 7 percent when estimated as DDD/FCE antibiotic use then increased in 2003/4 by 10.4 percent when estimated as DDD/100beddays and 12.6 percent when estimated as DDD/FCE. This year on year volatility may be the result of variation in the incidence of infectious disease within hospitals. The mean total quantity of antibiotic used was consistently higher than that found in previous studies which included hospitals in other countries where antibiotic prescribing rates of 41 to 51 DDD/100 beddays in Estonia, Sweden and Spain (Kiivet *et al.*,1998), 55 DDD/100 beddays in Italy (Poretta *et al.*, 2003), 37.2 to 42.5 DDD/100 beddays in Holland (Janknegt *et al.*, 2000) and 90 DDD/100 beddays in Canada (Hutchinson *et al.*, 2004) had been reported. The antibiotic usage in all of these studies is markedly less than that found in the current study and there are no apparent reasons for this difference. It is possible that because out-patient work is carried out in English hospitals that the antibiotic use in this

area of hospital practice contributes to a higher figure than that found in hospitals which operate in different healthcare models where out-patients are seen in Primary Care. Further work is required to define which elements of patient care are included and which excluded in the healthcare models operated in different countries to ensure that comparable and validated data (Ronning *et al.*, 2003) are used.

A longitudinal study over five to ten years is needed to establish whether there is any identifiable trend in antibiotic prescribing rates in the United Kingdom and enable comparison with worldwide studies. The impact of the UK Department of Health allocation of funding for each English hospital to use for promoting 'prudent use of antibiotics' (Department of Health 2003), may take a number of years to emerge. The initiative has enabled hospitals to commence to target clinical pharmacy initiatives related to antibiotic use and also address the collection of data from hospitals for national benchmarking. It is apparent that the majority of hospitals have used the allocation to part-fund a pharmacist and that part of their Job Description relates to matters associated with the control of the use of antibiotics.

The effect of the initiative may be measured in terms of reduction in rates of hospital acquired MRSA, incidence of *Clostridium difficile* and other more crude measures such as reductions in the amount spent on antibiotics within a hospital. These measures may fluctuate independently of pharmaceutical effort to influence antibiotic prescribing and are at best indicators of the incidence of infectious disease. It will be important to ensure that when decisions are taken as

to markers of success that more considered indicators are used. These might include quantification of antibiotic usage related to hospital workload, use of evidence-based policies, number of medical staff who have attended an educational session concerned with improving antibiotic prescription and clinical audit demonstrating improved outcomes.

4.3.5 Medicines Management and antibiotic use.

There was no correlation established between Medicines Management Scores (or Antibiotic Medicines Management Scores) and the quantity of antibiotic prescribed as measured by DDD/100 bedday or DDD/FCE. This might indicate that current medicines management initiatives do not seem to be having an impact on antibiotic prescribing. This is a highly important finding as one of the aims of medicines management activities is to influence the quantity of 'medicine' prescribed, for instance by abbreviating course length (Hendrikson and North, 1995; Marvin and Dowdall, 1998) and this could not be demonstrated It may be that this is a particular problem with antibiotics and is not applicable not to other classes of medication (such as anti-hypertensive agents). Other strands of research would usefully be able to investigate the generality of these findings.

5. The influence of population deprivation on secondary care prescribing of antibiotics.

5.1 Introduction

In order to reduce inequality in the provision of healthcare services in England, various strategies have been devised to apply to funding allocations for hospitals to account for the differences in health needs of local populations (Resource Allocation Working Party (RAWP),1976; Currie *et al.*, 1996; NHS Executive, 1996). The original RAWP revenue allocations were made on a Regional basis and included age and gender-specific hospital utilisation rates together with Standardised Mortality Ratios (SMR) in their calculation. This system was reviewed (DHSS 1988) using analysis of small area differences in hospital ulitisation rates and a weighted capitation formula was introduced to equalise funding allocations to Regions based on local need. A quantitative relationship was established between SMR and the use of hospital beds (Royston *et al.*, 1992). A number of weaknesses were later found in the use of the allocation formula, including the uncertainty with regard to the healthcare needs of specific groups such as the over 85's, and how socioeconomic factors influence the need for health services. The system was reviewed again in 1994 to take account of these factors (National Health Service Executive (NHSE), 1994) and following this review an index was developed by a team from the University of York (Smith *et al.*, 1994). Over time indices to quantify socioeconomic factors and deprivation have become more sophisticated. These indicators need not only be used for making decisions on allocation of financial resource but can be used to examine service provision for populations based on local need. Indices of

deprivation can also be used to inform discussion, when prescribing patterns are being critically reviewed.

Data to produce indices of multiple deprivation may be obtained from census returns or from administrative data (Carr-Hill and Chalmers-Dixon, 2002). Combining factors into indices can be used to produce ranking systems such as the Townsend or Jarman scores (Townsend, 1979; Jarman, 1984) which give an indication of local health needs. The index most widely used to compare deprivation of local populations is the Index of Multiple Deprivation 2000 (IMD 2000) developed by the Department of the Environment, Trade and the Regions (DETR) (Noble *et al.*, 2000). This index was updated in 2004 to produce the IMD 2004 (Noble *et al.*, 2004) by the Office of the Deputy Prime Minister.

The IMD 2000 and IMD 2004 are constructed from indicator data that are combined into a number of dimensions or domains, which are then weighted and summed to produce the index. The data to create the IMD indices are collated from the Census, Office of National Statistics and Department of Social Security. The individual domains and their weightings are detailed in table 5.1 (IMD 2000) and table 5.2 (IMD 2004).

Table 5.1 List of constituent domains and weightings for IMD 2000

Domain	Weighting
Income	25%
Employment	25%
Health & disability	15%
Education & skills	15%
Housing	10%
Geographical access to services	10%

Table 5.2 List of constituent domains and weightings for IMD 2004

Domain	Weighting
Income	22.5%
Employment	22.5%
Health & disability	13.5%
Education, skills & training	13.5%
Housing	9.3%
Crime	9.3%
Living environment	9.3%

Each domain consists of a number of indicators, for example, the Health and Disability domain being constructed from five indicators, as follows – Comparative Mortality Rates under 65, Attendance allowance or Daily Living allowance rates, People aged 16 – 59 receiving Incapacity benefit or Severe

Disablement allowance, Limiting long-term illness (self-report) – age-sex standardised and finally low birth weight.

The updated IMD 2004 has different indicators constituting the Health and Disability domain. These are - Years of potential life lost, Comparative Illness and Disability Ratio, Measures of Emergency Admissions to hospital and measure of adults under 60 suffering from mood or anxiety disorders. Although this and the indicators constituting the other domains have been reviewed, the resulting IMD 2004 shows only small changes from the first version (IMD 2000).

The IMD 2000 for every electoral ward in England has been calculated and grouped to Primary Care Trust level. The data for each PCT is accessible through PCT annual reports and via Regional Public Health Observatories.

The influence of the deprivation of the catchment population on the antibiotic prescribing rate within a hospital has not been widely investigated. It is intuitive to conclude that areas where there is a high degree of deprivation, for example poor housing, leading to damp conditions, will influence the incidence of respiratory illness. This in turn may lead to higher referral rates from General Practitioners to local hospital-based physicians. As a consequence an individual hospital might prescribe antibiotics for pneumonia and other related respiratory diseases to a greater extent than another hospital where these deprived housing conditions are not as prevalent. Thus, it is assumed that hospitals are not islands

of practice, but are subject to many environmental and human factors within the local population that they serve.

It is problematic to apply information derived from an individual's health status and relate that to larger aggregates of people such as Primary Care Trusts (Sheldon et al., 1993). However, as long as the limitations are realised then such epidemiological data may explain variations in prescribing of medicines in both primary and secondary care. There is also great variation between electoral wards within PCT's, which can lead to misleading average deprivation data when extrapolated to PCT level. This caveat is also applicable when individual PCT data is combined. However, use of deprivation data at higher levels of aggregation can be, and is useful in making health care resource allocation decisions provided its limitations are known. The value of aggregated deprivation data has been discussed and supported (Noble et al., 2004). The causes of deprivation, which is experienced by groups of individuals require an examination of area level influences. Further, indices relating to geographical areas and developed from data relating to individuals will be capable of allowing for the possibility of area causes of deprivation. For these reasons it is felt that use of aggregated data is useful in highlighting deprived areas.

5.2 Results

5.2.1 Individual hospital patient profiles identifying the PCT of treated patients and the associated IMD 2000 together with Primary Care antibiotic prescribing data.

The tables below contain the data for each study hospital and detail the number of different PCT's where patients originate together with the number of antibiotic items dispensed per 1000 patients in the PCT. All data relates to financial year 2001/2. All Welsh IMD data has been indicated *, as the Welsh Indicator of Multiple deprivation comprises different components to the English IMD 2000 to create the index and the two indices are not comparable. For this reason the data relating to these Welsh patients have not been included in the total number of valid patients when the weighted mean IMD 2000 score and weighted antibiotic prescribing mean for primary care patients referred to each hospital was calculated.

Table 5.3 details the PCT of origin for all patients treated at hospital one during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (72.01%) originate from a single PCT (Coventry), with a further twenty-three percent of patients being referred from PCT's which are geographically nearby (within 20 miles). The remaining four percent of patients originated from Midlands PCTs with a small number of patients from geographically distant PCTs (e.g Bedford, Birkenhead and Wallesey). The weighted mean IMD 2000 for hospital one was calculated as 29.20 and the weighted mean antibiotic prescribing rate was 679.04 items per 1000 patients.

Table 5.3 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 1 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Coventry	66246	72.01	33.57	701
Rugby	14280	15.52	16.49	608
North Warwickshire	4307	4.68	23.86	664
South Warwickshire	3374	3.66	11.68	585
Solihull	710	0.77	17.55	684
Harborough/Melton/Rutland	601	0.65	9.37	629
Blaby & Lutterworth	580	0.63	9.37	554
Redditch & Bromsgrove	309	0.33	16.93	599
Walsall	235	0.25	38.71	764
Wolverhampton	217	0.23	40.16	794
Heart of Birmingham	180	0.19	62.74	819
Burntwood,Lichfield & Tamworth	112	0.12	19.70	576
Eastern Birmingham	98	0.10	44.30	886
South Worcestershire	91	0.09	16.09	592
Wednesbury & West Bromwich	85	0.09	42.37	791
South Birmingham	78	0.08	33.65	600
North Birmingham	69	0.07	21.40	647
Oldbury & Smethwick	62	0.06	43.76	818
South Western Staffordshire	38	0.04	13.31	700
Dudley South	33	0.03	19.81	688
Leicester City West	27	0.02	43.93	673
Telford & The Wrekin	26	0.02	28.27	631
N E Oxfordshire	26	0.02	20.80	527
Northampton	20	0.02	21.15	595
Rowley Regis & Tipton	19	0.02	42.02	649
Shropshire County	17	0.01	18.50	591
Wyre Forest	15	0.01	21.44	588
Charnwood & N W Leicestershire	15	0.01	15.46	556
Northamptonshire heartlands	14	0.01	19.97	629
Milton Keynes	13	0.01	19.90	655
Daventry & Northamptonshire	12	0.01	9.53	705
Plymouth	9	0.009	30.35	618
Newham	9	0.009	56.18	629
Eastern Leicester	8	0.009	37.67	669
East Lincolnshire	7	0.007	26.18	723
Swindon	7	0.007	18.09	609
Slough	7	0.007	25.30	596
Dudley Beacon & Castle	7	0.007	32.94	692
East Staffordshire	7	0.007	20.83	650
Bedford	6	0.006	20.92	597
Birkenhead & Wallasey	6	0.006	98.10	705
Erewash	6	0.006	23.49	533
Powys	6	0.006	15.05*	790*

Table 5.4 details the PCT of origin for all patients treated at hospital two during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (85.70%) originate from four PCTs in North Staffordshire, with a further twenty-three percent of patients being referred from PCT's that are geographically nearby (within 30 miles) in Cheshire, Shropshire and South Staffordshire. The remaining patients originated from diverse geographical areas (e.g North Norfolk, Anglesey). The weighted mean IMD 2000 for hospital two was calculated as 30.61 and the weighted mean antibiotic prescribing rate was 718.71 items per 1000 patients.

Table 5.4 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 2 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
North Stoke	42245	34.19	41.68	681
South Stoke	23298	18.85	35.41	792
Newcastle under Lyme	21653	17.52	24.41	733
Staffordshire Moorlands	18707	15.14	20.42	736
South Western Staffordshire	6920	5.60	13.31	700
Central Cheshire	4081	3.30	12.51	614
Cannock Chase	2342	1.89	23.57	810
Shropshire County	1646	1.33	18.5	591
East Staffordshire	671	0.54	20.83	650
Telford & The Wrekin	394	0.32	28.27	631
Eastern Cheshire	384	0.31	7.57	564
Cheshire West	239	0.19	8.39	549
South Staffordshire	205	0.17	13.31	700
Walsall	185	0.15	38.71	764
Powys	115		15.05*	790*
High Peak & Dales	86	0.07	15.18	542
Derby Dales & South Derby	56	0.04	16.79	636
Burntwood,Lichfield & Tamworth	38	0.03	19.70	576
Wolverhampton	92	0.07	40.16	794
Wrexham	19		21.76*	930*

Wednesbury & West Bromwich	18	0.01	42.37	791
Redditch & Bromsgrove	28	0.02	16.93	599
Coventry	17	0.01	33.57	701
South Worcestershire	23	0.01	16.09	592
Wyre Forest	15	0.01	21.44	588
Heart of Birmingham	30	0.02	62.74	819
Oldbury & Smethwick	15	0.01	43.76	818
Cheshire West	14	0.01	8.39	549
Anglesey	13		24.42*	920*
Flintshire	13		14.29*	830*
Birmingham North	12	0.009	21.40	647
Charnwood & N W Leicestershire	11	0.008	15.46	556
Central Manchester	19	0.01	111.49	528
Ceredigion	10		17.60*	850*
North Norfolk	9	0.007	22.00	555
Dudley Beacon & Castle	8	0.006	32.94	692
South Warwickshire	7	0.005	11.68	585
Wyre	13	0.01	21.44	743
Dudley South	7	0.005	19.81	688
Stockport	7	0.005	39.73	659
North Manchester	7	0.005	116.33	808
Conwy	7		16.60*	840*
Herefordshire	7	0.005	19.94	552
South Wiltshire	6	0.004	13.73	576
Milton Keynes	6	0.004	19.90	655
Solihull	6	0.004	17.55	684
Trafford South	6	0.004	21.08	614
Broxtowe & Hucknall	6	0.004	20.08	551

Table 5.5 details the PCT of origin for all patients treated at hospital three during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT, to the total by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (86.23%) originate from five PCTs in Birmingham, with a further six percent of patients being referred from PCT's that are geographically nearby (within 15 miles) in the Black Country. The remaining patients originated from PCTs across the Midlands and also from diverse geographical areas (e.g Lambeth, Croydon). The weighted mean IMD 2000 for hospital three was calculated as 49.14 and the weighted mean antibiotic prescribing rate was 778.61 items per 1000 patients.

Table 5.5 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 3 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Heart of Birmingham	35848	50.08	62.74	819
Oldbury & Smethwick	13422	18.75	43.76	818
North Birmingham	7296	10.19	21.40	647
South Birmingham	5161	7.21	33.65	600
Eastern Birmingham	3384	4.72	44.3	886
Wednesbury & West Bromwich	2174	3.03	42.37	791
Solihull	714	0.99	17.55	684
Dudley South	677	0.94	19.81	688
Rowley Regis & Tipton	555	0.77	42.02	649
Walsall	487	0.68	38.71	764
Redditch & Bromsgrove	280	0.39	16.93	599
South Worcestershire	245	0.34	16.09	592
Burntwood,Lichfield & Tamworth	241	0.33	19.40	576
South Warwickshire	128	0.18	11.68	585
Wolverhampton	113	0.15	40.16	794
North Warwickshire	109	0.15	23.86	664
Wyre Forest	99	0.14	21.44	588
Coventry	91	0.13	33.57	701
Herefordshire	61	0.08	19.94	552
Dudley Beacon & Castle	59	0.08	32.94	692

Shropshire County	54	0.07	18.50	591
Cannock Chase	52	0.07	23.47	810
South Western Staffordshire	48	0.06	13.31	700
East Staffordshire	40	0.05	20.83	650
Telford & The Wrekin	29	0.04	28.27	631
Powys	27		15.05*	790*
Solihull	25	0.03	17.55	684
Staffordshire Moorlands	19	0.02	20.42	736
Lambeth	19	0.02	43.04	436
North Stoke	19	0.02	41.68	681
Milton Keynes	15	0.02	19.9	655
Derbyshire Dales & South Derby	12	0.01	16.79	636
Ceredigion	12		17.60*	850*
Charnwood & N W Leicestershire	11	0.01	15.46	556
Nottingham City	10	0.01	44.75	591
Caerphilly	10		33.77*	920*
Slough	9	0.01	25.30	596
Croydon	9	0.01	22.96	556
South Stoke	9	0.01	35.41	792
Cheltenham & Tewkesbury	7	0.009	13.90	508
Scarborough Whitby & Ryedale	7	0.009	26.87	632
Newham	7	0.009	56.18	629
Newcastle under Lyme	7	0.009	24.41	733
Newport	7		22.62*	840*
Harborough Melton & Rutland	7	0.009	9.37	554
Southwark	6	0.008	44.08	482
Bolton	6	0.008	65.72	709
City & Hackney	6	0.008	56.18	477

Table 5.6 details the PCT of origin for all patients treated at hospital four during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (97.54%) originate from four PCTs in South Staffordshire, Southern Derbyshire and North West Leicestershire. These are all geographically close (within 20 miles) to the hospital. The remaining patients originated from PCTs across the Midlands with a small number of patients originating from distant geographical areas (e.g Norwich). The weighted mean IMD 2000 for hospital four was calculated as 19.33 and the weighted mean antibiotic prescribing rate was 627.43 items per 1000 patients.

Table 5.6 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 4 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
East Staffordshire	26147	50.18	20.83	650
Derbyshire Dales & South Derby	10647	20.45	16.79	636
Burntwood,Lichfield & Tamworth	8854	17.00	19.7	576
Charnwood & NW Leics	5164	9.91	15.46	556
Cannock Chase	691	1.32	23.47	810
North Warwickshire	211	0.40	23.86	664
Birmingham North	60	0.11	21.40	647
South Western Staffordshire	50	0.09	13.31	700
Greater Derby	48	0.09	22.97	506
Staffordshire Moorlands	44	0.08	20.42	736
Harborough/Melton/Rutland	20	0.03	9.37	554
Walsall	20	0.03	38.71	764
Rushcliffe	16	0.03	9.34	557
Hinckley & Bosworth	15	0.02	11.99	629
South Stoke	11	0.02	35.41	792
Heart of Birmingham	10	0.01	62.74	819
North Birmingham	9	0.01	21.40	886
Rugby	8	0.01	16.49	608
Erewash	7	0.01	23.49	533
Wednesbury & West Bromwich	7	0.01	42.37	791
Newcastle under Lyme	7	0.01	24.41	733

Nottingham City	6	0.01	44.75	591
Shropshire County	6	0.01	18.50	591
Norwich	6	0.01	33.23	486
Broxtowe & Hucknall	6	0.01	20.08	551
North Warwickshire	6	0.01	23.86	664
North Stoke	6	0.01	41.68	681

Table 5.7 details the PCT of origin for all patients treated at hospital five during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (93.43%) originate from two PCTs in Mid-Hampshire and Eastleigh. These are both geographically close (within 20 miles) to the hospital. The remaining patients originated from PCTs across Hampshire, Dorset, Somerset and Wiltshire with a small number of patients originating from more distant geographical areas (e.g Kensington and Chelsea). The weighted mean IMD 2000 for hospital five was calculated as 9.02 and the weighted mean antibiotic prescribing rate was 529.47 items per 1000 patients.

Table 5.7 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 5 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Mid-Hants	29505	66.70	8.00	528
Eastleigh & Test Valley South	11823	26.73	10.60	521
South Wiltshire	1002	2.26	13.73	576
North Hampshire	964	2.17	11.30	583
East Hants	213	0.48	10.50	565
Fareham & Gosport	201	0.45	7.00	603
Central Southampton	132	0.29	29.20	570
New Forest	104	0.23	12.50	584
Portsmouth City	47	0.10	25.40	639
Newbury & Community	44	0.10	8.45	518
North Dorset	26	0.05	12.81	526
North Somerset	25	0.05	16.06	609
South Wiltshire	25	0.05	13.73	576
South & East Dorset	22	0.05	10.75	565
Swindon	16	0.03	18.09	609
Kensington & Chelsea	13	0.03	9.02	349
Western Sussex	11	0.02	13.10	647
Isle of Wight	11	0.02	29.30	625
Guildford & Waverley	8	0.02	8.16	581
Windsor Ascot & Maidenhead	8	0.02	7.20	582
Bournemouth	7	0.01	25.50	612

West Sheffield	6	0.01	34.00	616
Reading	6	0.01	19.70	566
West Wiltshire	6	0.01	14.15	563
Cheltenham & Tewkesbury	6	0.01	13.90	508

Table 5.8 details the PCT of origin for all patients treated at hospital six during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (93.49%) originate from two PCTs on the Wirral peninsula. These are both geographically close (within 20 miles) to the hospital. The remaining patients originated from PCTs across Merseyside, Cheshire and North Wales with a small number of patients originating from more distant geographical areas (e.g Hammersmith and Fulham). The weighted mean IMD 2000 for hospital six was calculated as 78.49 and the weighted mean antibiotic prescribing rate was 676.69 items per 1000 patients.

Table 5.8 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 6 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Birkenhead & Wallasey	63900	66.09	98.1	705
Bebington & West Wirral	26499	27.40	44.30	609
Ellesmere Port	5241	5.42	17.12	674
Cheshire West	307	0.31	18.39	549
Liverpool Central/West	115	0.12	118.79	658
Flintshire	113		14.90*	830*
North Liverpool	84	0.08	149.41	791
St. Helens	72	0.07	56.11	773
South Sefton	68	0.07	71.86	710
Halton	63	0.06	36.28	711
Central & South Knowsley	59	0.06	59.76	823
Liverpool South	58	0.06	91.36	711
Ashton Leigh & Wigan	47	0.05	63.59	773
Central Cheshire	39	0.04	12.51	614
Southport & Formby	31	0.03	41.28	691
West Lancashire	30	0.03	17.30	671
Warrington	21	0.02	25.17	631
Denbighshire	19		18.37*	930*
Wrexham	18		21.76*	930*
Eastern Cheshire	14	0.01	7.57	564
Conwy	12		16.60*	840*

Gwynedd	10		23.40*	870*
Blackpool	9	0.01	39.55	755
Hammersmith & Fulham	8	0.01	38.47	457
Broxtowe & Hucknall	7	0.007	20.08	551
Bury	6	0.006	41.03	664
Leeds North West	6	0.006	25.78	544

Table 5.9 details the PCT of origin for all patients treated at hospital seven during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (79.46%) originate from two PCTs in Dudley. These are both geographically close (within 10 miles) to the hospital. The remaining patients originated from PCTs in the Black Country, Staffordshire, Shropshire and Birmingham with a small number of patients originating from more distant geographical areas (e.g Gwynedd). The weighted mean IMD 2000 for hospital seven was calculated as 26.53 and the weighted mean antibiotic prescribing rate was 685.56 items per 1000 patients.

Table 5.9 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 7 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Dudley South	34570	51.97	19.81	688
Dudley Beacon & Castle	18286	27.49	32.94	692
Rowley Regis & Tipton	7844	11.79	42.02	649
South Western Staffordshire	2033	3.02	13.31	700
Wyre Forest	1064	1.60	21.44	588
Wolverhampton	883	1.32	40.16	794
Oldbury & Smethwick	561	0.84	43.76	818
Shropshire County	174	0.26	18.50	591
Wednesbury & West Bromwich	168	0.25	42.37	791
South Birmingham	165	0.25	33.65	600
Redditch & Bromsgrove	150	0.22	16.93	599
Walsall	146	0.22	38.71	764
Heart of Birmingham	90	0.13	62.74	819
South Worcestershire	69	0.10	16.09	592
North Birmingham	49	0.07	21.40	647
Solihull	49	0.07	17.55	684
Eastern Birmingham	40	0.06	44.30	886
South Warwickshire	37	0.05	11.68	585
Telford & The Wrekin	26	0.04	28.27	631
Burntwood,Lichfield & Tamworth	25	0.04	19.40	576
Cannock Chase	23	0.03	23.47	810

Coventry	18	0.02	33.57	701
Gwynedd	16		23.40*	870*
Herefordshire	15	0.02	19.94	552
Wrexham	10		21.76*	930*
East Staffordshire	9	0.01	20.83	650
Rugby	6	0.009	16.49	608

Table 5.10 details the PCT of origin for all patients treated at hospital eight during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (89.27%) originate from three PCTs in Wednesbury, West Bromwich, Smethwick and Tipton. They are geographically close (within 15 miles) to the hospital. The remaining patients originated from PCTs in Birmingham, the Black Country and South Staffordshire with a small number of patients originating from other parts of the Midlands. The weighted mean IMD 2000 for hospital eight was calculated as 42.35 and the weighted mean antibiotic prescribing rate was 764.2 items per 1000 patients.

Table 5.10 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 8 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Wednesbury & West Bromwich	24125	48.64	42.37	791
Oldbury & Smethwick	10551	21.27	43.76	818
Rowley Regis & Tipton	9603	19.36	42.02	649
Heart of Birmingham	1716	3.46	62.74	819
Walsall	1321	2.66	38.71	764
North Birmingham	945	1.90	21.40	647
Dudley South	667	1.34	19.81	688
Wolverhampton	150	0.30	40.16	794
South Birmingham	139	0.28	33.65	600
Dudley Beacon & Castle	101	0.20	32.94	692
Eastern Birmingham	61	0.12	44.30	886
Cannock Chase	46	0.09	23.47	810
Burntwood,Lichfield & Tamworth	43	0.08	19.40	576
South Western Staffordshire	30	0.06	13.31	700
Redditch & Bromsgrove	20	0.04	16.93	599
Wyre Forest	15	0.03	21.44	588
South Worcestershire	12	0.02	16.09	592
Shropshire County	8	0.01	18.50	591
Telford & The Wrekin	8	0.01	28.27	631
Coventry	8	0.01	33.57	701

Solihull	8	0.01	17.55	684
Herefordshire	7	0.01	19.94	552
East Staffordshire	6	0.01	20.83	650

Table 5.11 details the PCT of origin for all patients treated at hospital nine during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (86.15%) originate from three PCTs in Solihull and Central and Eastern Birmingham. They are geographically close (within 10 miles) to the hospital. The remaining patients originated from PCTs in Birmingham, Warwickshire, the Black Country and South Staffordshire with a number of patients originating from across the Midlands. A small number of patients originated from outside the Midlands (e.g Islington and Rochdale) The weighted mean IMD 2000 for hospital eight was calculated as 37.97 and the weighted mean antibiotic prescribing rate was 778.90 items per 1000 patients.

Table 5.11 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 9 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Solihull	36297	35.22	17.55	684
Heart of Birmingham	29615	28.74	62.74	886
Eastern Birmingham	22865	22.19	44.30	886
South Birmingham	7093	6.88	33.65	600
North Warwickshire	1382	1.34	23.86	664
North Birmingham	1357	1.31	21.40	647
South Warwickshire	669	0.64	11.68	585
Burntwood,Lichfield & Tamworth	645	0.62	19.40	576
Redditch & Bromsgrove	639	0.62	16.93	599
Walsall	360	0.35	38.71	764
South Worcestershire	276	0.26	16.09	592
Wednesbury & West Bromwich	216	0.21	42.37	791
Oldbury & Smethwick	209	0.20	43.76	818
Shropshire County	197	0.19	18.50	591
Dudley South	197	0.19	19.81	688
Coventry	167	0.16	33.57	701
Wolverhampton	152	0.15	40.16	794
Telford & The Wrekin	97	0.09	28.27	631

Cannock Chase	92	0.09	23.47	810
South Western Staffordshire	89	0.08	13.31	700
Herefordshire	84	0.08	19.94	552
Rowley Regis & Tipton	83	0.08	42.02	649
Powys	46		15.05*	790*
Charnwood & N W Leicestershire	36	0.03	15.46	556
Rugby	32	0.03	16.49	608
East Staffordshire	29	0.03	20.83	650
Dudley Beacon & Castle	27	0.03	32.94	692
Hinckley & Bosworth	21	0.02	11.99	629
Newcastle under Lyme	17	0.02	24.41	733
North Lincolnshire	16	0.01	24.98	670
South Stoke	15	0.01	35.41	792
Staffordshire Moorlands	13	0.01	20.42	736
Derby Dales & South Derby	10	0.009	16.79	636
West Gloucestershire	10	0.009	19.93	614
Rochdale	8	0.007	65.47	798
Northampton	7	0.006	21.15	595
Islington	7	0.006	44.08	472
City Central Leicester	6	0.006	43.93	673
Watford & Three Rivers	6	0.006	16.34	589

Table 5.12 details the PCT of origin for all patients treated at hospital ten during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (92.44%) originate from three PCTs in North Birmingham, South Staffordshire and Eastern Birmingham. They are geographically close (within 10 miles) to the hospital. The remaining patients originated from PCTs in Walsall, Birmingham, Warwickshire, and the Black Country with a number of patients originating from PCTs in the Midlands. A small number of patients originated from outside the Midlands (e.g Newham) The weighted mean IMD 2000 for hospital ten was calculated as 27.58 and the weighted mean antibiotic prescribing rate was 691.58 items per 1000 patients.

Table 5.12 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 10 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
North Birmingham	23159	42.38	21.40	647
Burntwood,Lichfield & Tamworth	14570	26.66	19.70	576
Eastern Birmingham	12788	23.40	44.30	886
Walsall	1462	2.67	38.71	764
Heart of Birmingham	852	1.56	62.74	819
North Warwickshire	734	1.34	23.86	664
Wednesbury & West Bromwich	267	0.49	42.37	791
Cannock Chase	263	0.48	23.47	810
Solihull	169	0.31	17.55	684
South Birmingham	122	0.22	33.65	600
East Staffordshire	87	0.16	20.83	650
Charnwood & N W Leicestershire	36	0.06	15.46	556
Oldbury & Smethwick	30	0.05	43.76	818
South Worcestershire	18	0.03	16.09	592
Dudley South	13	0.02	19.81	688
Wolverhampton	13	0.02	40.16	794
South Warwickshire	12	0.02	11.68	585
South Western Staffordshire	10	0.02	13.31	700

Shropshire County	8	0.01	18.50	591
Wyre Forest	8	0.01	21.44	588
Derbyshire Dales & South Derby	8	0.01	16.79	636
Newham	6	0.01	56.18	629
Hinckley & Bosworth	6	0.01	11.99	629

Table 5.13 details the PCT of origin for all patients treated at hospital eleven during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (61.53%) originate from Shropshire County PCT, which is geographically close (within 25 miles) to the hospital. A significant number of patients (35%) originated from Wales.The remaining patients originated from PCTs across the Midlands and Northern England. A small number of patients originated from more distant geographical areas (e.g. Devon). The weighted mean IMD 2000 for hospital eleven was calculated as 21.17 and the weighted mean antibiotic prescribing rate was 700.93 items per 1000 patients.

Table 5.13 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 11 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
Shropshire County	3404	61.53	18.50	591
Wrexham	770		21.76*	930*
Powys	705		15.05*	790*
Telford & The Wrekin	543	9.81	28.27	631
Flintshire	367		14.90*	830*
Gwynedd	316		23.40*	870*
Central Cheshire	290	5.24	12.51	614
Conwy	267		16.60*	840*
Denbighshire	245		18.37*	930*
Ceredigion	133		17.60*	850*
Cheshire Rural	124	2.24	12.51	549
Anglesey	121		24.42*	920*
Chester City	87	1.57	8.39	549
Newcastle under Lyme	86	1.55	24.41	733
North Stoke	84	1.52	41.68	681
Staffordshire Moorlands	79	1.42	20.42	736
Herefordshire	77	1.40	19.94	552
South Western Staffordshire	70	1.26	13.31	700

South Stoke	62	1.12	35.41	792
South Worcestershire	53	0.95	16.09	592
Eastern Cheshire	45	0.81	7.57	564
Wolverhampton	45	0.81	40.16	794
Pembroke	36		20.20*	860*
Cannock Chase	34	0.61	23.47	810
Redditch & Bromsgrove	30	0.54	16.93	599
Dudley South	28	0.50	19.81	688
South Sefton	21	0.37	71.86	710
Walsall	21	0.37	38.71	764
Bebington & West Wirral	20	0.36	44.35	609
Wyre Forest	19	0.34	21.44	588
South Warwickshire	18	0.32	11.68	585
Ellesmere Port	18	0.32	17.12	674
Carmarthen	17		23.24*	860*
Coventry	17	0.31	33.57	701
Central Manchester	15	0.27	111.49	528
Burntwood,Lichfield & Tamworth	15	0.27	19.49	576
St. Helens	15	0.27	56.11	773
Warrington	15	0.27	25.17	631
North Birmingham	14	0.25	21.40	647
Ashton, Leigh & Wigan	14	0.25	63.59	773
Rowley Regis & Tipton	13	0.23	42.02	649
North Lincolnshire	12	0.21	24.98	670
Wednesbury & West Bromwich	12	0.21	42.37	791
East Staffordshire	10	0.18	20.83	650
Ashfield	10	0.18	38.48	658
Southport & Formby	9	0.16	41.28	691
Solihull	9	0.16	17.55	684
Tameside & Glossop	8	0.14	59.57	721
Dudley Beacon & Castle	8	0.14	32.94	692
Ashford	8	0.14	19.00	591
Swansea	8	0.14	18.90	850
North Liverpool	8	0.14	149.41	791
Greenwich	8	0.14	37.87	610
Birkenhead & Wallasey	7	0.12	98.10	705
North Warwickshire	7	0.12	23.86	664
Heart of Birmingham	7	0.12	62.74	819
East Devon	7	0.12	15.64	643
North Tyneside	7	0.12	34.18	740
Rhondda Cynon Taff	7		32.57*	880*
Stockport	7	0.12	39.73	659
Trafford South	6	0.10	21.08	614
Scarborough, Whitby & Ryedale	6	0.10	26.87	632
Monmouth	6		9.42*	780*

Table 5.14 details the PCT of origin for all patients treated at hospital twelve during 2001/2. It includes the number of patients and the percentage contribution of patients from each PCT to the total, by PCT together with the IMD 2000 for each PCT and the number of antibiotic items dispensed per 1000 patients in each PCT in 2001/2. The majority of patients (94.48%) originate from two South Staffordshire PCTs, which are geographically close (within 20 miles) to the hospital. The remaining patients originated from PCTs in the West Midlands, with a small number of patients originating from Cheshire. The weighted mean IMD 2000 for hospital twelve was calculated as 18.65 and the weighted mean antibiotic prescribing rate was 748.19

Table 5.14 Rank order of number of patients (and percentage of total) treated by PCT of origin for 2001/2. Also, IMD 2000 plus number of antibiotic items dispensed per 1000 patients in Primary Care for 2001/2 hospital 12 are included.

PCT	No. patients	%	IMD 2000	No. antibiotic items
South Western Staffordshire	25678	48.64	13.31	700
Cannock Chase	24198	45.84	23.47	810
East Staffordshire	740	1.40	20.83	650
Burntwood,Lichfield & Tamworth	717	1.36	19.40	576
Telford & The Wrekin	310	0.58	28.27	631
Walsall	263	0.50	38.71	764
Birmingham North	221	0.42	21.40	647
South Stoke	139	0.26	35.41	792
Staffordshire Moorlands	122	0.23	20.42	736
Wolverhampton	118	0.22	40.16	794
North Stoke	106	0.20	41.68	681
Newcastle under Lyme	51	0.09	24.41	733
Shropshire County	30	0.05	18.5	591
Wednesbury & West Bromwich	18	0.03	42.37	791
Central Cheshire	10	0.02	12.51	614
North Warwickshire	9	0.02	23.86	664
Rowley Regis & Tipton	8	0.01	42.02	649
Dudley Beacon & Castle	8	0.01	32.94	692
Birmingham South	8	0.01	33.65	600
Oldbury & Smethwick	6	0.01	43.76	818
Dudley South	6	0.01	19.81	688
Heart of Birmingham	6	0.01	62.74	819
Derbyshire Dales & South Derby	6	0.01	16.79	636

Nottingham City	6	0.01	44.75	591

5.2.2 Weighted Mean Morbidity (IMD 2000) for each hospital.

The data for the percentage of patients treated from each PCT, was multiplied by the IMD for that PCT to produce a weighted value for each PCT. The individual PCT values were then summed to create a single weighted mean IMD 2000 value for each of the twelve hospitals. This data is detailed in table 5.15. The range of weighted mean IMD 2000 found for the hospitals in the study was from 9.02 to 78.49

Table 5.15 Weighted Mean Morbidity (IMD 2000) for patients treated in 2001/2 at each study hospital.

Hospital	Weighted Mean Morbidity (IMD 2000)
1	29.20
2	30.61
3	49.14
4	19.33
5	9.02
6	78.49
7	26.53
8	42.35
9	37.97
10	27.58
11	21.17
12	18.65

5.2.3 Weighted Mean Primary Care Antibiotic prescribing rates

The data for the percentage of patients treated from each PCT, was multiplied by the number of antibiotic prescription items per 1000 patients for that PCT, thus the contribution of each individual PCT to a total prescribing rate for each hospital may be calculated. The individual PCT prescribing rates were then summed to create a single primary care antibiotic prescribing rate for the patients

treated at each of the twelve hospitals. The data is detailed in table 5.16.The range of values found was from 529.47 to 778.90 antibiotic items prescribed per 1000 patients per year.

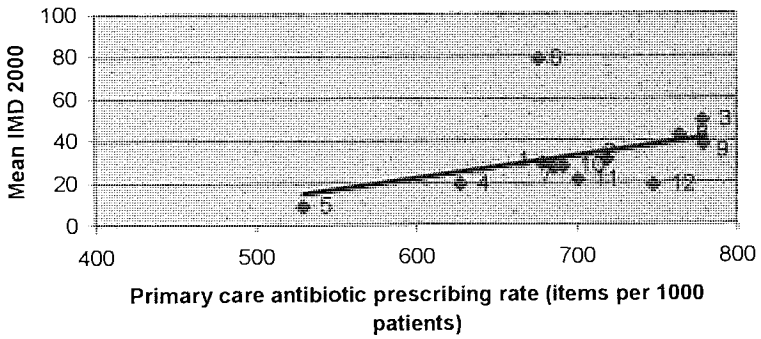
Table 5.16 Weighted Mean Primary Care Antibiotic Prescribing rate per 1000 patients in 2001/2 for each hospital.

Hospital	Weighted Mean antibiotic prescribing rate per 1000 patients 2001/2
1	679.04
2	718.71
3	778.61
4	627.43
5	529.47
6	676.69
7	685.56
8	764.20
9	778.90
10	691.58
11	700.93
12	748.19

5.2.4 Comparison of the Weighted Mean IMD 2000 and the Primary Care Antibiotic prescribing rate.

Figure 5.1 depicts the relationship between the weighted mean IMD 2000 and the Primary care antibiotic prescribing rate for 2001/2. There was no significant correlation (r = 0.407) between these parameters. However, hospital six was found to have a PCT referral population with an extremely high IMD 2000 (weighted mean IMD 2000 78.49) when compared to the rest of the sample. The total dataset was re-analysed with the exclusion of the single outlier data point (hospital 6). Analysis without data from hospital 6 showed a very significant correlation between the weighted Mean IMD 2000 and the Primary care antibiotic prescribing rate ($r = 0.803$, $p < 0.01$).

Figure 5.1. Weighted Mean Index of Multiple Deprivation (IMD 2000) and Primary Care Antibiotic Prescribing rate per 1000 patients 2001/2



5.2.5 Comparison of the Weighted Mean IMD 2000 and Secondary Care antibiotic prescribing rate.

Figure 5.2 depicts the relationship between the weighted mean IMD 2000 and the Secondary care Antibiotic prescribing rate (DDD/FCE) for 2001/2 data. These parameters were not found to be related ($r = 0.101$). However, hospital nine had a significantly higher antibiotic prescribing rate than the other hospitals in the study. Also, despite having a high weighted mean IMD 2000 hospital six had a relatively low antibiotic prescribing rate. Reanalysis of the total dataset excluding the data for hospitals six and nine did not affect the lack of relationship between these two parameters. The range of hospital antibiotic prescribing rates in 2001/2 was from 2.88 DDD/FCE (hospital 10) to 7.43 DDD/FCE (hospital 9).

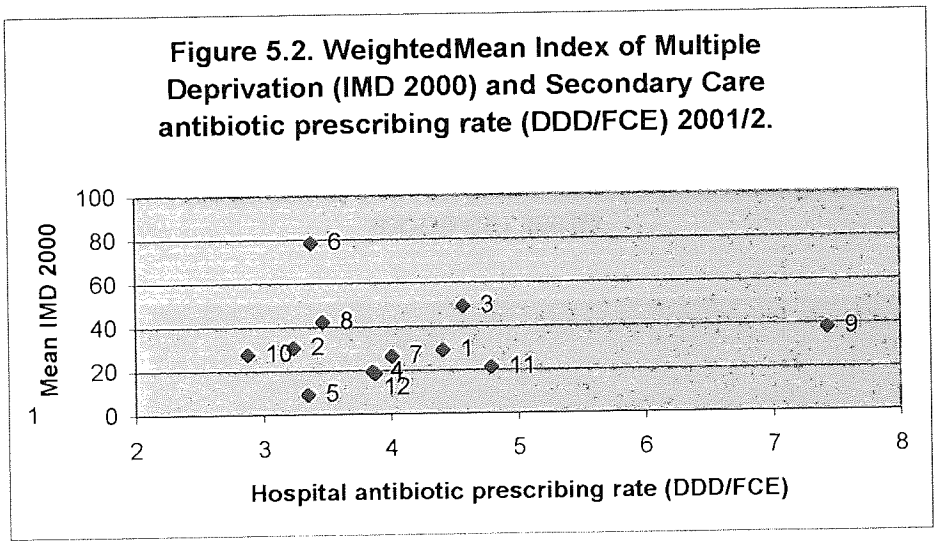
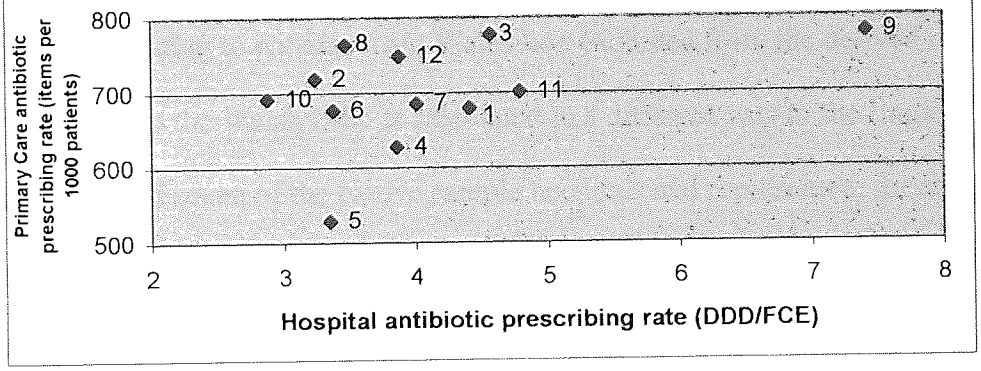


Figure 5.2. WeightedMean Index of Multiple Deprivation (IMD 2000) and Secondary Care antibiotic prescribing rate (DDD/FCE) 2001/2.

5.2.6 Primary Care antibiotic prescribing rates and Hospital antibiotic prescribing rates.

Figure 5.3 depicts the relationship between the Primary Care antibiotic prescribing rate (items per 1000 patients) and hospital antibiotic prescribing rate (DDD/FCE) in 2001/2. No significant relationship between these parameters was found ($r = 0.509$). Hospital nine had a higher prescribing rate (7.43 DDD/FCE) when compared to the referral PCT population antibiotic prescribing rate than the rest of the hospitals in the study. Hospital five had a lower primary care referral population antibiotic prescribing rate (529.47) than the other hospitals in the study. Reanalysis of the dataset excluding the data for hospitals five and nine did not demonstrate a relationship between these parameters.

Figure 5.3. Primary Care antibiotic prescribing rate (items per 1000 patients) and Hospital antibiotic prescribing rate (DDD/FCE) 2001/2.



5.3 Discussion

5.3.1 Weighted Mean IMD 2000 values.

The data contained in tables 5.3 to 5.14 shows the rank order of PCT of origin of patients treated by each hospital in the study. Patients from three or four local PCTs referred the majority of patients to each hospital, and accounted for an average of 87.96% (range 70.5 – 98.9%) of treated patients. These PCTs were all in the close geographic area of each hospital and this would be expected as most hospitals generally provide services for their local populations. Consequently, the data relating to a small number of PCTs had a major impact on the calculated weighted mean IMD 2000 indicator. This effect was particularly noticeable in hospital six with 66.09% of patients originating from a PCT with an extreme rate of deprivation. This resulted in this hospital having a weighted mean IMD 2000 of 78.49 which was outside the range for the sample (9.20 – 49.14), this data is listed in table 5.15.

The data relating to patients from Wales was excluded from the derived mean IMD 2000 as the Welsh IMD is calculated in a different way to the English IMD. This affected seven of the twelve sample hospitals and represented, for six of the hospitals, between 0.006% and 0.18% of patients and was unlikely to have had any impact on the calculated weighted mean IMD 2000. The impact of the Welsh data on hospital eleven was greater and related to 35% of patients treated. The remaining patients referred from English PCTs were included and the calculated mean IMD 2000 was derived from these data. It is not possible to state whether the inclusion of data for patients originating from Wales would have had an impact on the calculated mean IMD 2000. The mean IMD 2000 can be calculated

relatively simply and it is expected to be a relatively stable figure. This is because patient flows and referral patterns are relatively constant year on year showing little variation other than growth in absolute numbers of patients treated. This opinion is based on personal observation of annual patient activity data. There has been some change in PCT boundaries since 2001/2 with a number of mergers having taken place. This will reduce the number of individual PCTs that contribute to the calculation of the weighted mean IMD 2000.

5.3.2 Weighted Mean Primary Care Antibiotic prescribing rate per 1000 patients.

The calculated weighted mean primary care antibiotic prescribing rate per 1000 patients in 2001/2 is listed in table 5.16 and this varied from 529.47 to 778.61. The data for patients from Wales could be included as this is derived in the same way as the data for England and this shows uniformly much higher levels of antibiotic prescribing than that found in English PCTs, which may be due to higher levels of deprivation within the Principality. Other reasons for the higher rates of antibiotic prescribing may include variations in the provision of Continuing Medical Education, District Nurse services and Cottage Hospitals in Wales. These factors may increase prescribing rates of antibiotics if they are not as organised as their equivalent services in England.

The weighted mean IMD 2000 and the weighted mean Primary care antibiotic prescribing rate per 1000 patients were compared in figure 5.1 and there was a strong degree of correlation which was significant at the 0.01 level of confidence. This strength of correlation was only shown if the hospital (six) which lies at the

extreme end of the IMD 2000 range was excluded from the analysis. It was apparent that the link between deprivation and prescribing of antibiotics in primary care can be demonstrated within the general population but that the relationship breaks down at extremes of deprivation. These findings would appear to validate the hypothesis that population deprivation is a driver for the prescribing of antibiotics in primary care. This would be expected as Primary Care is the access point to the health service and will be the first point of contact for patients with acute infections when they are seeking treatment.

A previous study (Wilson *et al.*, 1999) which examined general practice characteristics and their relationship with prescribing, found that deprivation, as expressed by the LISI Index (a measure of the percentage of a practices prescriptions which are exempt from prescription charges), was associated with high levels of antibiotic prescribing in individual practices. This supports the results found in this study when using the IMD as an indicator of deprivation.

5.3.3 The relationship between deprivation and antibiotic prescribing in secondary care.

The weighted mean IMD 2000 data for each hospital was plotted against the secondary care antibiotic prescribing rate expressed as DDD/FCE (figure 5.2). No correlation was established, damaging the hypothesis that there is a link between these two parameters. This is a key finding, as there is anecdotal acceptance that deprivation increases prescribing of antibiotics in secondary care. It follows that other factors exert an influence on the antibiotic prescribing rate in secondary care. These factors will include the fact that the range of conditions

treated in secondary care may be different from those treated in primary care. Although, some deprivation related effects may occur from the impact of the treatment of chronically ill patients who are unable to be discharged from a hospital as there are no suitable care arrangements in the community. There will also be variability in the provision of district nursing, hospice and community hospital infrastructure, which will affect the impact of deprivation on secondary care services. Those conditions where an antibiotic may be required in the primary care environment and that are influenced by deprivation measures may not require secondary care intervention unless there is a treatment failure.

5.3.4 The relationship between primary care antibiotic prescribing rates and secondary care antibiotic prescribing rates.

The weighted mean primary care antibiotic prescribing rate per 1000 patients was plotted against the secondary care antibiotic prescribing rate expressed as DDD/FCE (figure 5.3) and no correlation between these two parameters was found. So, it cannot be assumed that hospitals which are located in and treat patients from areas where there may be a high rate of Primary care antibiotic prescribing will also be found to have high rates of antibiotic prescribing .

It is likely that this finding reflects differences between primary and secondary care in that the burden of disease in primary care is treated in that environment whilst the profile of conditions for which antibiotics are used in hospitals is different. Micro-organisms encountered within hospitals include resistant *Pseudomonas spp.* (Lang *et al.*, 2001), vancomycin resistant enterococci (VRE) (Amyes, 2000; Melo-Cristino *et al.*, 2002) and the different antibiotic sensivities affect the choice of antibiotic treatment (Stephenson, 2002). The hospital use of

antibiotics covers therapeutic indications such as neutropenia, surgical prophylaxis, post-transplant prophylaxis and conditions where there has been treatment failure in primary care and so both the range and indication for use of antibiotics will be different. This may explain why no relationship between primary and secondary care prescribing of antibiotics could be established.

6. Discussion

6.1 Introduction

The use of antibiotics in hospitals is a major driver for the development of resistance to antibiotics (McGowan, 1983; Ballow and Schentag, 1992; Richard *et al.*, 1994; Swartz, 1997; Bronzwaer *et al.*, 2002) and work has been published to demonstrate that antibiotic use is often inappropriate (Castle *et al.*, 1977; Griffiths *et al.*, 1986; Aswapokee *et al.*, 1990; Rho and Yoshikawa, 1995; Lutters *et al.*, 1998; Hooi *et al.*, 2001; Anand, 2002). Antibiotic use was associated with 25% of all adverse drug events in one study (Classen *et al.*, 1991) with the possible events including rash, diarrhoea, bone marrow depression and intravenous line infection. There is great variability in the rate of antibiotic prescribing between hospitals (Carling *et al.*, 1999) and therefore great difficulty in establishing an acceptable rate of antibiotic prescribing (Hogerzeil, 1995). The results found in the present study of a sample of English hospitals were a mean antibiotic prescribing rate during 2003/4 of 128 DDD/100beddays (4.35 DDD/FCE). Previous European studies found much lower hospital antibiotic prescribing rates of 55 DDD/100beddays (Poretta *et al.*, 2003) and 41 – 51 DDD/100beddays (Kiivet *et al.*, 1998).

Against this background it is vital to have a quantitative measure of use together with indicators of quality in relation to antibiotic prescribing. From this bedrock it will then be possible to objectively compare individual hospitals and look for explanations for variation. The internationally used DDD/100 bed-days has limitations that have been discussed (Curtis *et al.*, 2004) and which include a lack of sensitivity to case-mix in that this measure does not reflect the number of

patients who have been exposed to an antibiotic. It is vital that the DDD/100 bed-days is supplemented by an additional measure that takes account of patient numbers. The DDD/FCE takes account of variations in case-mix that impact on length of stay and will influence the quantity of antibiotic prescribed. Using both of these indicators it is possible to compare individual hospital specialties over time and also to compare hospitals to identify long-term trends. The use of the DDD/100 bed-days and DDD/FCE will enable the quantitative impact of medicines management interventions to be assessed. These results may then be used to determine whether a particular intervention is successful in changing practice and also to examine its cost-effectiveness.

Both of the DDD/FCE and DDD/100 beddays antibiotic indicators suffer from the weakness that they do not provide information on individual patient exposure to an antibiotic, such as the regimen, course length and whether the regimen was appropriate. This information can only be obtained from detailed clinical audit. The indicators do give an indication of the exposure to antibiotics of the patient population treated at an individual hospital and this is useful for for epidemiological studies and to obtain evidence of compliance with policies and more importantly for comparative purposes to enable effective benchmarking between hospitals.

Developments in the funding of healthcare such as 'Payment by Results' (Department of Health, 2003), which is a system for payment to hospitals for work carried out, will ensure that optimisation of antibiotic use remains a priority. Treatment of individual diagnoses will be paid based on a national tariff

based on the average cost of treating the condition and each diagnosis should therefore be treated using a standard evidence-based methodology that will involve a using a specific set of investigations, procedures and therapeutic interventions. It is essential that conditions are treated cost-effectively at a cost that is less than or equal to the national tariff. Effective use of antibiotics will contribute to this. For example, aspects of antibiotic use such as use of effective surgical prophylaxis, to avoid post-operative infection that might delay hospital discharge which must be avoided, as increased length of stay is associated with unnecessary additional cost. (Fraser *et al.*, 1997; von Gunten *et al.*, 2003). In addition, the incidence of antibiotic resistance must be controlled as treatment failure or the requirement to use a second-line antibiotic, will impact on the cost of treatment.(Acar, 1997; MacIntyre *et al.*, 2001; The Brooklyn Antibiotic Resistance Task Force, 2002). This development reinforces the need to have an objective comparator to apply to antibiotic prescribing.

6.2 Qualitative measures of antibiotic usage.

6.2.1 Medicines Management Scores

The MMAS for each of the hospitals in the present study was compared with the Antibiotic Medicines Management Score (AMS) and a correlation ($r = 0.74$) was found. This supported the hypothesis that the MMAS, which is an indicator of general medicines management control may be used as an indicator of antibiotic medicines management controls. The MMAS is widely known, but not widely used as a tool. However, the ability to use the MMAS without having to survey hospitals and calculate individual AMSs will facilitate further work to establish the impact of medicines management measures on the quality of antibiotic prescribing. In this study the range of MMAS reported, for the hospitals sampled was from nine to twenty-two (potential maximum of twenty-three) with a mean of 16.6. Hospitals should strive to implement medicines management programmes, in order to control antibiotic prescribing and which would be reflected in high values in the MMAS.

6.2.2 Therapeutic benchmarking measures

A number of indicators of prescribing quality have been examined in the present study and it is noteworthy that it was not possible to demonstrate a relationship between any of the indicators used and the MMAS for the hospitals in the study. This negative outcome may be because the effect of confounding factors that influence antibiotic prescribing, such that the impact of medicines management controls, may not be detectable. These may include local antibiotic resistance patterns that will influence which antibiotics are used or which necessitate the use of combinations of antibiotics or empirical therapy with broad-spectrum

agents. It may be that a larger sample size is required to demonstrate such a relationship. It is possible that the effects of medicines management controls are not demonstrable when examining quality indicators of antibiotic prescribing. If the latter possibility is a reality then it will not be possible to demonstrate qualitative improvements in antibiotic therapy as a result of medicines management controls and this may jeopardise continued investment in such initiatives, as the objective of medicines management is to effect the quality of prescribing. The Department of Health will only fund evidence-based measures as they have demonstrable positive impacts on antibiotic prescribing.

6.2.2.1 Penicillin use quality indicator.

The most widely used penicillins in the study were found to be co-amoxiclav and amoxicillin. The ratio comparing use of both antibiotics was found to vary between 0.4:1 and 3.4:1 (mean 1.93:1, see figure 3.4). An indicator for possible further investigation, would be a ratio of co-amoxiclav use compared with amoxicillin use exceeding 2:1. This concept is based on the premise that excessive use of broad-spectrum penicillins should be discouraged as being indicative of empirical therapy (and therefore not evidence-based), which is also more costly than narrow-spectrum agents such as amoxicillin (Lutters *et al.*, 1998). Also, inappropriate use of co-amoxiclav is likely to stimulate development of resistance to broad-spectrum penicillins, and their use should be reserved for cases where they are indicated (Burkett *et al.*, 1991; Bergan, 2001) by positive culture and sensitivity results.

6.2.2.2 Cephalosporin use quality indicator.

The proportion of total cephalosporin use that was represented by third generation cephalosporins (ceftazidime, cefotaxime and ceftriaxone) was felt to be a valuable antibiotic prescribing indicator as their use has been associated with emergence of MRSA (Wilcox, 2005). A national survey of hospital acquired bacteraemia (Public Health Laboratory Service, 2002) found links between ceftazidime use and rates of resistance among Gram negative bacteria. In secondary care there are normally restrictions on the prescribing of third generation cephalosporins (Godin *et al.*, 1988; Capri and Dellamano, 1993; Guglielmo *et al.*, 1994; Giamarellou and Antoniadou, 1997) this is both to retain their value as a therapeutic tool and also takes account of the fact that they have high acquisition costs. The data from the present study showed over the three-year study period a mean proportion of 0.24 in 2001/2, 0.26 in 2002/3 and 0.20 in 2003/4 of third generation to first and second generation cephalosporin use. It would be prudent to implement a value of 0.24 as the proportion of third generation to first and second generation cephalosporins used, which would act as the threshold when further investigation would be required within a hospital.

6.2.2.3 Quinolone use quality indicator.

From the present study, in relation to the use of quinolones it is possible to establish a benchmark which relates to the percentage of total use accounted for by parenteral formulations. The mean percentage of parenteral DDD of total quinolone usage for each year of the study was 8.6% in 2001/2, 5.7% in 2002/3 and 5.9% in 2003/4. In 2003/4 the range was from 2.2% to 10.7%. A realistic target might be for hospitals to aim to achieve a maximum of five percent of

quinolone doses being prescribed by the parenteral route with six percent or more being a trigger for further internal investigation.

6.2.2.4 Macrolide use quality indicator.

The uptake of use of long-acting macrolides (azithromycin and clarithromycin) was found to vary widely within the hospitals in the present study and also showed evidence of progressive increase over time. It is not possible to quantify what level of use might act as a trigger for further investigation. It is of greater importance that where long-acting macrolides are used that this was the outcome of informed decision making within the multidisciplinary team. This would be established by use of a survey instrument.

6.2.2.5 General quality indicators.

A general examination of which antibiotics are used within a hospital within each ATC category should demonstrate that rational choices have been made for formulary selection. It was found that the range of different antibiotics used in each hospital within the sample varied from thirty-three (hospital 11) to forty-nine (hospital 9) individual antibiotics. This was to be expected as hospital nine has an infectious diseases unit and therefore a case-mix which will drive the use of a wide variety of antibiotics.

It is possible to determine whether choices have been made within individual ATC categories to rationalise what is used. Scrutiny of cephalosporin use showed that within the sample eleven different antibiotics were used but that no site used all eleven products. It is of less importance which antibiotics were selected but

that a selection process had taken place in order to control the prescribing options (Pflomm, 2002; Janknegt, 1999). This detailed scrutiny will demonstrate that medicines management has taken place, in the rationalisation of which cephalosporin antibiotics are prescribed within a hospital, and may be used as an indicator of pharmacy activity in this area of practice.

6.3 Quantitative measures of antibiotic usage.

6.3.1 Background

A number of quantitative antibiotic indicators were examined and it was not possible to demonstrate any relationship between these quantitative indicators and the medicines management arrangements (as measured by MMAS scores) within the hospitals in the study. So, it was not possible to demonstrate an impact of medicines management on the volume of antibiotic prescribed within a hospital. It is likely that he reasons for these findings will be similar to the reasons for the inability to demonstrate a correlation between medicines management arrangements and qualitative indicators of prescribing. These reasons included the likelihood that other drivers such as case-mix and local resistance patterns may exert a more powerful effect on antibiotic prescription which mask the impact of the medicines management infrastructure.

6.3.2 The DDD/100 bed-days and the DDD/FCE prescribing indicators.

A strong correlation ($r = 0.74$, $p < 0.01$, for 2001/2; $r = 0.34$ for 2002/3 and $r = 0.80$, $p < 0.01$ for 2003/4) was demonstrated between the DDD/100 bed-days measure and the DDD/FCE measure of antibiotic usage. If antibiotic utilisation studies are to be carried out then both indicators should be calculated. The former measure enables comparison with similar work that may quote data in terms of DDD/100 bed-days and the DDD/FCE should be calculated to gain a perspective that takes account of length of stay changes which subsequently affects numbers of patients exposed to antibiotics. Both number of bed-days and number of FCE's data can be collated from information available in the public domain (Department of Health, 2004). So, from a medicines management perspective

there is little additional effort required to calculate both indicators. If only a single indicator is calculated and a comparative study involves a group of English hospitals then the DDD/FCE will be more useful in identifying sites requiring more in-depth study because of its utility in relation to casemix and length of stay.

Total antibiotic use averaged 119.98 (range 81.33 – 189.37) DDD/100 bed-days in 2001/2, 116.02 (range 70.27 – 147.59) DDD/100 bed-days in 2002/3 and 128.46 (range 72.09 – 216.83) DDD/100 bed-days in 2003/4. In terms of the DDD/FCE the comparable data is 4.15 (range 2.88 – 7.43) for 2001/2, 3.86 (range 2.87 – 5.55) for 2002/3 and 4.35 (range 2.87 – 7.36) for 2003/4. It is therefore possible to suggest a prescribing rate at which further investigation will be required. It would appear reasonable to set this threshold for levels of antibiotic use in excess of the mean from this study. So, hospitals where usage is found to be above 121 DDD/100 bed-days or 4.12 DDD/FCE might require further study. There is also value in further examination of the systems in place in those hospitals where antibiotic usage was found to be significantly less than the mean found in the present study. This would help to identify those practices which can be demonstrated to reduce antibiotic use and also identify whether there are situations where under prescribing of antibiotics has occurred.

The lower rate of antibiotic use found within the electronic prescribing cohort is likely to be important. Although, medicines management arrangements could not be correlated with antibiotic use, the use of electronic prescribing was associated with a lower use of antibiotics. It is difficult to establish the significance of this outcome as the sample consisted of three hospitals and the performance of one

hospital (hospital 6) was consistently better than the rest of the sample. There is therefore a need for a larger study to be carried out which includes a larger number of hospitals where electronic prescribing systems are in use.

It is not possible to quantify specific antibiotic usage levels in terms of DDD/FCE for individual categories of antibiotic that would indicate a need for further investigation. This is because the rate of use will reflect local recommendations within individual hospital antibiotic policies that in turn will be informed by local antibiotic susceptibility patterns. Therefore, changes in the total antibiotic prescribing rate (expressed as DDD/FCE and DDD/100 bed-days) when examined longitudinally are important in particular when compared with resistance rates (VRE, MRSA).

This quantitative use data when examined with qualitative data will present a comprehensive view of antibiotic prescribing within an institution and it is this range of data which must be collected nationally and disseminated in a positive manner to inform evidence-based prescribing over time. The value of this data cannot be overstated as it can also be used as a tool to enhance clinical audit to retrospectively examine treatment of specific infections and establish good practice for future care.

6.4 The influence of deprivation.

6.4.1 Index of Multiple Deprivation.

The present study has shown that it is possible to create an aggregate value for the Index of Multiple Deprivation (IMD) for the population referred to individual hospitals. This aggregate value can be calculated from data relating to the PCT of origin for patients treated at each hospital, provided on request from the Hospital Episode Statistics database, maintained by the Department of Health and relating this to the published IMD 2000 data for each Primary Care Trust. The calculated weighted mean IMD 2000 for the hospitals in the sample varied from 9.20 to 78.49. So, there was great variability in the mean calculated level of deprivation for the referral population that was treated at each hospital. It is recognised that PCT boundaries change and that applying individual deprivation data to large aggregates may be a source of inaccuracy (Carr-Hill and Chalmers-Dixon 2002).

It was notable that for all of the hospitals in the present study that the top three PCTs in terms of number of patients treated contributed an average of almost eighty-eight percent of total patients (range 70.5% – 98.9%). Therefore, a single PCT that has an extreme level of morbidity (as reflected in the IMD) can disproportionately affect the weighted mean IMD for the hospital referral population. So, caution will be required when interpreting the data for hospitals that treat populations where there are extreme levels of deprivation.

6.4.2 Primary Care Antibiotic Prescribing.

Primary Care antibiotic prescribing rates (for individual PCTs) expressed as the number of items per one thousand patients per year, are published by the

Prescription Pricing Authority, and are obtainable by request. Weighted mean prescribing rates calculated for the referral population for each hospital varied from 529.47 to 778.61. It was possible to compare the primary care antibiotic prescribing rate with the IMD 2000 and these two values were found to correlate ($r = 0.803$, $p<0.01$). This relationship was only found to be valid when the data for hospital six was excluded. This hospital had a weighted mean IMD 2000 at the extreme end of the range of IMD (78.49).

It was felt that population deprivation (as expressed by the IMD 2000) was shown to correlate with primary care antibiotic prescribing rates. This was expected as primary care is the gatekeeper to the healthcare system and is the first point of contact for individuals suffering ill health. Although, this may be subject to modification as changes in the availability of general practitioners lead increasing numbers of patients to attend hospital emergency departments in order to ensure that they receive rapid treatment for minor illnesses.

6.4.3 Secondary Care Antibiotic Prescribing.

No correlation was found between the weighted mean IMD 2000 data for each hospital and the secondary care antibiotic prescribing rate expressed as DDD/FCE ($r = 0.101$). This position was not altered significantly when the data from hospital six was excluded ($r = 0.326$). Assessing hospital antibiotic prescribing using the alternative measure of DDD/100 beddays produced a similar result. This finding damages the hypothesis that there is a simple relationship between the deprivation of the referred patient group and antibiotic use within hospitals. It follows that other factors exert a major influence upon the

antibiotic prescribing rate within secondary care. The primary influence is likely to be casemix (which will be dependent on the range of services offered at each hospital).

6.4.4 Relationship between antibiotic prescribing rates in primary and secondary care.

It was not possible to demonstrate any simple relationship between the weighted mean primary care antibiotic prescribing rate per 1000 patients and the secondary care antibiotic prescribing rate measured by the DDD/FCE indicator ($r = 0.509$). This position was not altered significantly by the exclusion of data from hospital six ($r = 0.432$). It is likely that this finding reflects the maintenance of core differences between activity in primary and secondary care. It would appear that where infectious disease can be treated in the primary care sector then it is and that the bulk of activity observed in secondary care for which antibiotics are used differs markedly. It therefore follows that the quantity and range of antibiotics used in hospitals is not necessarily influenced by the deprivation of patients experienced in their primary care environment. It is possible that a confounding factor may be the inappropriate prescribing of antibiotics that occurs to such an extent that it obscures the influence of deprivation (Kurin *et al.*, 1990; Hooi *et al.*, 2001).

6.5 Future Work.

The collection of antibiotic use data from this sample of hospitals over a longer period of time is required to establish whether trends identified over the three years in the present study are continued for five to ten years. This would also enable the usage data to be compared with resistance data, such as published rates of MRSA incidence. In addition, more detailed work into the impact of case-mix on antibiotic use is required. This will involve selecting specific diseases and comparing their treatment at a number of hospitals over time with the objective of identifying best practice in terms of antibiotic use.

There would be great value in quantifying the impact of individual medicines management initiatives and such results will then be used as a lever to demonstrate the benefits in investment in hospital pharmacy infrastructure. Related work to ascertain the rate of compliance by medical staff with hospital antibiotic policies has not been adequately studied in England, together with identification of the reasons for non-compliance.

6.6 Recommendations.

This work has identified the need for a national database of antibiotic usage that should be compiled each year with data from every hospital in the United Kingdom and should include information on the number of DDDs used for each antibiotic. In addition, this should be linked to a national database that includes microbial resistance data expressed as specific antibiotic and micro-organism combinations.

Individual hospitals should monitor both qualitative and quantitative indicators of antibiotic use and use this data for comparative purposes both over time and with neighbouring hospitals. This data should also be discussed by multidisciplinary teams within hospitals and these should include representatives from pharmacy, microbiology and infection control. The data should be available as both DDD/100 bed-days to enable comparison with international work and also the DDD/FCE to take account of changes in length of stay.

The impact on antibiotic prescribing of individual medicines management initiatives, such as a targeted training programme, should be measured so that their use may be validated. Also, initiatives with a proven outcome may then be disseminated across the NHS.

7. Conclusions

There is an on-going focus of attention on the appropriate use of antibiotics at all levels of healthcare and numerous recommendations have been published worldwide to ensure that antibiotics retain their value for future treatment of infectious disease (Alliance for the Prudent Use of Antibiotics, 2001; Commission of the European Communities, 1.2001; Department of Health UK, 2000; Standing Medical Advisory Committee, 1998) . The findings of the present study showed that there was an increased level of use of antibiotics within the hospitals included in the study over the period observed. The increase may be caused by a greater awareness of the need to treat infection and changes in casemix associated with the greater degree of intervention of modern medical practice. Another possible explanation is that the quality of hospital prescribing is deteriorating; if this is the case then the reasons must be identified and corrective action taken.

Specific conclusions:

- The DDD/FCE was found to correlate with the DDD/100 bed-days $r = 0.74$, $p<0.01$ (highly significant). This provides an indicator that reflects the exposure of numbers of patients to antibiotics.
- Antibiotic use within the sample of twelve hospitals increased during the study period from 4.16 DDD/FCE in 2001/2 to 3.86 DDD/FCE in 2002/3 and 4.35 DDD/FCE in 2003/4.
- The cohort of three hospitals using electronic prescribing systems were shown to have a lower level of antibiotic usage 3.48 DDD/FCE in 2001/2, 3.08 DDD/FCE in 2002/3 and 3.34 DDD/FCE in 2003/4, compared to the hospitals without electronic prescribing systems.

- No correlation was found between prescribing rates of glycopeptide antibiotics and MRSA rates or Medicines Management scores.
- There was a correlation between the Medicines Management self-assessment scores (MMAS) and Antibiotic Medicines Management scores (AMS), $r = 0.74$, $p<0.01$ (highly significant). This validates the use of the MMAS as an indicator of control of antibiotic use.
- A number of qualitative indicators which should act as triggers for more detailed audit were proposed:

  Ratio of co-Amoxiclav to amoxicillin use (as DDD) greater than 2:1.

  Proportion of third generation to first/second generation cephalosporin use (as DDD) greater than 0.24.

  Ratio of intravenous to oral quinolone use (as DDD) greater than five percent.
- It was not possible to demonstrate any correlation between the Medicines Management self-assessment score (MMAS) and any of the proposed qualitative indicators of antibiotic use. Further work is required to identify whether medicines management activities can be shown to influence the quality of antibiotic prescribing.
- It was possible to demonstrate a correlation ($r = 0.803$, $p<0.01$) highly significant) between the weighted mean Index of Multiple Deprivation (IMD 2000) and the Primary care antibiotic prescribing rate per 1000 patients.
- It was not possible to demonstrate a correlation between secondary care antibiotic prescribing rates (DDD/FCE) and the weighted mean IMD 2000 for the secondary care referral population because other factors

exert a greater influence on secondary care antibiotic prescribing.

- It was not possible to demonstrate a correlation between secondary care antibiotic prescribing rates (DDD/FCE) and primary care antibiotic prescribing rates per 1000 patients for the referral population, because the activities which would influence antibiotic use and which take place in the two care settings are different.

There is a need for further work over a five to ten year timescale to examine trends in secondary care antibiotic use in both quantitative and qualitative dimensions. In particular, the present work has highlighted that antibiotic use in the English secondary care setting appears to be at a higher level than that found in published studies in other countries.

Further work is required to identify the relationship between antibiotic use and local microbial resistance patterns in English hospitals. This may be linked with audit of treatment of specific infectious diseases. There is a pressing need for the establishment of a national database of secondary care antibiotic use and of the control initiatives in place at each hospital. Regular dissemination of comparative benchmarking data should enable hospitals to make informed decisions with regard to their local situation.

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Appendix 1

Antibiotic Medicines Management Assessment.

1. Regular audit takes place of antibiotic usage (at least 1 audit per year).
   detail of last audit carried out –

2. Antibiotic policy contains advice on treatments for specific diseases.

3. Antibiotic usage reported at Drug & Therapeutics committee.

4. Data sharing between pharmacy and microbiology.

5. Educational initiatives directed at junior medical staff.

6. Liaison with infection control.

7. Pharmacists empowered to discontinue antibiotic treatment under defined conditions
   Data to demonstrate that this occurs – number of pharmacist interventions related to antibiotic usage.

8. Pharmacists empowered to change IV therapy to Oral, under defined conditions
   Data to demonstrate that this occurs – IV/Oral ratio for quinolones and cephalosporins.

9. Antibiotic CIVAS – minibag plus, preparation of erythromycin etc.

10. Rationalisation of treatment eg quinolones, cephalosporins.

11. Pharmacist with specific responsibility for involvement in antibiotic usage.

Each element will contribute to an overall antibiotic medicines management score. Each element may be scored 0= No, 1=partial, 2 = Yes giving a possible maximum total score of 22.

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