THE EPIDEMIOLOGY OF ANTIBIOTIC UTILISATION: A STUDY OF ANTIBIOTIC USE IN INSTITUTIONAL SETTINGS AND COMMUNITY PRACTICE

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THE EPIDEMIOLOGY OF ANTIBIOTIC UTILISATION: A STUDY OF ANTIBIOTIC USE IN INSTITUTIONAL SETTINGS AND COMMUNITY PRACTICE

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ABSTRACT

The frequent use of antibiotics, and the ensuing increase in bacterial resistance, has caused much concern in the medical community in recent years. This study examines antibiotic prescribing from various perspectives, utilising prescribing information from several sources including market research databases, a provincial prescription drug plan, hospital records and patient-specific information obtained through chart review. Overall quantities and types of antibiotics prescribed have been studied at a national level comparing both Canada and the USA, at a provincial level using prescription claims data for specific facets of the Newfoundland population, at the community practice level utilising chart review of a representative sample of patients in the communities of St. John's and Mount Pearl, Newfoundland and at the hospital level using chart review.

Examination of national prescribing databases and the Newfoundland provincial database has demonstrated similar prescribing trends. Amoxicillin was the most commonly used antibiotic, penicillins accounted for the greatest proportion of total antibiotic prescriptions, a decrease in the amount of penicillins used was noted, and an increase in macrolide use was seen across all three longitudinal databases. The cross-sectional study of community practices in St. John's demonstrated that amoxicillin was the most frequently used antibiotic, and the proportions of total antibiotic use comprised by each antibiotic drug class were similar to those seen in Canada.

The Ontario Anti-infective Guidelines for Community-acquired Infections[1] was chosen as the tool for measuring prescription appropriateness in community practice. When the physicians' diagnoses were assumed to be correct, 59% of prescriptions were appropriate. Using a criteria-based decision tree to predict etiology, 88% of respiratory tract infections were likely to be viral, while the physicians thought that only 44% were viral. The treatment recommendations outlined by the Canadian Community Acquired Pneumonia Consensus Conference Group[2] were used to assess appropriateness of antibiotic treatment in patients admitted to hospital with community acquired pneumonia. Sixty five percent of initial antibiotics and 59% of secondary oral antibiotics were appropriate. However prescribing guideline adherence was much lower for patients with less severe community-acquired pneumonia.

To decrease inappropriate and excessive antibiotic use, it is necessary to first determine the nature of antibiotic prescribing. The results from this analysis allow for specific problematic areas in antibiotic prescribing to be identified. From this, interventions to improve prescribing behaviours can be implemented.

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I dedicate this dissertation to my husband, Dr. Scott Kraft, who embodies the true meaning of significance.

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LIST OF ABBREVIATIONS

Chronic Obstructive Pulmonary Disease	COPD
Community-Acquired Pneumonia	CAP
Defined Daily Doses	DDDs
Emergency	ER
General Practitioners	GPs
Health Sciences Centre	HSC
Intensive Care Unit	ICU
Intercontinental Medical Statistics	IMS
Lower Respiratory Tract Infection	LRTI
Medical Care Plan	MCP
Methicillin Resistant *Staphylococcus aureus*	MRSA
Newfoundland and Labrador Prescription Drug Program	NLPDP
Penicillin Binding Proteins	PBPs
Pneumonia Severity Index	PSI
Prescriptions	Rxs
Salvation Army Grace General Hospital	SAGGH
Skin/Soft Tissue Infection	SSTI
St. Clare's Mercy Hospital	SCMH
Standard Deviation	SD

Trimethoprim/Sulfamethoxazole	TMP/SMX
Upper Respiratory Tract Infection	URTI
Urinary Tract Infection	UTI
Vancomycin Resistant Enterococci	VRE

CHAPTER I – INTRODUCTION

1.1 Background of Study

The development of antibiotics has greatly contributed to the eradication of many infections which were once untreatable before the advent of antimicrobial agents. However this pharmacological advancement in clinical medicine has not occurred without consequence. In order to survive environmental pressures and attacks on viability, bacteria have developed several mechanisms to resist eradication. Most notably bacteria have the capability to become resistant to antibiotics. Several lines of evidence have suggested a causal relationship between antibiotic use and the development of antibiotic resistance in bacteria.[3-10] At present, bacterial infections have emerged in which the causal organism is resistant to most or all available antibiotics, thus making some infections untreatable.[11, 12] In response to this very serious public health issue, it is necessary to ensure that antibiotics are only prescribed for scenarios in which medical indication warrants their use. As bacterial resistance is a response to antibiotic use, the problem of resistance may be controlled by judicious antibiotic prescribing.

In Canada, antibiotics for human consumption can only be obtained through prescription by a physician. Therefore these agents can be prescribed in such places as a hospital or in community practices by both general practitioners and specialists. Each of these care facilities or locations pose unique problems with regard to antibiotic resistance. In the hospital, resistance is perpetuated by the abundant use of broad spectrum agents, prescribed because of the severity of illness of many patients requiring care. Furthermore, the close proximity of patients in hospital promotes the spread of infection among patients, thus requiring further antibiotic use, as well as the spread of resistance genes among bacteria. Approximately 80% of all antibiotics are prescribed in community practice settings.[13] It has previously been proposed that many of these prescriptions are unnecessary; one of the most common reasons for an antibiotic prescription by a family doctor is for respiratory tract infections, such as the common cold, which are predominantly viral in nature. As a result, many more antibiotics are being prescribed and consumed than medically indicated. IMS Health Canada has determined that approximately 10% of all prescriptions issued are for antibiotics. This amounts to 25.4 million antibiotic prescriptions for a population of approximately 30 million people. Therefore, on average, about one antibiotic prescription is administered for each Canadian citizen in a one year period. It is likely that this excessive use has contributed to the problem of bacterial resistance.

1.2 Purpose of Study

The problems surrounding antibiotic use have been a topical issue in recent years. As a result, investigators have undertaken studies examining how antibiotics are prescribed in the various health care sectors. Valid drug use data are essential for determining how antibiotics are prescribed. Medical practice patterns of antibiotic use utilising patient specific data impart valuable information that can be used for intervention purposes focussed on improving the prescribing habits of the physicians. Furthermore, because of the concern for antibiotic resistance, antibiotic utilisation data can aid in predicting future dilemmas regarding bacterial resistance that may arise as a direct result of antibiotic use.

Geographic variations in the prescribing of antibiotics exist. Therefore it is important to study local antibiotic prescribing practices in order to specifically determine potential prescribing problems that may be present in the defined population of interest. This study has obtained valid data in order to study the determinants of antibiotic prescribing in St. John's, Newfoundland examining both prescribing in community practices, as well as in-hospital antibiotic prescribing for patients with community-acquired pneumonia. Specifically, a chart review study was conducted in general practitioners' offices to investigate antibiotic prescribing for community infections. In addition to this, antibiotic prescribing databases were obtained from the Newfoundland and Labrador Prescription Drug Program and IMS Health Canada for comparison with the community antibiotic prescribing trends captured in the chart review study. A chart review study was also conducted to investigate how antibiotics are prescribed for patients admitted to hospital with the diagnosis of community-acquired pneumonia.

Although quantification studies provide important insights into the types of antimicrobial agents that are regularly used and the indications for which they are prescribed, it is also important to examine the appropriateness of these prescriptions. It has been suggested that measures of appropriateness have been avoided because of difficulties in assigning a tangible and quantifiable definition of appropriateness as it relates to antibiotics.[14] Part of this problem stems from the sources of prescribing information that are available (i.e. administrative databases compared to patient-specific information obtained through chart review). The current study has utilised a chart review process to obtain maximum information so that one may accurately assign appropriateness ratings. Furthermore several appropriateness rating tools have been employed such as the Anti-infective Guidelines for Community-acquired infections[1] as well as the Canadian clinical practice guidelines for the treatment of community acquired pneumonia.[2] Once appropriateness has been evaluated, specific prescribing problems can be easily identified. With knowledge of these specific prescribing problems, focussed interventions to change prescribing behaviour can be developed and implemented with the aim of decreasing unnecessary antibiotic use.

CHAPTER II – LITERATURE REVIEW

2.1 Bacterial Resistance

2.1.1 Definition of Antibiotics and Mechanisms of Action

Antibiotics are defined as compounds, either occurring naturally or produced synthetically, that can kill bacteria directly (bactericidal), or prevent the growth and proliferation of these microorganisms (bacteriostatic).[15] It is thought that antibiotics originated from microorganisms as natural products made to protect these same microorganisms in their ecosystem.[16] For example soil streptomycete intrinsically produces the antibiotic streptomycin. To survive, however, the soil streptomycete had to be resistant to its own antibiotic that it produced.[17] Therefore the phenomenon of antibiotic resistance occurred naturally, long before antibiotic therapy became a routine part of clinical medicine. The bacterial resistance genes presumably continued to evolve as a result of interspecies competition. Retrospective studies have demonstrated that certain microorganisms were resistant to particular antibiotics, before these antibiotics were developed for medicinal purposes, thus demonstrating that antibiotic resistance occurs naturally.[18]

Antibiotics act on and eventually kill bacteria by inhibition of one or more of the following five bacterial cellular events: cell wall synthesis, cell membrane function, protein synthesis, nucleic acid synthesis and metabolic pathways. Antibiotics can be classified according to their mechanisms of action. Antibiotics which inhibit cell wall synthesis are the β-lactams, which include penicillins, cephalosporins, carbapenems, and monobactams. Generally these antibiotics combat bacteria by crossing the bacterial cell wall and binding to structures called penicillin binding proteins (PBPs). Under normal circumstances, the activity of PBPs involves catalyzing the cross-linking of peptidoglycan chains in the bacterial cell wall. These cross-links provide the structural support of the cell wall. When the β-lactam drugs bind to the PBPs, the peptidoglycan cross-linking is inhibited, thus compromising the strength and integrity of the bacterial cell wall, which inevitably leads to osmotic rupture and cell lysis.[19] These antibiotics are therefore bactericidal.

Antibiotics which disrupt protein synthesis include the tetracyclines, aminoglycosides, macrolides, chloramphenicol, clindamycin and spectinomycin. The tetracyclines act by binding to the 30S subunit of the bacterial ribosome. This binding inhibits bacterial protein synthesis by preventing the amino acyl-tRNA from forming a complex with the mRNA-ribosome. The aminoglycosides and spectinomycin also bind to the 30S ribosomal subunit and block protein synthesis or cause the ribosome to misread the genetic code. Macrolides and clindamycin bind to the 50S ribosomal subunit, thereby inhibiting the translocation step of protein synthesis. Chloramphenicol also binds to the 50S subunit, but prevents protein synthesis by inhibiting the peptidyl transferase reaction.[19]

The anti-bacterial action of the quinolone groups of antibiotics is facilitated through the inhibition of DNA replication. This is accomplished by interfering with the activity of the DNA gyrase enzyme called topoisomerase II. This enzyme is responsible for unwinding the bacterial DNA in preparation for replication. The quinolones inactivate the DNA gyrase enzymes, thereby preventing DNA replication.[19]

The group of antibiotics which act through inhibition of metabolic pathways is the sulfonamides. This is accomplished by either inhibiting folate synthesis or preventing folate reduction. The active form of folate is required by bacteria to aid in absorption of folic acid. Many of the sulfonamides, which are similar in structure to p-aminobenzoic acid (PABA) (a substrate required to synthesize folate), compete with PABA for the activity of the enzyme dihydropteroate synthetase, thus preventing the synthesis of folate. Trimethoprim is an inhibitor of folate reduction. For folate to be active, it must be reduced by the enzyme dihydrofolate reductase. Trimethoprim is a potent inhibitor of this specific enzyme.[19]

2.1.2 Mechanisms of Antibiotic Resistance

Bacteria have the ability to overcome the eradicating effects of antibiotics in a variety of ways. There are three well described methods in which bacterial resistance to antibiotics is manifested. These combative resistance mechanisms include production of antibiotic inactivating enzymes, changes in cell wall permeability and altered structural targets.[20-23]

The first method of bacterial resistance is through enzymatic degradation of the antibiotic. For example some bacteria produce β-lactamases which function to cleave the β-lactam ring. Antibiotics which act through the destructive mechanisms of β-lactam, are rendered ineffective in the presence of β-lactamases.[21] However some β-lactam antibiotics have been developed which are resistant to the enzymatic activity of β-lactamase (ex. methicillin, oxacillin, cloxacillin, dicloxacillin).[20]

A second mechanism of resistance involves changes in the bacterial cell wall permeability. For example, some bacteria have developed cell membrane permeability resistance through the production of efflux pumps. Efflux pumps function to actively extrude antibiotics from the bacterial cell immediately after the antibiotic has entered. Therefore a high enough concentration of the antibiotics is never reached to ensure that the antibiotic can act against the bacteria. This type of resistance has been effective against tetracyclines, macrolides and quinolones.[22]

A third mechanism of resistance involves altered structural targets that antibiotics bind to. For example the β-lactam antibiotics require binding to PBPs for the action of the antibiotic to occur. Some organisms have developed resistance to B-lactams by altering the structure of these PBPs, therefore preventing the binding of β-lactams. One example of this phenomenon is the emergence of methicillin resistant *Staphylococcus aureus* (MRSA). This microorganism produces PBP2a, which is a structurally altered form of PBP, encoded for by the MecA gene. Consequently β-lactams cannot successfully bind to it and disrupt peptidoglycan cross-linking.[23]

2.1.3 Transmission of Antibiotic Resistance

The resistance of bacteria to an antibiotic can either be intrinsic or acquired. Intrinsic resistance is common to and expressed by all members of the genus or species. This type of resistance involves a natural characteristic that bacteria may posses by the nature of their morphology (ex. gram-negative bacteria resistant to vancomycin) or by inductive expression of a latent chromosomal gene.[19] Acquired resistance is a result of the transfer of resistance determinants or genes from one microorganism to another. Therefore this particular resistance phenomenon is found only in a few members of the genus or species.

In general, bacteria can acquire resistance through two mechanisms. The simplest mechanism by which bacteria can develop resistance is through gene mutation. The more predominant method is through gene acquisition.[24, 25] Through the former process, a random mutation in a bacterial gene may, for example, produce structural changes in the bacterium itself. This change may alter the binding site for the antibiotic or change the permeability of the bacterial cell wall.[22, 23] As a result, the antibiotic can no longer pass into the bacterium or bind to a specific target within and is therefore rendered ineffective. The development of resistance in *Mycobacterium tuberculosis* is an example of this phenomenon. Sequential genetic mutations have resulted in strains of *M. tuberculosis* which are resistant to at least five antibiotics due to mutational alterations in the affinity of antibiotic binding.[26] Bacteria containing these random genetic mutations are selected for in environments in which antibiotic use is substantial.

The second mechanism for developing bacterial resistance involves the acquisition of heterologous resistance genes by bacteria.[27] The exogenous genes presumably originate from bacteria that are intrinsically resistant to antibiotics.[24] The exogenous determinants may be transferred between bacteria by plasmids, transposons, or insertion-sequence mechanisms.[25] This exchange of genetic material can occur via transformation (direct exchange of chromosomal DNA), transduction (genetic exchange via bacteriophages) or by conjugation of plasmids (cell to cell contact through a sex pilus for the purposes of exchanging extrachromosomal DNA).[19, 28] Transposons are small groups of mobile genes that typically travel from one organism and are incorporated into another organism via the travels of bacteriophages.[19] Because of this effective ability to transmit genetic information, including resistance genes, from one bacterial species to another, a wide variety of bacterial microorganisms can quickly inherit resistance traits which serve to protect the bacteria from the harmful effects of various antibiotics.

2.1.4 Implications of Resistance in Clinical Practice

Use of antibiotics exerts a selective pressure on the development of resistance traits in bacteria. Because of this, the overuse of antibiotics has significantly contributed to the erosion of the efficacy of antibiotic treatment.[24] It has been proposed that because of this decreased efficacy of antibacterial treatment, we are returning to the pre-antibiotic era in which some bacterial infections were untreatable.[29]

Several common pathogens giving rise to infections in the community have become increasingly resistant to standard therapy.[25, 29] Pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarhallis*, which are common respiratory pathogens, are demonstrating increased resistance to antibiotics.[25] This is clinically important in that the vast majority of antibiotic use in community practice is for respiratory infections.[30, 31] Given that antibiotic use exerts selective pressure for the survival of bacteria with resistant traits against the antibiotics that pathogens are exposed to, it is possible that future bacterial respiratory infections may become difficult to treat. Pneumococci, for example, are the leading cause of community-acquired infections such as otitis media, sinusitis, meningitis and community-acquired pneumonia.[11] A recent study examined factors associated with increased mortality from confirmed pneumococcal pneumonia (community-acquired) requiring hospitalization.[32] When deaths that had occurred within the first four days of hospitalization were removed from the analysis, increased mortality was associated with penicillin and cefotaxime resistance in pneumococcal isolates.[32] Methicillin-resistant *Staphylococcus aureus* (MRSA), which was previously only a factor in nosocomial infections, has been detected in community infections as well.[33] Therefore resistant organisms causing community-acquired infections are becoming an increasing community public health problem, due to decreased efficacy of the antibiotics used to previously treat these same infections.

Antibiotic resistance has typically been a much greater problem in hospitals. Resistance rates are higher among pathogens giving rise to nosocomial infections, as compared to community-acquired infections.[25] For example Archibald and colleagues collected bacterial isolates from both inpatients and outpatients at eight hospitals in the US.[34] The investigators tested the isolates for specific combinations of pathogens and antibiotic resistance and found that resistance was much higher among the samples taken from inpatients, particularly those admitted to the intensive care unit.[34]

Bacterial resistance has become an increasing clinical problem in hospitals. A poignant example is the very serious problem associated with escalating resistance in Enterococci species. Enterococci species are the second leading cause of nosocomial infections and the third most commonly isolated bacteria in positive blood cultures in the United States.[35] Surveillance studies on enterococcal resistance in hospitals have revealed that resistance to vancomycin has increased from 0.4% of isolates in 1989 to 13.6% in 1992.[36] Incidentally some strains of enterococci have developed resistance to all other antibiotics normally used to treat these particular bacteria (i.e. ampicillin and aminoglycosides) and are intrinsically resistant to other antibiotic classes (i.e. penicillins, cephalosporins and macrolides).[37] Therefore enterococcal species, which are now resistant to vancomycin (VRE), represent a particular strain of bacteria present in hospitals that are potentially untreatable. VRE were predominantly limited to the ICU, but spread throughout the rest of hospitals has occurred.[37] The mortality rate associated with bacteremia caused by VRE may be as high as 50%.[38]

Bacterial resistance to antibiotics is a serious clinical problem with potentially very severe adverse consequences. The nature of bacteria and their ability to adapt to their environment make the problem of resistance a difficult one to solve. However prudent use of antibiotics would help to ensure that further development of resistance would be minimized, thus preserving the armamentarium we presently have against bacterial pathogens.[37]

2.2 Global Antibiotic Use

2.2.1 Quantification of Use

In 1987, Col and O'Connor published a study which examined worldwide total antibiotic use, combining inpatient and outpatient prescriptions.[39] Although this study had several limitations related to the questionable quality and quantity of the available drug utilisation data across various countries and differences in how this data was collected, nonetheless a striking trend emerged. The investigators discovered that there were large differences in the patterns of antibiotic use across the various studied countries. These differences not only were evident in the overall quantity of antibiotic use, but also in the types of antibiotics that were dispensed. The authors found that antibiotics comprised between 3% and 25% of all prescriptions in 1983, with the higher proportions found in Latin America rather than European countries.[39] Developed countries tended to use less antibiotics than developing countries.[39] With regard to specific patterns of use, some examples of trends include increased use of tetracycline and amoxicillin in developed countries and higher use of ampicillin in developing countries.[39] At the time the study took place (early 1980's), Spain had the highest use of TMP/SMX, while Japan had the highest use of cephalosporins.[39] The United States used the most erythromycin while Australia had the greatest number of prescriptions for doxycycline and tetracycline.[39]

McManus et al. used data from Intercontinental Medical Statistics (IMS) to demonstrate how retail sales of oral antibiotics compared across selected developed countries using Defined Daily Doses (DDDs)/1000 Population/Day.[40] The World Health Organization Collaborating Centre for Drug Statistics Methodology defines a DDD as the assumed average daily dose of a drug for its main indication in adults.[41] According to this data source the ranking of countries, from highest consumption in 1994 was as follows: France, Australia, United States, Canada, Italy, United Kingdom and West Germany.[40] The United States sold approximately 24 DDDs/1000/Day while Canada sold approximately 21 DDDs/1000/Day.[40] The authors also demonstrated that between 1989 and 1994, all the studied countries except Australia and Canada demonstrated a growth in antibiotic sales, ranging from 2% in the United States to almost 5% in West Germany.[40]

Other studies have been conducted in various countries examining overall antibiotic utilisation trends, including antibiotics prescribed in both inpatient and outpatient settings, within a specific geographical region. For example, a 1978 study in the United States reported a steep rise in antibiotic use from 1965 to 1973, but then a 7.5% decline occurred between 1973 and 1977.[42] Within the scope of the study's timeframe, the highest use of antibiotics occurred in 1973 in which 199.5 million retail antibiotic prescriptions were documented.[42]

One Swedish study, reporting consumption between 1975 and 1987, found that total antibiotic consumption changed very little over the twelve year period of study in this country. During this time, the consumed amount varied between 49 and 51 million DDDs, for a population of approximately 8 million people.[43] Trends related to specific antibiotic groups were noted. For example, aminoglycoside use remained constant, while cephalosporin use had increased between 1982 and 1987.[43] This increased use was thought to be due to an increased trend towards using cefaclor for the treatment of otitis media in children. The authors noted a decreased use of the folate inhibitor group of drugs such as the sulfonamides and TMP/SMX.[43] The most commonly used antibiotic in Sweden during this time was penicillin, although national consumption was lower than that of other Scandinavian countries.[43]

Birkett and colleagues profiled antibiotic use in Australia between 1987 and 1989.[44] Market research data was used to compare Australia's use of antibiotics with that of Sweden and Norway. The authors found that patterns of use in Australia differed substantially from the comparison countries. For example, 76% of antibiotics used in Australia were tetracyclines, broad spectrum penicillins and TMP/SMX. For Sweden and Norway, the comparable proportion of total antibiotic use was 35% and 46% respectively.[44] Conversely penicillin comprised 6% of antibiotics in Australia, while this same drug accounted for 45% and 34% of use in Sweden and Norway respectively.[44]

Overall antibiotic use had increased by 26% in Australia between 1987 and 1989, going from 36.1 DDDs/1000 population/Day to 45.6 DDDs/1000 population/Day.[44]

Both England and Scotland experienced an increase in antibiotic prescribing in the early 1990's. Between 1990 and 1991, antibiotic prescribing increased by 10% in England rising from 38,212,000 prescriptions to 42,090,000.[45] Similarly Scotland increased its antibiotic prescribing from 4,685,000 prescriptions in 1992 to 5,226,000 prescriptions in 1993, representing a 12% rise.[45] For both countries, part of the increase in prescriptions was attributable to a rise in the use of ampicillin. For England in particular, there was a 50% increase in the use of quinolones.[45]

All of the aforementioned studies only attempted to examine the quantity of antibiotics that were used for human consumption. Although human use would presumably represent the greatest proportion of antibiotic use, antibacterial drugs are also used in veterinary medicine and agriculture and could potentially contribute to the problem of bacterial resistance. The most comprehensive study of antibiotic use was undertaken in Norway in which consumption of antibiotics in humans as well as domestic animals and farmed fish was examined between 1992 and 1996.[46] When all areas of use were combined, an overall decrease in antibacterial use within the studied timeframe was discovered. Notably there was a 67% decrease in antibiotic use in domestic animals and farmed fish for both therapeutic and feed additive purposes. Human consumption during this timeframe remained relatively constant, with a minor 0.6% increase in use.[46] With regard to specific antibiotics prescribed, prescriptions for penicillins constituted between 54% and 57% of total prescriptions. Substantial declines in the use of quinolones and tetracyclines were noted, namely 92% and 68% reductions respectively.[46] When all routes of administration were considered, antibacterial use for human medicine was responsible for 45% of total use in 1992 and 71% in 1996. Overall 76,955 kilograms of active substance were administered in 1992 compared with 48,792 kilograms in 1996.[46]

2.3 Antibiotic Use in Community Practice

The vast majority of antibiotic use in humans is prescribed in community practice. In Canada, 80.4% of all antibiotic prescriptions are written by general practitioners or family physicians.[13] However, given this substantial rate of antibacterial use, no studies exist examining their use in the community practice setting, addressing the combined issues of quantification, indications and appropriateness for all infections seen by GP's.

2.3.1 Quantification of Use

In 1986, Bro and Mabeck published one of the earlier reports of general practice antibiotic use in five selected counties in Denmark, comparing prescribing patterns in 1979 and 1983.[47] In this particular study, participating physicians (accounting for 66% of total physicians in the selected study areas) were asked to record all antibiotic prescriptions, and other relevant clinical information in relation to the prescriptions, written within a five day time span in the month of March in the years 1979 and 1983. In both study years, penicillin was the most commonly prescribed antibiotic, accounting for 2.1 DDDs/1000 inhabitants/day in 1979 and 2.25 DDDs/1000 inhabitants/day in 1983.[47] The average duration of treatment for all antibiotics, except tetracycline, was approximately seven days.[47] The authors noted that, over the four year period, a change in the number of antibiotic treatments had occurred, increasing from 505 to 583 treatments/1000 inhabitants/year due to an increase in the use of broad spectrum penicillins, erythromycin and sulfonamides.[47]

In 1989, Fris et al. published a follow-up study to Bro and Mabeck's 1986 Denmark study using the same study methodology.[48] In this updated report, which included 60% of all GP's in the study region, the authors found that 44% of all antibiotics prescribed were for penicillin, 17% were for topical antibiotics, 14% were for ampicillin and 10% were for erythromycin.[48] Compared to the 1986 study, an increase in the use of erythromycin was observed.[48]

An Australian study published in 1988 also examined antibiotic use in general practice.[49] Munro et al. employed a method whereby various medical students collected prescribing information for 75 consecutive patients seen by 53 different doctors, resulting in information obtained for 3980 consultations. The authors found that 15.9% of all recorded consultations resulted in an antibiotic prescription, with the majority of these prescribed to children (30%). Amoxicillin was the most commonly prescribed antibiotic (35.5% of total antibiotic prescriptions), followed by TMP/SMX (18.7%), erythromycin (9.7%), doxycycline (8.9%) and cephalexin (6.9%).[49]

Wyatt and colleagues undertook an audit of antibiotic prescribing in the general practices of Northern Ireland over a five year period.[50] Using administrative databases of the Central Services Agency, which records the numbers of prescriptions and doses of each prescription by pharmacists and doctors, the authors were able to study antibiotic prescribing practices of general practitioners between 1983 and 1987. Over the five years of analysis, the authors noted that the number of antimicrobials prescribed remained fairly constant at approximately two million prescriptions per year.[50] Seventy per cent (70%) of antibiotic use was for broad spectrum penicillins such as amoxicillin and ampicillin, TMP/SMX, penicillin V and erythromycin. Although the total number of antibiotic prescriptions remained constant, there were notable changes in the patterns of types of antibiotics prescribed. For example the investigators determined that within the study period there was decreased ampicillin use, but increased amoxicillin use. Similarly tetracycline prescriptions decreased with a concomitant increase in the numbers of minocycline and doxycycline prescriptions. Therefore this study demonstrated a trend in the increased use of newer or more broad spectrum antibiotics while older or narrower spectrum antibiotics became less popular to prescribe.[50]

McCaig and Hughes studied antibiotic prescribing of office-based physicians in the United States utilizing the National Ambulatory Medical Care Surveys (NAMCS) from 1980, 1985, 1989 and 1992 [51] The number of antibiotic prescriptions increased from 86 million in 1980 to 110 million in 1992, although the percent of antibiotics to total drugs remained fairly constant at approximately 13%. Over the 13 years of data collection, the most commonly used antibiotic group was the broad spectrum penicillins, with amoxicillin the most frequently prescribed drug overall. Cephalosporins were the second most frequently prescribed group. Like the Wyatt et al. study, McCaig and Hughes noted an increased trend in the prescribing of expensive or broad spectrum agents like amoxicillin and the cephalosporins and a decrease in the prescribing of the cheaper or narrow spectrum drugs such as penicillin. No changes were noted in prescription trends for TMP/SMX, macrolides and tetracyclines.[51]

A second Australian study on antibiotic prescribing was published in 1997.[40] This investigation focussed on the community use of antibiotics between 1990 and 1995 and captured all government subsidised prescriptions as well as an estimate of nonsubsidised prescriptions. Over the five year period, the authors noted that the rate of antibiotic use remained stable at approximately 25 DDDs/1000/day. In 1995, the top five dispensed antibiotics were amoxicillin, amoxicillin/clavulanic acid, cefaclor, doxycycline and cephalexin. The authors noticed in their study, as in previously reported studies, that although the numbers of antibiotics prescribed remained constant, changes in the type of drugs prescribed were evident in that more broader spectrum and newer agents were being used.[40]

Majeed and Moser studied the age and gender specific prescribing patterns in general practices of England and Wales, analyzing data from the General Practice Research Database.[52] This database allowed the authors to investigate antibiotic prescribing in 288 general practices with a patient population totalling 2.1 million. It was determined that antimicrobials were prescribed at a rate of 607 Rxs/1000/year for males and 852 Rxs/1000/year in females. Use was found to be highest in children less than 5 years of age and in the elderly over the age of 75 years. Broad spectrum penicillins were the most commonly prescribed antibiotic for both males and females, representing approximately 40% of total antibiotic prescriptions. Macrolides were the second most frequently prescribed group representing 12-13% of total prescriptions. Interestingly, the authors noted a substantial variation in rates of antibiotic prescription among the practices monitored, ranging from 333 Rxs/1000/year to 1616 Rxs/1000/year.[52]

Lindbaek et al.'s 1999 study correlated the national consumption of antibiotics in Norway and the prescribing patterns of Norwegian general practitioners for the treatment of respiratory tract infections in particular with community resistance patterns of respiratory tract pathogens.[53] Similar to Canada, 85% of antibiotics in Norway were prescribed by GPs. Between 1981 and 1987, the rate of use was approximately 12 DDDs/1000/day. This rate increased to 16 DDDs/1000/day in 1993 and then decreased to 14 DDDs/1000/day in 1997. The 30% increased rate of use observed between 1987 and 1993 did not correlate with any known changes in disease patterns. In all years studied, penicillin V was the most commonly used agent representing 27-34% of total prescriptions. The authors found that macrolide consumption increased only slightly, even after the introduction of both clarithromycin and azithromycin.[53]

The only published Canadian study examining antibiotic use examined the community use of antimicrobials in the province of Manitoba from 1995 to 1997.[14] This study utilised the provincial Drug Programs Information Network, a pharmaceutical claims database that captures 90% of prescriptions dispensed in the province. During the study time period, the total rate of antibiotic use was calculated to be 894 Rxs/1000/year, with the most commonly used agent being amoxicillin accounting for 36% of all antibiotic prescriptions. The next most frequently prescribed antibiotic was TMP/SMX accounting for 13% of prescriptions followed by erythromycin (12%) and penicillin V (6%). In a manner similar to previous studies, the authors observed that the total rate of antibiotic use did not increase during the time period under investigation. However there were significant changes in how antibiotics were prescribed. For example an increase in the rate of use was noted for newer or broader spectrum agents such as the fluoroquinolones, cephalosporins, clarithromycin, azithromycin, minocycline and doxycycline. At the same time, decreased numbers of prescriptions were dispensed for older or narrow-spectrum agents such as penicillin V, tetracycline and erythromycin. Even though an intervention was in place to decrease prescriptions for fluoroquinolones, some cephalosporins and amoxicillin/clavulanic acid, the use of these restricted agents increased during the study period.[14]

2.3.2 Medical Indications

Respiratory tract infection is the most common diagnostic category giving rise to physician consultations (source: IMS Health Canada), many of which are treated with antibiotics. However the role of antibiotic therapy in the management of these infections is controversial, particularly when a bacterial etiology for the infection has not been confirmed. In general practice settings, diagnostic tests to establish bacterial etiologies for any type of infection may not be readily available and results of such tests often take several days to be completed. Therefore GPs often prescribe antibiotics to treat what would only be presumptive bacterial infections. As a result, an understanding of the range of medical indications for which GP's routinely prescribe antibiotics is important in the development of interventions to assist in alleviating unnecessary antimicrobial use.

Fris and colleagues' 1989 study investigating the use of antibiotics in general practices in Denmark found that the most common diagnoses in which antibiotic treatment was administered were tonsillitis and bronchitis/pneumonia, each accounting for 16% of all antibiotic prescriptions, followed by sinusitis (12%), conjunctivitis (11%), urinary tract infection (11%) and otitis media (8%).[48] Therefore treatment of respiratory tract infections was responsible for 48% of all antibiotics prescribed. Similarly, the 1999 Norwegian study by Lindbaek et al. found that respiratory tract infections constituted 42% of diagnoses leading to antibiotic therapy, with bronchitis accounting for 14% of prescriptions, colds accounting for 8%, tonsillitis accounting for 8%, sinusitis giving rise to 7% and pneumonia accounting for 5%.[53]

Other comprehensive studies investigating the medical indications for antibiotic therapy have reported far greater proportions of antibiotics prescribed for the treatment of respiratory tract infections. Although specific data on proportions of antibiotic prescriptions were not reported, an Australian study listed the top six conditions treated with antibiotics as acute upper respiratory tract infection (i.e. common cold), acute tonsillitis, acute otitis media, infections of the lower respiratory tract (including tracheitis, laryngitis, bronchiolitis and pneumonia), urinary tract infections and sinusitis.[49] McCaig and Hughes 1995 US study also determined that respiratory tract infections accounted for a substantial bulk of all antibiotics prescribed.[51] The authors reported that the diagnoses of otitis media, cold, bronchitis, pharyngitis and sinusitis accounted for 76% of all antibiotic prescriptions.[51] Further to this, the five most common patient complaints giving rise to an antibiotic prescription were cough, sore throat, fever, nasal congestion and ear-ache.[51]

2.3.2.1 Lower Respiratory Tract Infections

Several studies have examined the indications for antibiotic prescribing by focussing specifically on respiratory tract infections. With regard to lower respiratory tract infections, Macfarlane et al. found that 75% of adult patients who consulted a GP with the primary complaint of cough were prescribed an antibiotic.[54] Kuyvenhoven and colleagues completed a study of antibiotic prescribing for lower respiratory tract infections as well. They found that, for respiratory tract infections in general, 30% of patients were treated with antibiotics. However when a lower respiratory tract infection was present, 79% of patients diagnosed with bronchitis and 73% of patients diagnosed with pneumonia received antibiotics.[55] In terms of cough and the diagnosis of bronchitis in particular, it has been determined that between 66% and 85% of patients with this diagnosis received an antibiotic prescription.[30, 56, 57] Nyquist et al. found that 75% of children with this same diagnosis also were treated with antibiotics.[58] Signs and symptoms associated with antibiotic therapy in the treatment of bronchitis included purulent nasal discharge and sinus tenderness.[56] The high rate of antibiotic use to treat this specific condition is of concern in light of current literature which does not support this practice.[59-61]

2.3.2.2 Upper Respiratory Tract Infections

Mazzaglia et al. focussed on antibiotic treatment for all upper respiratory tract infections in primary care practices in Italy.[31] The authors discovered that treatment for URTIs amounted to 22% of all antibiotics prescribed. Within this 22% of prescriptions, pharyngitis was responsible for 40%, 26% for tonsillitis, 15% for laryngitis and tracheitis, 13% for suppurative otitis media, and rhinitis and non suppurative otitis media were responsible for the remaining 6% of prescriptions.[31] Gonzales and colleagues reported that, in a US study, 51% of patients diagnosed as having acute rhinitis (common cold) and 52% of patients diagnosed with an upper respiratory infection of multiple or unspecified sites received an antibiotic prescription.[30] Mainous and Hueston discovered that 60% of outpatient episodes of care in which any diagnosis of upper respiratory tract infection was made, including the common cold, resulted in an antibiotic prescription being filled.[62, 63] For acute tonsillitis or pharyngitis in particular, studies have reported prescription rates of up to 90% for this diagnosis.[64, 65]

2.3.3 Appropriateness of Antibiotic Use in Community Practice

Measuring appropriateness of community practice antibiotic prescriptions is an arduous and complex task. Many studies have relied on administrative databases to capture information and have made indirect conclusions from this information on antibiotic prescribing appropriateness. For example the total number of antibiotic prescriptions has increased in the USA from 86 million in 1980 to 128 million in 1998.[51] For the most part, this increase in use was viewed as unnecessary given that many of the prescriptions were written to treat respiratory tract infections.[51] It has been argued that physicians have become less skilled in their decisions to prescribe antibiotics thus warranting physician education interventions. However the increase in prescriptions, when evaluated in a cursory sense from database information, may not directly indicate increased inappropriateness of prescribing. For example it has been suggested that the increase in prescriptions may be due to improvements in access to primary care and more children attending day care at an earlier age, thus increasing infection rates.[66] Therefore it is necessary to view not only the trends in total antibiotic prescriptions, but also the medical indications for which antibiotics are used to treat.

The National Ambulatory Medical Care Survey (NAMCS) undertaken in the USA has been used to demonstrate the level of inappropriateness of antibiotic prescribing, by examining the combined issues of numbers of prescriptions and medical indications for the prescriptions, using patient record forms and ICD-9 -CM (International Classification of disease, Ninth Revision, Clinical Modification) diagnosis codes.[30, 51, 58] Although these studies represent the most comprehensive investigations addressing the issues of appropriateness of antibiotic prescribing, inherent characteristics of the studies' methodologies limit the conclusions which may be drawn. More precisely these studies assume that the diagnoses made by the physicians are correct. It has been suggested, however, that in some cases physicians may be recording a diagnosis which warrants a prescription when perhaps the patient most likely manifests a viral infection instead.[56, 66, 67] Undoubtedly a prescription for a patient diagnosed as having the common cold is inappropriate. However, with only information on the primary diagnosis, it is unclear whether a prescription for pharyngitis is appropriate or not. Furthermore appropriateness of antibiotic prescribing encompasses more than just medical indication. Choice of antimicrobial therapy for a given diagnosis in addition to dose and duration of treatment are also important in determining how appropriately physicians are prescribing antibiotics. Unfortunately such comprehensive studies are lacking in the literature.

2.3.4 Factors Influencing Antibiotic Use in Community Practice

Antibiotics are used to treat a broad array of illnesses ranging from potentially fatal bacterial infections to mild and often self-limited conditions.[68] Clearly medical indication will influence the decision to prescribe antibiotics. However other factors which have been addressed or identified as influencing antibiotic prescription decisions include diagnostic uncertainty, diagnostic labelling,[69] patient expectation (both real and assumed), certain patient characteristics or demographics, prescriber habits or characteristics, and visit termination strategies/time constraints.[68] Therefore other non-clinical factors may play a role in antibiotic prescription decisions. As has been previously described, over-prescribing of antibiotics exists. It is necessary to determine why physicians unnecessarily use antibiotics for cases in which antibiotic use is not warranted or medically indicated. An understanding of the factors which influence antibiotic use is required before successful interventions to decrease use can be implemented.

In general practice, antibiotics are presumably prescribed after the diagnosis of an infection is made. Often this diagnosis is made with a considerable degree of uncertainty, particularly with regard to respiratory tract infections, compounded by delays in receiving the results of diagnostic tests. Diagnostic tests used to arrive at a definitive diagnosis of bacterial infection often require several days to complete; in many cases the patient has since become well during this time and the test results then typically serve as a retrospective analysis of treatment.[70] McIsaac and Butler hypothesized that clinical estimation errors may be an important factor in unnecessary antibiotic use.[71] Their findings revealed that clinical uncertainty may be impacting current antibiotic prescribing practices; overestimation of the likelihood of bacterial pharyngitis was associated with unnecessary antibiotic use in that the greater the overestimation, the more likely an antibiotic would be prescribed.[71]

Interestingly Bradley has shown that antibiotics are the most frequently mentioned class of drugs that give rise to physician discomfort when making the decision to prescribe. Respiratory tract infections were the most common conditions in which the doctors felt uncomfortable with prescribing decisions.[72, 73] Given that most respiratory tract infections are viral in nature[74] and therefore antibiotics may not be medically indicated in these scenarios, it is plausible to suggest that doctors may be prescribing antibiotics in response to non-medical or social influences. For example Howie has demonstrated that prescribing for sore throats may be influenced by clinical information of a non-physical nature such as professional affiliations, the distance from the patient's residence to the clinic, and patient stress levels.[75] In another study, Howie showed that children of mothers who were high users of psychotropic drugs more frequently consulted a physician for respiratory complaints and received more antibiotics than those children whose mothers were low or non-users of psychotropic medications.[76] These early studies begin to elucidate the potential influences of non-clinical or social factors on antibiotic prescribing.

Certain physician or practice characteristics have also been shown to be associated with antibiotic prescribing. Petursson's evaluative work on his own practice indicated that an increased patient load resulted in a higher rate of antibiotic prescription per total patients seen.[77] He speculated that the increased number of patients in his practice decreased his direct contact time with patients and therefore afforded him less opportunity to convince his patients of the uselessness of antibiotics in treating viral respiratory infections.[77] On a similar note with regard to patient volume in primary care practices, Hutchinson and Foley found that increased patient volume for both salaried and fee-for-service Canadian GP's was associated with increased rates of antibiotic prescription, particularly with fee-for-service physicians.[78] Incidentally fee-for-service physicians were found to prescribe antibiotics at a higher rate than salaried physicians overall, regardless of patient volume.[78] Increased rates of antibiotic prescriptions were also found with increased patient list sizes in the Netherlands.[79] Other physician or practice characteristics associated with antibiotic prescription include increased years since medical school graduation,[79-81] solo practices,[79, 80] rural practices,[80] increased use of other drugs,[82] greater use of cultures and urinary susceptibility tests (but decreased use of throat swabs),[82] non-pediatricians,[81] and practices which are not involved in medical training.[83] Finally Cars and Hakansson have suggested that physicians habits or tendencies in diagnosing bacterial infections also influences physician antibiotic prescription decisions.[69]

Patient or parent expectation for an antibiotic has frequently been hypothesized as one of the contributing factors in antibiotic prescription. In Vinson and Lutz's study, the doctors sensed that parents expected an antibiotic for their children in 15.4% of physician encounters in which the presenting complaint was cough.[84] As well, the authors determined that if parental expectation was perceived, the doctors were twice as likely to diagnose a bacterial infection as compared to a viral cold and an antibiotic prescription was more likely to be issued.[84] Another study reported physician perceived patient/parent expectation at a rate of 48% of encounters involving suspected infections.[85] However the doctors in that study felt that in 80% of these pressured encounters, the patients' expectation for an antibiotic prescription had no influence on their decision to prescribe.[85] Bauchner et al., in a study involving only pediatricians, detailed that 96% of the study physicians had parents request antibiotics when the antibiotic prescription was felt to be not indicated.[86] Fifty-four percent (54%) of these same physicians felt that parental pressure for antibiotics was the major contributor of inappropriate oral antibiotic use.[86] In 44% of cases in which an antibiotic was prescribed in a study of acute lower respiratory tract infection, the doctor admitted that non-clinical factors, predominately patient pressure, influenced prescribing.[87] In this same study, 72% of patients indicated that they wanted antibiotics and 88% of these patients received a prescription.[87]

Although studies suggesting patient expectation does influence antibiotic prescribing decisions exist, it appears that patients do not understand appropriateness and effectiveness of antibiotic therapy, and that physicians are not accurate in determining patient expectation for an antibiotic prescription.

Studies have focussed on the knowledge of the general public with regard to the effectiveness of antibiotics for community-acquired infections and have discovered that there is a lack of general understanding by the public in this area.[88-90] Many of the subjects surveyed in Palmer and Bauchner's study indicated that antibiotics could effectively treat ear infections (93%), throat infections (83%), colds (32%), cough (58%) and fever (58%).[88] In another survey, 55% of respondents stated that antibiotics were helpful for viral infections, while only 21% correctly identified that antibiotics were both helpful for bacterial infections and not helpful for viral infections such as the common cold or flu.[90] For those surveyed who thought that antibiotics were useful for colds and flu, a positive association was found with previous antibiotic use in these subjects.[90] Hong et al. also found that patients who desired antibiotics for respiratory infections were more likely to have previously used antibiotics for similar symptoms.[91] It has been suggested that previous antibiotic use prescribed for likely viral respiratory infections may encourage patients to believe that antibiotic therapy is useful in that the administered therapy coincided with the natural recovery of these predominate self-limited infections. Therefore patients are inclined to seek antibiotic therapy, and believe that this therapy is effective, for each event of minor respiratory illness, thus creating a cycle of repeat and perhaps unnecessary consultations.[87, 89]

In light of the suggestion that physicians' antibiotic prescribing decisions are influenced to some degree by patient expectation, researchers have set out to determine how accurate physicians' perceptions of patient expectation are as compared to actual expectation of the patients for an antibiotic prescription. Hamm and colleagues discovered that the doctors correctly identified patients who desired an antibiotic in only half of the cases.[92] The study physicians identified patients as desiring antibiotics in 36% of patients who stated that they did not want a prescription.[92] The authors therefore concluded that a large degree of inaccuracy exists with regard to physicians' perception of patient expectation.[92] Further to this, it has been suggested that the reason physicians succumb to patient expectation for a prescription is simply to satisfy the patient. Therefore satisfaction of patients who received an antibiotic was compared with patients who did not receive an antibiotic. The authors found that patient satisfaction was correlated with the thought that the doctor had spent enough time with the patient explaining the illness and the choice of treatment. Satisfaction was not correlated with receipt of an antibiotic prescription.[92] No differences in patient satisfaction comparing those who did and did not receive an antibiotic prescription were also seen in an earlier study.[93] Therefore the conclusions drawn from this collection of studies indicate that doctors are indeed influenced by patient expectation, possibly in an effort to satisfy patients. However physicians are very poor in correctly discriminating which patients desire antibiotic treatment from those who do not. In addition, patient satisfaction is not correlated with receipt of an antibiotic prescription. Rather patients are more satisfied if the doctor simply spends time explaining their illness and why an antibiotic is not indicated.

2.3.5 Summary

Upon review of the literature examining antibiotic prescribing in community practice, it becomes apparent each study is unique in its approach to study methodology and presentation of results. Because of this, it is challenging to make direct comparisons about how and why antibiotics are prescribed in different regions from the available published studies. Nonetheless some notable trends are apparent. Firstly several authors have described a progression of prescribing that moves away from the use of older and/or more narrow spectrum antimicrobials with a concomitant increase in the use of newer and/or more broader spectrum agents. This is a concerning trend which may have disastrous consequences with regard to the growing problem of bacterial resistance. Secondly the penicillin group of antibiotics appear to be the most frequently prescribed by physicians, regardless of study community or country. Furthermore the medical indications for which antibiotics are prescribed are of concern. Regardless of geographical region, many doctors prescribe antibiotics for conditions in which treatment is not warranted due to the likely viral etiology of the infection, that is respiratory tract infections. Therefore more antibiotics are being prescribed than are necessary which also may have deleterious effects on bacterial susceptibility to antibiotics. Further to this, several factors unrelated to medical indication have been shown to influence prescribing decisions. Ultimately it appears that doctors are making poor choices in deciding when to prescribe antibiotics, in addition to inappropriate decisions regarding which antibiotic should be used, and are commonly influenced to prescribe by non-medical or social factors.

2.4 Antibiotic Use For the In-Hospital Treatment of Community-Acquired Pneumonia

2.4.1 The Epidemiology of Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) is a common disease with notable morbidity and mortality. In the United States, approximately four million cases are reported each year. In terms of mortality rates, CAP ranks as the sixth leading cause of death.[94] It is also the most common cause of death due to infection.[94] In a study conducted by Marston et al., the authors calculated the incidence of CAP requiring hospitalization to equal 2.66 per 1000 per year.[95] However, because CAP is not a reportable disease, true estimates of incidence rates for those in the community and those requiring hospitalization are difficult to calculate.

2.4.2 In Hospital Antimicrobial Treatment of Community-Acquired Pneumonia

Several studies have examined the in hospital antibiotic treatment of CAP. Although it would be expected that clinical factors related to the patient or local bacterial susceptibility patterns would dictate the choice of antimicrobial therapy, it is evident that other non-clinical factors, such as local prescribing habits or trends, may influence treatment decisions. Because of this, differences in antibiotic treatment choices across geographical regions and hospitals exist. For example Guglielmo et al. undertook a study examining the in-hospital prescribing trends in 1998/1999 for the treatment of selected infections, one of which was community-acquired pneumonia.[96] The authors reported that for 68% of patients diagnosed with CAP, single therapy antibiotics were administered, while 23% received two antibiotics and 9% received three or more drugs. For patients treated with single therapy, the most common pharmaceutical choice was third generation cephalosporins (36% of patients), followed by aminopenicillins (18%). Third generation cephalosporins were also commonly used in multiple drug therapy (44% of patients). The investigators also found that younger patients were more commonly treated with antibacterial agents that would be active against "atypical" pathogens, while older patients were typically treated with broad spectrum antibiotics. Information on etiology of infections and patient outcome was not available in this study.[96]

In Sweden, only 4% of hospital patients with CAP were treated with two or more antibiotics.[97] Of the remaining 96% of patients that were treated with single therapy, over half received benzylpenicillin treatment. The next most common single treatment choice was a cephalosporin, in which cefuroxime was the most popular choice. Etiologic data were available in this study and it was determined that *Streptococcus pneumoniae* was the most common infecting agent. Four percent (4%) of patients in this study had died.[97]

Studies conducted primarily in the US, but which also included a limited number of Canadian hospitals, have concluded that aminoglycoside use was commonplace in

North America in the late 1980's for the in-hospital treatment of CAP.[98, 99] In these studies *Streptococcus pneumoniae* or *Haemophilus influenzae* were the most common infecting organisms in patients with positive culture results. The proportion of patients treated with a single antimicrobial agent was approximately 70%. Cefuroxime was the most common single agent chosen for treatment (19.5%), followed by cefazolin (17.2%) and ampicillin (9.9%). Approximately one quarter of CAP patients were treated with a combination antibiotic therapy and, of these patients, the majority were treated with an aminoglycoside. Cefazolin was most frequently used in combination with an aminoglycoside. Overall, approximately one third of CAP patients were treated with an aminoglycoside, with most patients receiving treatment with gentamicin.[98, 99]

Route of administration, in addition to choice of antimicrobial therapy, is also an important consideration in the management of patients with CAP. In a prospective study conducted by Ramirez and colleagues, the efficacy of an early switch to oral antibiotics from initial intravenous (IV) antimicrobial therapy was assessed.[100] Patients were switched to oral therapy once specific clinical criteria were met, including improvement in cough and shortness of breath, decreased temperature, a normalizing white blood cell count and adequate oral intake. The authors concluded that a significant proportion of patients could effectively be switched from IV to oral antibiotic therapy and that patient outcome was not affected.[100]

2.4.3 Appropriateness of Community-Acquired Pneumonia Treatment Among Hospitalized Patients

A Canadian study investigated the adherence of in hospital community-acquired pneumonia treatment with management guidelines endorsed by the American Thoracic Society.[101] As a whole, this study examined the variation in treatment and processes of care that exists among Canadian hospitals for patients admitted with CAP. Although the specific methods of the assessment of guideline utilisation were not described, it was found that on average almost 80% of patients admitted with CAP were treated according to selected management guidelines. However a substantial amount of variation in guideline adherence was discovered; in some hospitals only 48% of patients were treated in a manner recommended by the American Thoracic Society, whereas in other hospitals, guideline adherence was as high as 100%. Mortality rates did differ across the 11 teaching hospitals which took part in the study, however an assessment between management guideline adherence and mortality was not performed.[101]

Marras and Chan also assessed the use of American antibiotic prescribing guidelines for the in-hospital treatment of community-acquired pneumonia.[102] Utilising both prospective and retrospective research methodologies, the authors found that antibiotic prescribing guidelines were widely used; approximately 80% of all patients were treated according to the American Thoracic Society guidelines. Seventy seven percent (77%) of younger patients with no comorbid conditions were treated in accordance with the guidelines. Among those who were not, therapy involved a quinolone. Eighty one percent (81%) of older patients with comorbid conditions were treated according to guideline recommendations. The authors compared the length of stay and in-hospital mortality for patients who were appropriately treated according to guidelines with those who were not. No significant differences were noted in either of the two variables.[102]

An American retrospective study examined the associations between mortality and initial antimicrobial treatment.[103] After adjusting for differences in treatment because of differences in severity of illness, the authors reported that three treatment regimens resulted in lower 30 day mortality rates. Specifically these treatment regimens were initial treatment with a second generation cephalosporin plus a macrolide, a non-pseudomonal third generation cephalosporin plus a macrolide, and a fluoroquinolone alone. It is important to note that this study was carried out in patients over the age of 65 years only and therefore may not be generalizable to all patients admitted.[103]

CHAPTER III – METHODS

3.1 Oral Antibiotic Use in Community Practices of St. John's, NF

3.1.1 Recruitment and Participation

General practitioners (GPs) in St. John's, NF and surrounding areas were invited to participate in an antibiotic utilisation study. Ninety six (96) GPs were identified as eligible to participate. Physicians were initially contacted by a mailed out letter followed by a phone call conducted by Dr. J. Hutchinson, the principal coordinator of the project, inviting their participation in the research study. Of the original 96 GPs identified, 73 agreed to participate and provided written consent, thus constituting 76% of the original eligible identified sample.

3.1.2 Method of Data Collection

The participating physicians were informed that a research assistant would visit their offices on one occasion without any prior notice. The office visits occurred between October 1, 1997 and January 30, 1998. During this office visit, all charts from the patients who were seen during the immediate preceding two days of regular practice were reviewed. During the chart review process, those patients with an infection related illness were identified. Information collected during the chart review process included patient demographics, presenting complaints, signs and symptoms, diagnoses and types and quantities of antibiotics prescribed. In addition to information extracted from the charts, the treating physicians were also interviewed in order to complete data collection. The physician interviews occurred within 2 to 3 days of chart extraction and were used to achieve further clarification on information obtained from the charts. As well the physicians were asked to rate several factors which may have influenced their decision to prescribe antibiotics.

3.1.3 Antibiotic Prescription Costs

The specific antibiotic prescribed, dose, duration and frequency of administration for each antibiotic prescription event was abstracted from patients' charts. Based on this information, the retail cost for each antibiotic prescription was calculated using a drug cost list formulated by IMS Health Canada for the fiscal year 1997/1998, which coincides with when this study took place. In cases in which the dose prescribed did not coincide with unit prices outlined in the drug cost list, the closest lowest dose unit price was used. This resulted in lower calculated prescription costs.

The IMS Health Canada drug cost list provides the dispensed prescription prices from retail pharmacies in Canada and includes mark-ups such as pharmacist professional fees. This data is obtained through electronic collection from a representative sample of retail pharmacies stratified by province, store size and store type. Projected estimates of retail drug costs are then calculated for each province from this sample. Drug costs for each individual province, in addition to national costs, are provided however data from the provinces of Newfoundland and Prince Edward Island are combined. All costs are represented in Canadian dollars.

3.1.4 Estimation of Population Rates

Population rates of infection and antibiotic use were calculated from the sample of patients identified in the chart review process. To account for location of residence of the patient sample (and therefore utilise population census data obtained from Statistics Canada) and adjust for the proportion of physicians who participated in the study, a correctional calculation adjustment was performed.

In 1997, 608,361 GP visits were made to physicians in St. John's/Mount Pearl (data provided by the Medical Care Plan for the province of Newfoundland and Labrador). Of these total visits, 474,542 visits were made to the 73 physicians who participated in the study. Therefore the proportion of 1997 GP visits made to the study GPs was 78% (474,542/608,361).

The study captured 4218 patient visits in total, of which 949 were for acute infections. The total visits therefore represented 0.89% (4218/474542) of total 1997 GP visits made to the study GPs. The proportion of patients with acute infections in the study specifically from St. John's/Mount Pearl was calculated to be 0.847 (804/949).

In order to determine how many patients in the community of St. John's/Mount Pearl in a one year period were represented by one patient in the study population, the following calculation was performed. The proportion of patients with acute infections in the study who were from St. John's/Mount Pearl (0.847) was divided by the proportion of annual visits to family doctors in St. John's/Mount Pearl represented by the sample (0.0089) multiplied by the proportion of total visits in the year seen by the study GPs (0.78). Therefore $0.847 \div (0.0089 \times 0.78) = 122$. Therefore one patient visit in the study represented 122 patient visits by residents of St. John's/Mount Pearl for acute infection in one year. The number of prescription events or cases of infections for each age category was multiplied by this calculated multiplier of 122 and divided by the population in St. John's/Mount Pearl for the corresponding age category, thus yielding a measure of the number of prescriptions or infections presented to the doctor per person per year.

3.1.5 Evaluation of Appropriateness of Antibiotic Prescriptions

The appropriateness of antibiotic prescriptions was evaluated using the criteria outlined by the Anti-infective Guidelines for Community-acquired Infections 2nd Edition.[1] All extracted patients' charts in which an antibiotic was prescribed were reviewed and the anti-infective guidelines were applied in these instances. In a small minority of cases in which determination of appropriateness was unclear, consensus was reached by consultation with Dr. J. Hutchinson, although this process was unnecessary in the majority of cases.

The appropriateness of prescriptions was assessed from four perspectives. These were medical indication, correctness of drug choice, correctness in choices of lines of therapy (the Anti-infective Guidelines suggest first, second and sometimes third lines of therapy), and dose of treatment. Judgments of medical indication involved determining whether the diagnosis assigned by the physician for each patient warranted an antibiotic prescription. Evaluation of correctness of drug choice examined whether the prescribed antibiotic provided effective coverage for the probable microorganism giving rise to the diagnosed infection. Examination of correctness in choices of lines of therapy looked at whether the prescribed antibiotic was the least costly and had the most narrow spectrum of antimicrobial coverage available for the diagnosed infection. Dose of therapy compared the physicians' decisions regarding dose of treatment with the recommendations of the anti-infective guidelines. For this analysis, only antibiotic prescriptions administered to adults were used. Dosing recommendations for children are based on the patient's weight; information on the patients' weights was not available for this study.

For determination of overall appropriateness, the diagnoses made by the physicians were assumed to be correct. In addition the diagnoses of respiratory tract infections such as pharyngitis, bronchitis, pneumonia and sinusitis as well as otitis media were considered to be of bacterial etiology, even though it has been shown that >80% of these infections are most likely to be viral in origin.[1, 74] This conservative approach to etiology affected the determination of medical indication. Upper respiratory tract infections (i.e. colds) were always considered to be viral in nature. If the doctor had indicated that a patient was allergic or intolerant or to have failed therapy with a recommended first line antibiotic, then any second line agent was considered to be appropriate, even in cases where other first line agents were available. This approach impacted the determination of correctness of choices in lines of therapy available. Patients who were thirteen years of age or older were considered to be adult for assessment of appropriateness, as it was felt that oral solid medication was a more likely formula. This mainly affected the assessment of appropriateness for amoxicillin therapy for pharyngitis.

3.1.6 Criteria-Based Decision Tree for Assessment of Viral Etiology of Respiratory Tract Infections

Based on the presenting complaints, signs and symptoms for each patient 15 years of age or older with a respiratory tract infection, an evaluation of the likelihood that the etiology for the infection was either bacterial or viral was undertaken, based on published diagnostic criteria.[1, 104-108] For patients diagnosed as having pharyngitis, the etiology was accepted as being potentially bacterial if the patient presented with throat pain and at least two of the following three symptoms: tonsillar exudate, tender or swollen anterior nodes, and fever. If cough was present, a viral etiology was assigned.[106] The diagnosis of bronchitis or pneumonia was accepted as being potentially bacterial if the patient presented with symptoms indicative of pneumonia, namely presence of abnormalities in vital signs (heart rate $\geq$ 100 beats/min, respiratory rate $\geq$ 24 breaths/min or oral temperature $\geq$ 38°Celsius) and abnormalities in chest examination (i.e. focal consolidation).[107] Therefore if a patient presented with cough and dyspnea/wheezing/rales/crackles, combined with an increased rate of respiration or heart beats, or fever, then the etiology was assumed to be potentially bacterial. Sinusitis was considered to be bacterial if the patient presented with purulent nasal discharge with maxillary tooth pain, facial pain or sinus tenderness.[105] Symptom documentation of post-nasal drip or sputum was considered as purulent nasal discharge. For all cases in which no symptoms or presenting complaints were documented, a conservative assumption of bacterial etiology was made. In all cases in which the diagnosis was upper respiratory tract infection (i.e. cold), the etiology was considered to be viral.[108]

3.1.7 Evaluation of Influencing Factors for Prescribing Antibiotics

For each patient given an antibiotic prescription, the physicians were asked to rate four factors which may have played a role in their decision to prescribe antibiotics. Their answers were coordinated with the use of a five point Likert scale. The following four factors were evaluated: medical indication (uncertain - very clear), patient/parent expectation or demand (no influence - strong influence), time constraint (no influence - strong influence), and the sense that the patient would attend another physician if they did not receive an antibiotic (no influence - strong influence).

For the factor of medical indication, the Likert scale was as follows: 1=Uncertain, 2=Somewhat Uncertain, 3=Somewhat Clear, 4=Clear, and 5=Very Clear. For the purposes of analyses, categories 1, 2 and 3 were combined to represent the category of Not Completely Clear, and categories 4 and 5 were combined to represent the category of Clear to Very Clear. This same categorization of results was done for the patient/parent expectation or demand.

3.1.8 Patient Follow-Up Information

All patients identified as having an infection related illness and whose charts were used for analysis were contacted via their GP who had participated in the study. Permission was requested and granted from 97% of the patients to obtain information on their use of primary care services one month following the captured GP visit of this analysis. Follow-up information on use of primary care services was obtained from Medical Care Plan (MCP), the provincial Medicare agency. This consisted of numbers of office visits to any physician in the 30 days following the captured doctor-patient encounter. The following billing/fee codes were used to identify all possible physician visits: 112 - general assessment, 121 - ordinary office visit and 125 - partial assessment of a patient who is aged 65 or older.

3.1.9 Physician Characteristics and Prescribing Habits

Subsets of participating physicians were identified based on their prescribing habits. Each doctor was designated as a high cost or low cost antibiotic prescriber based on each physician's mean antibiotic prescription cost. The mean antibiotic prescription cost was calculated for each physician by summing the total antibiotic prescription costs and dividing this total by the number of antibiotic prescriptions written for adult patients only. Those physicians with a mean antibiotic prescription cost in the lowest quartile, where prescription costs were less than $12.14, were designated low cost prescribers. The remainder were designated high cost prescribers. Seven physicians were excluded from this analysis; four only prescribed antibiotics for children and three did not prescribe any antibiotics.

Doctors were also categorized by their appropriateness of prescribing. The number of prescriptions for each doctor that was deemed appropriate was divided by the total number of antibiotic prescriptions written. Doctors were defined as the least appropriate prescribers if their rate of prescribing appropriateness was below or equal to the 25^{th} percentile, where $\leq$ 47.2% of prescriptions were deemed appropriate. All remaining physicians were categorized as the most appropriate prescribers. Three physicians were excluded from this analysis because they did not prescribe any antibiotics.

3.1.10 Statistical Analysis

The characteristics of patients and physicians were compared using Student's t test for continuous variables and chi-square analysis for categorical variables. For physician characteristics, Student's t test was used for analysis of the following variables: mean age, mean number of years since medical school graduation, mean number of patients seen, mean number of patients with acute infections seen, and mean prescribing rate for infections. Chi-square analysis was used for the following variables: gender of prescriber, proportion of graduates from a Canadian medical school, proportion in group practice, and proportion of appropriate antibiotic prescriptions. For patient characteristics, Student's t test was used to analyze mean duration of antibiotic therapy by diagnosis and age, and mean retail antibiotic prescription costs by diagnosis and age. Chi-square analysis was used for the following: appropriateness of prescriptions by age, influencing factors, proportion of return visits, gender, proportion with a drug plan, presenting complaints, and diagnoses. A two-tailed P-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows (release 9.0.1; SPSS Inc., Chicago IL, 1998).

3.2 Community Oral Antibiotic Use in the Province of Newfoundland - NLPDP

The Newfoundland and Labrador Prescription Drug Program (NLPDP) is a provincial government social program which allows for prescription drug coverage for a specific facet of the province's population, namely low-income families and seniors (residents 65 years old or greater) who are receiving government financial social assistance (Guaranteed Income Supplement). Numbers of prescriptions for oral antibiotics paid for by the provincial drug program and numbers of claimants covered by the program were obtained from the provincial health department for the fiscal years 1994/1995 to 1999/2000, inclusive. The data was obtained as printouts of the number of prescriptions for all antibiotics covered by the program. Specific antibiotics in these printouts were classified by drug identification numbers (DIN). All oral antibiotics were grouped into the following categories and entered into an Excel database: cephalosporins, macrolides, penicillins, quinolones, sulfonamides, tetracyclines, and other (neomycin, chloramphenicol, clindamycin, fusidic acid, lincomycin and vancomycin). Topical preparations and injectables were systematically excluded from the analysis by careful review of pharmaceutical brand and generic names. Oral routes of administration were confirmed using the Compendium of Pharmaceutical Substances (CPS).[109]

3.3 Community Oral Antibiotic Use in Canada and USA – IMS Market Databases

Data on estimated totals of antibiotics prescribed by office-based physicians in Canada and the USA in the years 1992 to 1996 were obtained from Intercontinental Medical Statistics (IMS) Health Canada and IMS Health USA, a market research company that collects data on pharmaceutical sales from a representative sample of retail pharmacies. In the USA, IMS records dispensing information for 34,000 pharmacies, representing greater than 50% of all retail pharmacies in the country. In Canada, approximately 4,400 retail pharmacies supply IMS with dispensing data. Therefore IMS Health Canada draws its data from approximately 66% of all retail pharmacies in Canada.

A comparison of numbers of oral antibiotic prescriptions (solids and liquids) written by office-based physicians (i.e. prescriptions written outside hospitals and nursing homes by general practitioners and specialists) was undertaken for selected groups of antibiotics. The IMS databases provided numbers of prescriptions for each antibiotic agent, grouped according to therapeutic class. Antibiotics were re-categorized into the following broader groups: cephalosporins, macrolides, penicillins, quinolones, sulfonamides, tetracyclines and other. For Canadian data, category of other included the following antibiotics: chloramphenicol, clindamycin, dapsone, fusidic acid, lincomycin, metronidazole, neomycin, nitrofurantoin, rifabutin, rifampin and vancomycin. The USA category of other antibiotics included chloramphenicol, clindamycin, dirithromycin, lincomycin, methenamine, metronidazole, neomycin, nitrofurantoin and vancomycin.

Rates of antibiotic use were expressed as number of prescriptions per one thousand persons per year, using population denominators obtained from publicly accessible government census records. In order to evaluate only oral antibiotic prescriptions, both the Canadian and US databases were modified such that only oral prescriptions were included. Oral formulations were confirmed using the Compendium of Pharmaceuticals and Synthetics (CPS).[109]

3.4 Antibiotic Use in Acute Care for the Treatment of Community-Acquired Pneumonia

3.4.1 Data Collection

All patients aged 18 years of age and older who were admitted to hospital in St. John's, NF with the discharge diagnosis of community-acquired pneumonia in the fiscal years April 1, 1995 to March 31, 1996 and April 1, 1998 to March 31, 1999 were identified from hospital records. Patients were identified using the CMG 13 code representing a clinical diagnosis of community-acquired pneumonia. During this time, three acute care centres were in operation in St. John's, NF, namely the Salvation Army Grace General Hospital (SAGGH), St. Clare's Mercy Hospital (SCMH) and the Health Sciences Centre (HSC). Patients' charts were abstracted and reviewed to collect data on demographics, symptoms, co-morbid conditions, laboratory, radiographic and physical examination findings, antibiotic treatment in hospital and on discharge, length of stay and occurrence of death within thirty days of admission. A thirty day mortality calculation was used because it was assumed that death after thirty days of admission was unlikely to be the result of community-acquired pneumonia.[101, 110]

3.4.2 Assessment of Severity of Disease

A validated clinical prediction rule (Pneumonia Severity Index – PSI) assessing the risk of death within thirty days for patients with community-acquired pneumonia was utilised.[110] This prediction rule classifies patients into one of five groups based on a cumulative score for each patient. Scores are calculated by determining the presence of specific patient characteristics, co-morbid conditions, physical findings and laboratory findings. Appendix I outlines the point scoring systems as defined by Fine et al. and utilised in this analysis.[110] Because patient information on glucose concentration was not available for data abstraction, patients with diabetes, as noted in the chart, were assigned points in the same manner as patients with a glucose concentration of 14 mmol/liter, which was the criteria utilised in the development of the clinical prediction rule.

PSI scores classify patients into one of five risk classes. Patients in risk classes I (no risk factors for scoring and an estimated 30-day mortality of 0%) and II (patients with scores ≤ 70 and an estimated 30-day mortality of <1.9%) are at low risk for death within thirty days due to community-acquired pneumonia. Fine and colleagues recommend that these patients are suitable for outpatient treatment of their community-acquired pneumonia.[110] Those patients with a PSI score of between 71 and 90 points may be at moderate risk for death (estimated mortality of 1.9% and 3.6%) and it is therefore recommended that these patients remain in the emergency department for 24 hours for observation.[110] Patients assigned to risk classes IV and V (score >90) are at higher risk for death within thirty days (estimated mortality of 3.7% to 12.1% and >12.1%) and should therefore be admitted to hospital.[110] Assuming that PSI scores predicting thirty day mortality are an indicator for severity of disease, the PSI was used to compare severity of disease, appropriateness of antibiotic treatment and outcome.

3.4.3 Length of Stay

The number of days in hospital (length of stay) was calculated by subtracting the admission date from the discharge date. All analyses of length of stay excluded patients who died in hospital in order to avoid the confounding influence of in-hospital mortality on length of stay.

3.4.4 Appropriateness of Antibiotic Treatment

Information on the type, dose, route of administration and duration of antibiotic treatment was abstracted from patients' charts. Each episode of antibiotic treatment was evaluated for appropriateness by comparison with the recommendations for the treatment of community-acquired pneumonia in adults outlined by the Canadian Community Acquired Pneumonia Consensus Conference Group.[2] Appendix II outlines how the guidelines were applied for patients in each risk class.

Antibiotic courses for each patient were deemed appropriate if all antibiotics prescribed were in complete accordance with the guidelines. The assessment of overutilisation was made if more than one antibiotic was administered and only one of the medications used was recommended in the guidelines. Underutilisation occurred when only a macrolide was administered to more severely ill patients, where the guidelines recommend that macrolides be used in combination therapy. If none of the administered antibiotics were included in the guideline recommendations, the assessment of wrong drug was made.

3.4.5 Statistical Analyses

The characteristics and comorbid conditions of patients admitted with CAP were compared using a Student's *t* test for continuous variables and chi-square analysis for categorical variables. A two-tailed *P*-value $\leq$ 0.05 was considered statistically significant.

To assess the effects of several predictor variables on appropriateness of antibiotic treatment, a logistic regression analysis was performed. Several variables were assessed for statistical significance using bivariate analysis ($P \leq 0.10$). Those that were significant were added to the logistic regression model. Indicator variables for pneumonia risk classes I through IV (group V was the referent), as well as indicator variables for hospital sites SAGGH and SCMH (HSC was referent), were used in the analyses.

To determine if appropriateness of antibiotic treatment affected length of stay, a linear regression analysis was performed. The natural logarithm of the length of stay values was used, as the distribution of length of stay was skewed to the right. In the first regression model, only the pneumonia risk groups were entered as a predictor variable. In the second model, patient variables that were not considered in the PSI scoring system, but were considered to be clinically important and that were statistically significant on bivariate analysis ($P \leq 0.10$) were added to the model. These variables included presence of chronic obstructive pulmonary disease (COPD), presence of interstitial lung disease, and a positive blood culture. Finally the variable of appropriateness of antibiotic treatment was added. Indicator variables for pneumonia risk classes II through V were used in the analyses. The adjusted R^2 values were compared to determine the effects that severity of illness, patient characteristics and appropriateness of antibiotic treatment had on length of stay.

In hospital thirty day mortality across disease severity and appropriateness of initial empiric antibiotic treatment was assessed using Kaplan-Meier survival curves and the log-rank statistic. A Cox proportional hazards model was used to determine the influence the aforementioned variables had on survival. All statistical analyses were performed using SPSS for Windows (release 9.0.1; SPSS Inc., Chicago IL, 1998).

CHAPTER IV – RESULTS

4.1 Oral Antibiotic Use in Community Practices of St. John's, NF

4.1.1 Comparison of Physician Participants and Non-Participants

A comparison of the seventy three (73) participating physicians and the twenty three (23) non-participating physicians is presented in Table 1. The proportion of male physicians in both groups was the same, as was the mean number of years since medical school graduation and the proportion of physicians in both groups who had graduated from a Canadian medical school. The mean ages of the participating and non-participating physicians did differ however. The mean age of the study participants was approximately 45 years while the mean age of study non-participants was almost 50 years (p=0.040).

Table 1. Baseline characteristics comparing physicians who participated in the study with non-participating physicians (number (percent) unless indicated).

Physician Characteristic	Study Participants n=73	Study Non-Participants n=23	*P*-Value
Mean Age (Years)	45.1	49.5	**0.040**
Number of Male Physicians	40 (57.1)	14 (63.6)	0.589
Mean Number of Years Since Graduation	18.9	22.5	0.104
Number of Canadian Med School Graduates	59 (84.3)	19 (86.4)	0.813

4.1.2 Characteristics of the Study Population

The chart review of two days of regular practice for the 73 participating general practitioners captured 4218 visits. Of these visits 1158, or 27%, were identified as infection related illnesses with 949 of these visits identified as newly acquired, or *de novo* infections. Table 2 illustrates the age and gender distribution of those with newly acquired infection. Approximately one third of the group were children (age < 15 years) and the gender distribution in this category was equal. However, among the adults, twice as many women presented to the doctor as compared to men.

Table 2. Age and gender of patients in the study population with newly acquired infections.

Age Category	**Population with *De Novo* Infection**	**No. (% of 949)**	
	Total	**Male**	**Female**
0-4 Years	148 (15.6)	73 (7.7)	75 (7.9)
5-14 Years	159 (16.8)	78 (8.2)	81 (8.5)
15-49 Years	465 (49.0)	156 (16.4)	309 (32.6)
≥ 50 Years	177 (18.7)	55 (5.8)	122 (12.9)
Total	949 (100)	362 (38.1)	587 (61.9)

Table 3 illustrates the diagnoses of the patients with newly acquired infections separated by age categories. Across all age categories, respiratory tract infections (i.e. URTI, pharyngitis, LRTI, sinusitis) were the most common infection related diagnoses made. The diagnosis of otitis media was most frequently made in children under the age of five years. Overall the proportion of patients diagnosed with respiratory tract infections (URTI, pharyngitis, LRTI, or sinusitis) was 65% (n=626), 11% for otitis media (n=101), 11% for other infections (n=101), 7% for urinary tract infection (n=68), and 6% for skin and soft tissue infection (n=53).

Table 3. Diagnosis of patients with newly acquired infection separated by age (number (percent)).

Diagnosis	Age Categories No. (%)				
	0-4 Years	5-14 Years	15-49 Years	≥50 Years	Total
URTI	54 (36.5)	49 (30.8)	124 (26.7)	49 (27.7)	276 (29.1)
Pharyngitis	18 (12.2)	52 (32.7)	82 (17.6)	11 (6.2)	163 (17.2)
Otitis Media	44 (29.7)	24 (15.1)	28 (6.0)	5 (2.8)	101 (10.6)
LRTI	17 (11.5)	14 (8.8)	47 (10.1)	29 (16.4)	107 (11.3)
Sinusitis	2 (1.4)	8 (5.0)	55 (11.8)	15 (8.5)	80 (8.4)
UTI	4 (2.7)	3 (1.9)	34 (7.3)	27 (15.3)	68 (7.2)
SSTI	2 (1.4)	1 (0.6)	34 (7.3)	16 (9.0)	53 (5.6)
Other	7 (4.7)	8 (5.0)	61 (13.1)	25 (14.1)	101 (10.6)
TOTAL	148 (100)	159 (100)	465 (100)	177 (100)	949 (100)

*URTI = Upper Respiratory Tract Infection (i.e. cold), LRTI = Lower Respiratory Tract Infection (i.e. Bronchitis/Pneumonia), UTI = Urinary Tract Infection, SSTI = Skin/Soft Tissue Infection.

Of the 949 patients with newly acquired infection, 604 received a prescription for oral antibiotics. This represents 64% of all patients with *de novo* infections (604/949) and 14% of total patients who presented to the doctor (604/4218), excluding prescriptions written for anti-viral, anti-fungal or topical antibacterial agents. The age and gender distribution of patients who received antimicrobial therapy are presented in Table 4. Patients within the age range of 15 to 49 years received half of all antibiotic prescriptions written and consultations for pediatric patients 4 years and younger resulted in the lowest percentage of antibiotic prescriptions. After the age of 15 years, more females than males received antibiotics, although more females within this age group presented to the doctor with infection related illnesses. The percentages for age and gender distribution of all infection patients who presented to the doctor (Table 2) closely resemble the percentages for age and gender distribution of those patients who received antibiotics.

Table 4. Age distribution of patients with newly acquired infections who received antibiotics (number (percent) unless indicated).

Age Category	Population Receiving Antibiotics No. (%)			Percent Within Age Group Receiving Antibiotics %		
	Total	**Male**	**Female**	**Total**	**Male**	**Female**
0-4 Years	86 (14.2)	48 (7.9)	38 (6.3)	58.1	65.8	50.7
5- 14 Years	100 (16.6)	50 (8.3)	50 (8.3)	62.9	64.1	61.7
15-49 Years	301 (49.8)	107 (17.7)	194 (32.1)	64.7	68.6	62.8
≥50 Years	117 (19.4)	36 (6.0)	81 (13.4)	66.1	65.5	66.4
Total	604 (100)	241 (39.9)	363 (60.1)	63.6	66.6	61.8

The distribution of antibiotics across the diagnostic categories is as follows: 7% of all antibiotics were prescribed for URTI, 23% for pharyngitis, 15% for LRTI, 16% for otitis media, 12% for sinusitis, 9% for urinary tract infections, 8% for skin/soft tissue infections and 10% for all other infections. Figure 1 represents the proportion of antibiotics given within each diagnostic category. With the exception of URTI and other infections, greater than 80% of all patients within each diagnostic category received an antibiotic prescription. Most notably, 97% of all patients diagnosed with otitis media in particular were treated with antimicrobial therapy.

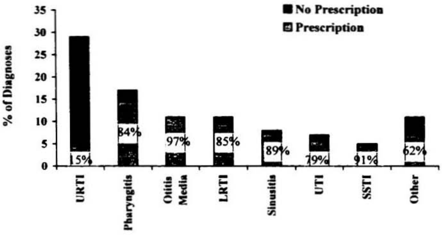

Figure 1. Distribution of diagnoses and proportion of antibiotics given within each diagnostic category.

4.1.3 Analysis of Prescribed Antibiotics

In patients under the age of 15 years, prescriptions for penicillins accounted for 66% of all antibiotic prescriptions written, whereas 43% of prescriptions were for penicillins among the adult patients (Table 5). Cephalosporins and quinolones were prescribed more frequently in adults. Overall penicillins and macrolides were the most commonly prescribed antibiotics in the study, accounting for 70% of all prescriptions captured . Amoxicillin was the single most commonly prescribed agent, giving rise to 35% of total prescriptions.

Table 5. Numbers (percent) of prescriptions in each antibiotic drug class for pediatric and adult age groups (n=604).

Prescription Class	**Pediatric (0-14 Years)** No. (%)	**Adult (≥ 15 Years)** No. (%)	**Total** No. (%)
Cephalosporins	**9 (4.8)**	**44 (10.5)**	**53 (8.8)**
Cefaclor	3 (1.6)	3 (0.7)	6 (1.0)
Cefuroxime	—	24 (5.7)	24 (4.0)
Macrolides	**40 (21.5)**	**80 (19.1)**	**120 (19.9)**
Erythromycin	38 (20.4)	52 (12.4)	90 (14.9)
Penicillins	**122 (65.6)**	**180 (43.1)**	**302 (50.0)**
Amoxicillin	100 (53.8)	109 (26.1)	209 (34.6)
Quinolones	—	**40 (9.6)**	**40 (6.6)**
Ciprofloxacin	—	20 (4.8)	20 (3.3)
Sulfonamides	**13 (7.0)**	**40 (9.6)**	**53 (8.8)**
TMP/SMX*	13 (7.0)	40 (9.6)	53 (8.8)
Tetracyclines	**2 (1.1)**	**22 (5.3)**	**24 (4.0)**
Minocycline	1 (0.5)	9 (2.2)	10 (1.7)
Other	—	**12 (2.9)**	**12 (2.0)**
Metronidazole	—	7 (1.7)	7 (1.2)
All Antibiotics	**186 (100)**	**418 (100)**	**604 (100)**

*TMP/SMX = trimethoprim/sulfamethoxazole. Percent totals may not equal 100 due to rounding; other includes metronidazole, nitrofurantoin and trimethoprim.

Table 6. Numbers of prescriptions (%) in each antibiotic class separated by diagnosis.

	URTI	Pharyngitis	Otitis Media	LRTI	Sinusitis	UTI	SSTI	Other	Total
Cephalosporins	1 (2.4)	4 (2.9)	6 (6.1)	12 (13.2)	15 (21.1)	1 (1.9)	13 (27.1)	1 (1.6)	53 (8.8)
Macrolides	19 (45.2)	27 (19.7)	15 (15.3)	34 (37.4)	9 (12.7)	—	5 (10.4)	11 (17.5)	120 (19.9)
Penicillins	19 (45.2)	103 (75.2)	67 (68.4)	34 (37.4)	35 (49.3)	3 (5.6)	25 (52.1)	16 (25.4)	302 (50.0)
Quinolones	1 (2.4)	—	3 (3.1)	2 (2.2)	3 (4.2)	21 (38.9)	4 (8.3)	6 (9.5)	40 (6.6)
Sulfonamides	2 (4.8)	2 (1.5)	7 (7.1)	6 (6.6)	5 (7.0)	25 (46.3)	—	6 (9.5)	53 (8.8)
Tetracyclines	—	1 (0.7)	—	3 (3.3)	4 (5.6)	—	1 (2.1)	15 (23.8)	24 (4.0)
Other	—	—	—	—	—	4 (7.4)	—	8 (12.7)	12 (2.0)
Total	42 (100)	137 (100)	98 (100)	91 (100)	71 (100)	54 (100)	48 (100)	63 (100)	604 (100)

*URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection, UTI = Urinary Tract Infection and SSTI = Skin/Soft Tissue Infection.

Table 6 displays the numbers and types of antibiotics prescribed within each diagnostic class. With the exception of urinary tract infections and other infections, the most commonly prescribed antibiotic group within each diagnostic category was the penicillins. Equal numbers of penicillins and macrolides were prescribed for LRTI. Cephalosporins were most commonly prescribed in cases of sinusitis and skin/soft tissue infections. Most urinary tract infections were treated with either TMP/SMX or quinolones.

Overall 74% of antibiotic prescriptions were written for a duration of 10 days or greater (Table 7). The mean duration of antibiotic treatment for all age groups and antibiotic classes equalled 10.5 days (Table 8). The treatment of respiratory tract infections encompassed, on average, 9 days of treatment. Urinary tract infections were treated, on average, for 7 days and for four or more days in 87% of cases in which this diagnosis was made.

Table 7. Duration of antibiotic treatment by diagnosis groups (number (percent) of prescriptions).

	3 Days	4-9 Days	≥ 10 Days
Respiratory Tract	---	68 (20.4)	265 (79.6)
Otitis Media	---	13 (13.7)	82 (86.3)
Urinary Tract	7 (13.5)	28 (53.9)	17 (32.7)
Skin/Soft Tissue	---	17 (40.0)	27 (60.0)
Other	---	20 (37.2)	33 (62.8)
Total	7 (1.2)	145 (25.4)	423 (73.4)

Table 8. Mean (± SD) duration of antibiotic treatment by diagnosis and drug class.

	Respiratory Tract	Otitis Media	UTI	SSTI	Other	Total
Penicillins	9.4 ± 1.4	9.9 ± 0.8	10.0 ± 0.0	8.3 ± 1.8	8.4 ± 1.6	9.4 ± 1.4
Macrolides	9.2 ± 1.7	8.9 ± 2.1	—	26.0 ± 35.8	11.3 ± 11.7	10.1 ± 8.4
Cephalosporins	9.1 ± 2.1	8.2 ± 2.0	10.0 ± 0.0	9.4 ± 2.0	7.0 ± 0.0	9.1 ± 2.0
Quinolones	9.5 ± 1.2	8.7 ± 2.3	6.5 ± 2.4	8.5 ± 1.7	30.3 ± 30.5	11.0 ± 14.0
Tetracyclines	10.0 ± 0.0	—	—	—	25.5 ± 19.4	19.3 ± 16.7
Other	10.2 ± 1.3	9.3 ± 1.4	7.3 ± 2.3	—	45.6 ± 71.2	13.8 ± 28.3
Total	9.4 ± 1.5	9.5 ± 1.4	7.2 ± 2.4	10.7 ± 12.2	22.8 ± 36.1	10.5 ± 11.9

*Respiratory Tract = cold, pharyngitis, bronchitis/pneumonia and sinusitis. UTI = Urinary Tract Infection, SSTI = Skin/Soft Tissue Infection.

Table 9. Mean (± SD) duration of antibiotic treatment (days) separated by age groups and diagnosis.

	0-14 Years	≥ 15 Years	*P*-Value
URTI	9.8 ± 0.9	8.8 ± 1.7	0.083
Pharyngitis	9.7 ± 0.9	9.1 ± 1.6	**0.010†**
Otitis Media	9.8 ± 1.2	9.1 ± 1.7	**0.039†**
LRTI	9.5 ± 1.2	8.9 ± 1.8	0.138
Sinusitis	10.5 ± 1.4	10.0 ± 1.6	0.363
UTI	7.3 ± 2.5	7.2 ± 2.4	0.906
SSTI	8.0 ± 1.7	10.8 ± 12.7	0.710
Other	16.7 ± 11.5	23.2 ± 37.1	0.766
Total	9.8 ± 1.9	10.8 ± 14.3	0.466

† = Significant at *P*-value ≤ 0.05

Table 9 demonstrates a comparison between mean duration of antibiotic between age groups of patients. For the most part, duration of therapy was similar across diagnostic categories. However duration was approximately one day longer for children treated for pharyngitis (P=0.010) and otitis media (P=0.039) as compared to adults.

At the time the study was undertaken, 11 of the 30 different types of antibiotics prescribed by the study physicians were under patent in Canada. Table 10 depicts the proportions of unpatented (or older) agents compared to patented (or newer) agents prescribed for each diagnosis group. Older, unpatented agents were prescribed in 74% of cases. Older agents were primarily prescribed in respiratory tract infections (75%), skin/soft tissue infections (92%) and other infections (81%). An increase in newer agents was used for treating otitis media (37%) and urinary tract infections (39%).

Table 10. Number of prescriptions written for older/unpatented agents compared to newer/patented agents by diagnosis groups.

Diagnosis	Older/Unpatented Agents No. (%)	Newer/Patented Agents No. (%)
Respiratory Tract	257 (75.4)	84 (24.6)
Otitis Media	62 (63.3)	36 (36.7)
Urinary Tract	33 (61.1)	21 (38.9)
Skin/Soft Tissue	43 (89.6)	5 (10.4)
Other	51 (81.0)	12 (19.0)
Total	446 (73.8)	158 (26.2)

*Respiratory tract infections include URTI, pharyngitis, LRTI and sinusitis. Patented agents = amoxicillin/clavulanic acid, azithromycin, cefaclor, cefixime, cefprozil, cefuroxime, ciprofloxacin, clarithromycin, erythromycin ES/sulfisoxazole, norfloxacin and ofloxacin.

4.1.4 Antibiotic Prescription Costs

Of the 604 antibiotic prescriptions events captured in the study, 556 were used for the analysis of retail antibiotic prescription costs. Of the 48 prescription events which were excluded from the analysis, 16 prescription events did not indicate a frequency with which the antibiotic was to be administered, 14 provided no data on the intended duration of therapy, 9 lacked dose information and 9 further prescriptions were excluded due to absence of cost information in the IMS drug cost list (6 prescriptions for bacampicillin, 2 for ampicillin and 1 for trimethoprim).

The mean retail cost of antimicrobial therapy for all patients receiving prescriptions was $19.73 (± $32.54). Prescription costs ranged from a minimum of $1.60 to a maximum of $576.00. Mean costs for each antibiotic drug class are depicted in Table 11. This analysis did not account for differences in durations of therapy, although the mean duration of therapy for all drug classes was approximately 10 days as was previously described. Prescriptions written for penicillins comprised the lowest average retail prescription cost ($12.19) while the most expensive prescriptions were for quinolones ($65.48).

Table 11. Mean (± SD) retail prescription drug costs separated by antibiotic class.

Antibiotic Drug Class	Mean Prescription Cost
Cephalosporins	$29.10 ± $17.37
Macrolides	$19.96 ± $20.27
Penicillins	$12.19 ± $10.28
Quinolones	$65.48 ± $92.55
Sulfonamides	$16.63 ± $34.30
Tetracyclines	$18.43 ± $18.68
Other	$10.55 ± $8.71
Total	$19.73 ± $32.54

Table 12 outlines mean prescription costs for the treatment of each diagnostic category separated by age groups. Overall, prescription costs increased with age. Treatment for infections such as bacterial vaginosis, epididymitis, acne, dental infections, gastroenteritis and prostatitis, which are included in the category of "Other" infections, gave rise to the greatest mean antibiotic prescription cost of $49.24 when all age groups were combined. Sinusitis possessed the second highest overall average prescription cost of $27.45. The diagnostic category resulting in the lowest mean prescription cost, namely $10.78, was pharyngitis. For patients under the age of 5 years, sinusitis was the most expensive condition to treat. Combining the diagnostic categories of URTI, pharyngitis, LRTI and sinusitis, the mean retail cost of an antibiotic prescription for the treatment of respiratory tract infections equalled $17.10.

Table 12. Mean (± SD) retail prescription costs separated by diagnostic category and age.

Diagnosis	0-14 Years	≥ 15 Years	Total	*P*-Value
URTI	$5.18 ± $3.89	$20.22 ± $12.67	$15.07 ± $12.70	**0.004†**
Pharyngitis	$6.86 ± $4.60	$14.22 ± $6.54	$10.78 ±$6.78	**<0.001†**
Otitis Media	$6.14 ± $5.56	$24.63 ± $15.68	$12.44 ± $13.41	**<0.001†**
LRTI	$6.59 ± $7.10	$24.70 ± $16.87	$18.60 ± $16.68	**<0.001†**
Sinusitis	$13.39 ±$11.14	$29.27 ± $18.55	$27.45 ± $18.51	0.150
UTI	$7.19 ± $2.47	$18.38 ± $14.46	$17.72 ± $14.28	0.509
SSTI	$5.32 ± $3.77	$25.04 ± $27.42	$23.29 ± $26.92	0.641
Other	$17.63 ±$17.64	$51.30 ±$94.32	$49.24 ±$91.76	0.938
RTI Total	$7.09 ± $6.16	$22.24 ± $15.69	$17.10 ± $15.06	**<0.001†**
Total	$6.91 ± $6.27	$25.82 ±$37.81	$19.69 ±$32.54	**<0.001†**

*URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection, UTI = Urinary Tract Infection, SSTI = Skin/Soft Tissue Infection , RTI = Respiratory Tract Infection.
† = Significant at p-value ≤ 0.05

The mean retail prescription cost for those patients with a drug plan was $22.08, while the cost for those patients who did not have a drug plan, or drug plan information was not known for the patient, was $16.46 ($p$=0.026). There were no differences in the proportions of patients in each diagnosis group with a drug plan as compared to those not covered by a plan (P=0.307).

4.1.5 Estimated Population Rates

Although the four months of this study occurred during the fall and winter, and therefore is subject to seasonal bias, estimations of annual population rates of both antibiotic prescriptions and infections per person per year were calculated. The estimated annual infection rate by age and diagnosis is presented in Table 13. It is anticipated that children will become infected with a respiratory tract infection and present to the doctor once a year (excluding otitis media) with colds being the most common infection type. Half of all adults will acquire a respiratory tract infection and present to a GP in a one year period. Overall the rate of infections presented to a doctor in children is 1.56 infections per person per year while the rate in adults decreases to 0.76 infections per person per year.

Table 13. Estimated annual population rates of infection in children and adults per person per year by diagnosis.

	Estimated Annual Rate		
	Pediatric (0-14 Years)	**Adult (≥15 Years)**	**Total**
No. of Patients in Study	307	642	949
Population	23,990	103,465	127,455
URTI	0.52	0.20	0.26
Pharyngitis	0.36	0.11	0.16
Otitis Media	0.35	0.04	0.10
LRTI	0.16	0.09	0.10
Sinusitis	0.05	0.08	0.08
UTI	0.04	0.07	0.07
SSTI	0.02	0.06	0.05
Other	0.08	0.10	0.10
Total	1.56	0.76	0.91

*URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Infection, UTI = Urinary Tract Infection, SSTI = Skin/Soft Tissue Infection. These estimates have a seasonal bias as the prescription events occurred in the fall/winter.

The estimated antibiotic prescription rate by age and diagnosis is presented in Table 14. The prescription rate for URTI, pharyngitis, LRTI, sinusitis (i.e. respiratory tract) and otitis media in children less than 15 years was 0.90 antibiotic prescriptions per person per year. This rate declined to 0.31 prescriptions per person per year for those aged 15 years or greater.

Table 14. Estimated annual population rates of antibiotic prescriptions in children and adults per person per year by diagnosis.

	Estimated Annual Rate		
	Pediatric (0-14 Years)	**Adult (≥15 Years)**	**Total**
No. of Patients in Study Population	186 23,990	418 103,465	604 127,455
Respiratory Tract	0.56	0.27	0.33
Otitis Media	0.34	0.04	0.09
Urinary Tract	0.02	0.06	0.05
Skin/Soft Tissue	0.02	0.05	0.05
Other	0.02	0.07	0.06
Total	0.95	0.49	0.58

*Respiratory tract = cold, sinusitis, pharyngitis and bronchitis/pneumonia. These estimates have a seasonal bias as the prescription events occurred in the fall/winter.

Table 15 depicts the projected rate of antibiotic use based on prescriptions captured during the study period. The penicillin group of antibiotics is expected to account for half of all antibiotics prescribed in the study region in a one year period, with a rate of 289 prescriptions per 1000 persons per year. Amoxicillin in particular is the most frequently prescribed within the penicillin group. The rate of use of macrolides is expected to equal 115 prescriptions per 1000 persons per year. The tetracycline group of antibiotics is expected to be the least frequently prescribed group of antimicrobials.

Table 15. Estimated annual rates of antibiotic prescriptions for acute infections per 1000 per year by drug class.

	Estimated Annual Rate Per 1000
Cephalosporins	**51**
Cefuroxime	23
Cephalexin	14
Macrolides	**115**
Azithromycin	11
Clarithromycin	18
Erythromycin	85
Penicillins	**289**
Amoxicillin	199
Amoxicillin/Clavulanic Acid	34
Cloxacillin	23
Penicillin	18
Quinolones	**38**
Ciprofloxacin	19
Norfloxacin	17
Sulfonamides	**51**
TMP/SMX	51
Tetracyclines	**23**
Tetracycline	7
Other*	**12**
Metronidazole	7
Nitrofurantoin	4
TOTAL	**578**

*Other includes metronidazole, nitrofurantoin and trimethoprim.

4.1.6 Appropriateness of Antibiotic Prescriptions

Accepting that the diagnoses made by the physicians are correct, 59% of all antibiotic prescriptions were appropriate while 41% were inappropriate. Of the inappropriate prescriptions, 19% were for the wrong drug, 13% were not indicated and in 9% of cases a more appropriate lower line of antibiotic was available for prescription (Figure 2).

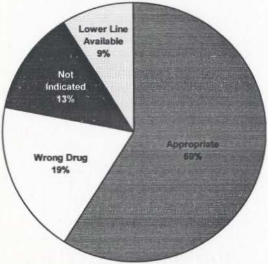

Figure 2. Appropriateness of antibiotic prescriptions as determined by the Anti-infective Guidelines For Community-acquired Infections 2nd Edition. This analysis is based on the general practitioners' diagnoses.

Table 16 shows the appropriateness of antibiotic prescriptions by diagnosis and the reasons for inappropriateness. The overall appropriateness rate was 45% for respiratory tract infections (URTI, pharyngitis, LRTI and sinusitis) and 79% for otitis media. The appropriateness rate was substantially higher for non-respiratory tract infections, namely 79% for urinary tract infection, 81% for skin/soft tissue infection and 76% for all other infections.

Table 16. Appropriateness of antibiotic prescriptions by diagnosis groups based on the physicians' diagnoses.

	Appropriate	Not Indicated	Wrong Drug	Lower Line	Total
URTI	---	42 (100.0)	---	---	42 (100)
Pharyngitis	74 (54.0)	3 (2.2)	53 (38.7)	7 (5.1)	137 (100)
Otitis Media	77 (78.6)	---	7 (7.1)	14 (14.3)	98 (100)
LRTI	36 (39.6)	23 (25.3)	27 (29.7)	5 (5.5)	91 (100)
Sinusitis	43 (60.6)	6 (8.5)	10 (14.1)	12 (16.9)	71 (100)
UTI	43 (79.6)	---	1 (1.9)	10 (18.5)	54 (100)
SSTI	35 (81.4)	---	7 (16.3)	1 (2.3)	43* (100)
Other	31 (75.6)	3 (7.3)	5 (12.2)	2 (4.9)	41* (100)

*No guideline was available to assess 4 further decisions for skin/soft tissue infection and 22 other decisions. URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection, UTI = Urinary Tract Infection, SSTI = Skin/Soft Tissue Infection.

The 74 prescriptions not indicated for respiratory tract infections (URTI, pharyngitis, LRTI and sinusitis) were for viral infections as indicated by the diagnosis made by the doctor or by the assessment of probable etiology (bacterial or viral) made by the doctor and documented in the patients' charts. Forty two (57%) were diagnosed as colds by the doctor (i.e. URTI), 17 (23%) were cases of LRTI/bronchitis in children, and

15 (20%) were other respiratory infections deemed of likely viral etiology by the doctor and were recorded as such in the patients' charts.

In 26% of prescriptions written for respiratory tract infections (n=90), the wrong antibiotic was prescribed. In these cases, the prescribed antibiotic did not provide adequate coverage to eradicate the probable micro-organism associated with the diagnosis that the physician had made. For pharyngitis, the most commonly prescribed antibiotic which was deemed to be the wrong drug was amoxicillin used to treat adults (n=42). For LRTI's, the predominant wrong drug used was also amoxicillin (n=17), although 7 wrong drug prescriptions were for a cephalosporin. Three ciprofloxacin prescriptions were administered to patients with sinusitis who were given a wrong drug.

The wrong drug was prescribed in 7%, 2%, 16% and 12% of diagnosed cases of otitis media, urinary tract infections, skin and soft tissue infections and other infections respectively. For these prescriptions, ciprofloxacin was the most commonly prescribed wrong drug for all diagnostic categories, except for UTI where the one wrong drug prescription was for ampicillin.

In 19% of cases diagnosed with urinary tract infection and treated with antibiotics, a lower line of antibiotic therapy was considered more appropriate by the guidelines. A lower line of antimicrobial therapy, according to the guidelines, provides a more narrow spectrum of coverage and therefore is less likely to contribute to the growing problem of bacterial resistance. Prescription events for which a lower line was deemed to be available for the treatment of UTI primarily involved the use of norfloxacin. In only 7% of respiratory tract infections treated with antibiotics, a lower line of therapy was recommended.

Table 17. Top five agents for inappropriate prescriptions.

	No. (%) of Prescriptions
Not Indicated (n=77)	
Amoxicillin	33 (42.9)
Erythromycin	15 (19.5)
Erythromycin/Sulfisoxazole	7 (9.1)
Clarithromycin	6 (7.8)
TMP/SMX	6 (7.8)
Wrong Drug (n=110)	
Amoxicillin	59 (53.6)
Ciprofloxacin	11 (10.0)
Erythromycin	8 (7.3)
Cefuroxime	6 (5.5)
Bacampicillin	5 (4.5)
Lower Line Available (n=51)	
Amoxicillin/Clavulanic Acid	15 (29.4)
Norfloxacin	7 (13.7)
Erythromycin	7 (13.7)
Azithromycin	5 (9.8)
Clarithromycin	4 (7.8)

* Only top five agents are listed; percentages do not total 100.

For each of the three categories of inappropriateness for all diagnostic categories, the top five inappropriately administered agents were determined and documented in

Table 17. In 54% of wrong drug cases and 43% of not indicated cases, the inappropriately prescribed antibiotic was amoxicillin. The combination agent of amoxicillin/clavulanic acid was prescribed in 29% of cases in which a lower line of therapy was more appropriate.

Table 18. Appropriateness of antibiotic prescriptions by age groups based on the physicians' diagnoses.

Age Group	**Appropriateness** No. (%)			
	Appropriate	**Not Indicated**	**Wrong Drug**	**Lower Line**
0-4 Years	56 (65.1)	22 (25.5)	3 (3.5)	5 (5.8)
5-14 Years	62 (63.3)	12 (12.2)	17 (17.3)	7 (7.1)
15-49 Years	159 (56.2)	25 (8.8)	71 (25.1)	28 (9.9)
≥50 Years	62 (56.4)	18 (16.3)	19 (17.3)	11 (10.0)
P-Value	0.349	<0.001	<0.001	0.885

*No guideline was available to assess 2 prescriptions in the 5-14 years group, 18 prescriptions in the 15-49 group, and 7 prescriptions in the ≥50 group.

The proportion of antibiotic prescriptions which were deemed appropriate did not differ by age groups of the patients (P= 0.349) (Table 18). However a greater proportion of prescriptions administered to children under the age of 5 years were considered to be not indicated (P<0.001) while less prescriptions in this same group were for the wrong drug, as compared to the remaining age groups (P<0.001). Proportions of antibiotic prescriptions in which a lower line of antibiotic was available were similar across age groups (P=0.885).

Those cases in which an antibiotic prescription was given to an adult and that the prescription was deemed "appropriate" or "lower line available" in the previous analysis were selected. One hundred and eighty five (185) prescriptions met these criteria. These prescriptions were then used to evaluate the appropriateness of the prescribed dose. In total, 155 prescriptions were written for an appropriate dose (84%) while 30 (16%) prescriptions were inappropriately dosed. Of the 30 prescriptions which were inappropriately dosed, 20 were the result of under-dosing and were primarily prescriptions for amoxicillin used for the treatment of respiratory tract infections.

4.1.7 Criterion-Based Decision Tree for Viral Versus Bacterial Etiology of Respiratory Tract Infections

Upon examining the presenting complaints, signs and symptoms for each adult patient diagnosed with a respiratory tract infection, cases of likely viral etiology were identified and compared with the decisions of the physicians to prescribe an antibiotic (Table 19). The physicians' determinations of micro-organism etiology were deemed bacterial if an antibiotic was prescribed and viral if no prescription was provided. Patients diagnosed as having otitis media were excluded from this analysis. Overall, the doctors deemed 44% of the patients to possess a viral respiratory tract infection, whereas the criterion-based decision tree deemed 88% of these same infections to be viral in nature. Although some semblance of agreement of etiology was found for the diagnosis of upper respiratory tract infection (83% vs. 100%), marked differences in determination of etiology were seen for the diagnoses of pharyngitis (17% vs. 84%), LRTI (18% vs. 87%) and sinusitis (10% vs. 63%).

Table 20 demonstrates the numbers of possible unnecessary prescriptions written within each antibiotic drug class for those cases in which the criterion-based decision tree deemed the infection likely to be viral in nature. In 274 cases of the 553 cases identified as being potentially viral in nature, an antibiotic prescription was given. Fifty seven percent (57%) of the potentially unnecessary prescriptions were written for those drugs classified as penicillins. Macrolides accounted for 24% of possible unnecessary prescriptions.

Table 19. The likelihood of viral etiology as determined by a decision tree.

Diagnosis	**Physicians' Decision** (not to prescribe an antibiotic)	**Criteria-Based Decision**	**Total**
	No. (%)	No. (%)	No.
URTI	144 (83.2)	173 (100.0)	173
Pharyngitis	16 (17.2)	78 (83.9)	93
LRTI	14 (18.4)	66 (86.8)	76
Sinusitis	7 (10.0)	44 (62.9)	70
Total	181 (43.9)	361 (87.6)	412

*URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection.

Table 20. Numbers of possible unnecessary antibiotic prescriptions for respiratory tract infections using the criteria based decisions for probable viral etiology (%).

Drug Class	Number of Prescriptions
Cephalosporins	15 (8.1)
Macrolides	50 (27.0)
Penicillins	103 (55.7)
Quinolones	5 (2.7)
Sulfonamides	8 (4.3)
Tetracyclines	4 (2.2)
Total	185 (100)

4.1.8 Factors Influencing Antibiotic Prescriptions

In over half (54%) of all cases in which an antibiotic prescription was written, the doctor felt the medical indication for the prescription was not very clear (Table 21). For the most part, a physician-perceived very clear medical indication for an antibiotic prescription occurred less for diagnoses associated with respiratory tract infections. Conversely, in 72% of cases in which a prescription was given for the diagnosis otitis media, the doctors felt the medical indication was very clear.

Table 21. Medical indication as a factor influencing the decision to prescribe an antibiotic.

	Uncertain	Somewhat Uncertain	Somewhat Clear	Clear	Very Clear	Total
URTI	1 (2.6)	12 (30.8)	10 (25.6)	14 (35.9)	2 (5.1)	39 (100)
Pharyngitis	1 (0.7)	4 (2.9)	18 (13.2)	58 (42.6)	55 (40.4)	136 (100)
Otitis Media	---	---	3 (3.1)	24 (24.5)	71 (72.4)	98 (100)
LRTI	---	3 (3.3)	21 (23.1)	34 (37.4)	33 (36.3)	91 (100)
Sinusitis	1 (1.4)	5 (7.0)	12 (16.9)	27 (38.0)	26 (36.6)	71 (100)
UTI	---	3 (5.7)	7 (13.2)	15 (28.3)	28 (52.8)	53 (100)
SSTI	1 (2.2)	1 (2.2)	6 (13.0)	9 (19.6)	29 (63.0)	46 (100)
Other	3 (4.8)	2 (3.2)	10 (16.1)	18 (29.0)	29 (46.8)	62 (100)
Total	7 (1.2)	30 (5.0)	87 (14.6)	199 (33.4)	273 (45.8)	596 (100)

In Table 22, diagnostic categories and factor results were combined. In this analysis, less prescriptions administered for respiratory tract infections were based on clear to very clear indication in the physicians' opinion as compared to all other infections. ($P<0.001$).

Table 22. Medical indication as a factor influencing the decision to prescribe an antibiotic in combined diagnostic categories and factor results (number (percent) of prescriptions).

	Clear to Very Clear	**Not Completely Clear**	***P*-Value**
Respiratory Tract Infections	249 (73.9)	88 (26.1)	**<0.001**
Other Infections	223 (86.1)	36 (13.9)	
Total	472 (79.2)	124 (20.8)	

Those prescriptions in which the doctor felt the medical indication was clear or very clear, and the guidelines assessed as either appropriate or not indicated were selected. A comparison was made between respiratory tract infections and all other infections (Table 23). Only 3.6% of these particular prescription events were considered not indicated by the guidelines in non-respiratory tract infections. However, for respiratory tract infections, 39% of the prescriptions were considered not indicated by the guidelines, even though the physicians felt the medical indication for an antibiotic was clear to very clear ($P<0.001$).

Table 23. Appropriateness of prescriptions in which the physicians felt the medical indication for the prescription was clear to very clear, by combined diagnostic categories and factor results (number (percent) of prescriptions).

	Appropriate	Not Indicated	*P*-Value
Respiratory Tract Infections	127 (60.8)	82 (39.2)	**<0.001**
Other Infections	159 (96.4)	6 (3.6)	
Total	286 (76.5)	88 (23.5)	

Table 24. Patient/parent expectation as a factor influencing the decision to prescribe an antibiotic by diagnostic categories (number (percent) of prescriptions).

	No Influence	Mostly No Influence	Some Influence	Somewhat Strong Influence	Strong Influence	Total
URTI	14 (35.9)	9 (23.1)	11 (28.2)	2 (5.1)	3 (7.7)	39 (100)
Pharyngitis	95 (69.9)	17 (12.5)	14 (10.3)	8 (5.9)	2 (1.5)	136 (100)
Otitis Media	77 (78.6)	9 (9.2)	6 (6.1)	6 (6.1)	---	98 (100)
LRTI	43 (47.3)	24 (26.4)	15 (16.5)	4 (4.4)	5 (5.5)	91 (100)
Sinusitis	32 (45.1)	16 (22.5)	12 (16.9)	10 (14.1)	1 (1.4)	71 (100)
UTI	36 (67.9)	9 (17.0)	7 (13.2)	1 (1.9)	---	53 (100)
SSTI	27 (58.7)	13 (28.2)	1 (2.2)	4 (8.7)	1 (2.2)	46 (100)
Other	37 (59.7)	8 (12.9)	7 (11.3)	7 (11.3)	3 (4.8)	62 (100)
Total	361 (60.6)	105 (17.6)	73 (12.2)	42 (7.0)	15 (2.5)	596 (100)

The perceived expectation of patients that they would receive an antibiotic prescription had some degree of influence on the physicians' decision making in 39% of the cases (Table 24). For cases in which an antibiotic prescription was written for the diagnosis of respiratory tract infection, patient expectation was more of an influence as compared to non-respiratory tract infections (P=0.007) (Table 25).

Table 25. Patient/parent expectation as a factor influencing the decision to prescribe an antibiotic in combined diagnostic categories and factor results (number (percent) of prescriptions).

	No/Mostly No Influence	Some Influence	*P*-Value
Respiratory Tract Infections	250 (74.2)	87 (25.8)	**0.007**
Other Infections	216 (83.4)	43 (16.6)	
Total	466 (78.2)	130 (21.8)	

Appropriateness of the prescriptions for which the doctor felt that patient or parent expectation for an antibiotic had some influence on the decision to prescribe was assessed (Table 26). A great proportion of patient influenced prescriptions for respiratory tract infections was found to be inappropriate as compared to patient influenced antibiotic prescriptions for all other infections ($P<0.001$).

Table 26. Appropriateness of prescriptions in which the physicians felt there was some influence by the patient/parent on the decision to prescribe, by combined diagnostic categories and factor results (number (percent) of prescriptions).

	Not Appropriate	Appropriate	*P*-Value
Respiratory Tract Infections	51 (58.6)	36 (41.4)	**<0.0001**
Other Infections	7 (21.2)	26 (78.8)	
Total	58 (48.3)	62 (51.7)	

Time constraint and the thought that the patient might seek an antibiotic prescription from another doctor if one was not given were considered to have had no influence in 90% of prescription decisions, regardless of diagnostic category (Table 27 and Table 28). In only 2 prescription events captured did time constraint completely dictate the prescription of an antibiotic.

Table 27. Time constraint as a factor influencing the decision to prescribe an antibiotic by diagnostic categories (number (percent) of prescriptions).

	No Influence	Mostly No Influence	Some Influence	Somewhat Strong Influence	Strong Influence	Total
URTI	36 (92.3)	2 (5.1)	—	—	1 (2.6)	39 (100)
Pharyngitis	123 (90.4)	10 (7.4)	2 (1.5)	1 (0.7)	—	136 (100)
Otitis Media	88 (89.8)	8 (8.2)	1 (1.0)	1 (1.0)	—	98 (100)
LRTI	77 (84.6)	10 (11.0)	2 (2.2)	2 (2.2)	—	91 (100)
Sinusitis	63 (88.7)	7 (9.9)	—	—	1 (1.4)	71 (100)
UTI	49 (92.5)	2 (3.8)	2 (3.8)	—	—	53 (100)
SSTI	43 (93.5)	3 (6.5)	—	—	—	46 (100)
Other	57 (91.9)	4 (6.5)	1 (1.6)	—	—	62 (100)
Total	536 (89.9)	46 (7.7)	8 (1.3)	4 (0.7)	2 (0.3)	596 (100)

Table 28. Patient attendance at another physician as a factor influencing the decision to prescribe an antibiotic by diagnostic categories (number (percent) of prescriptions).

	No Influence	Mostly No Influence	Some Influence	Somewhat Strong Influence	Strong Influence	Total
URTI	36 (92.3)	9 (6.6)	—	1 (0.7)		39 (100)
Pharyngitis	126 (92.6)	9 (6.6)	—	1 (0.7)	—	136 (100)
Otitis Media	88 (89.8)	6 (6.1)	3 (3.1)	1 (1.0)	—	98 (100)
LRTI	76 (83.5)	11 (12.1)	3 (3.3)	1 (1.1)	—	91 (100)
Sinusitis	61 (85.9)	6 (8.5)	3 (4.2)	1 (1.4)	—	71 (100)
UTI	51 (96.2)	2 (3.8)	—	—	—	53 (100)
SSTI	41 (89.1)	4 (8.7)	1 (2.2)	—	—	46 (100)
Other	58 (93.5)	3 (4.8)	—	1 (1.6)	—	62 (100)
Total	537 (90.1)	44 (7.4)	10 (1.7)	5 (0.8)	—	596 (100)

4.1.9 Patient Outcomes

Table 29. Proportion of patients who made return visits within one month after the captured visit, separated by receipt of antibiotic at captured visit.

	No AB Prescribed	AB Prescribed	*P*-Value
No Visits Made	155 (47.8)	249 (42.6)	0.125
Visits Made	169 (52.2)	336 (57.4)	

The proportion of patients who made a return visit to a doctor within 30 days of the captured visit was the same for those patients who had received an antibiotic prescription as compared to those who didn't (P=0.125) (Table 29). Similarly, among those patients who did make a return visit, there was no statistical difference in the proportions of patients making 1 visit, 2 visits, or 3 or more visits among those who received an antibiotic during the captured visit compared to those patients who did not receive an antibiotic (Figure 3).

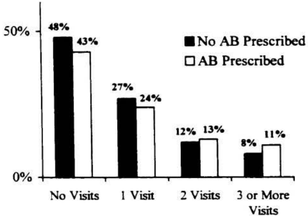

Figure 3. Proportion of patients who consulted a physician one month after the capture visit, separated by receipt of an antibiotic prescription during the captured visit.

4.1.10 Low Cost Versus High Cost Prescribing Physicians

Because average prescription costs were lower for patients who are 14 years or younger (Table 12), those prescriptions administered to patients 15 years or older were selected for analysis of low cost versus high cost prescribing physicians. Physicians assigned to the low cost prescribing group (n=13) had a mean retail prescription cost of $12.35 for all adult patients, while the average retail prescription cost for the high cost prescribing group (n=53) equalled $27.39 ($p$<0.0001). A comparison of patient characteristics of the two prescribing groups (Table 30) determined that the mean age of adult patients seen by the high cost prescribing group (~41 years) was slightly greater than that of the patients seen by the low cost prescribing group (~38 years), but this difference was not statistically significant. Significantly more patients seen by high cost prescribers were male (p=0.014) and had a drug plan (p=0.019). There were no statistically significant differences in presenting complaints or diagnoses in patients seen by the two prescribing groups (Tables 30 and 31).

Table 30. Comparison of patient characteristics seen by low and high cost prescribers.

Patient Characteristics	**Patients of Low Cost Prescribers** n=87	**Patients of High Cost Prescribers** n=543	***P*-value**
Mean Age (Years)	38.1	41.2	0.131
Proportion of Male Patients	21.8%	35.2%	**0.014**
Proportion With Drug Plan	43.9%	59.9%	**0.019**
Presenting Complaints			0.129
Upper Respiratory Illness	37 (45.1%)	175 (35.5%)	
Lower Respiratory Illness	17 (20.7%)	83 (16.8%)	
Ear Symptoms	3 (3.7%)	19 (3.9%)	
Flu Symptoms	10 (12.2%)	44 (8.9%)	
Urinary Symptoms	6 (7.3%)	50 (10.1%)	
GI Symptoms	—	7 (1.4%)	
Other	9 (11.0%)	115 (23.3%)	

Table 31. Comparison of diagnoses made by low and high cost prescribers.

Diagnoses	Patients of Low Cost Prescribers n=87	Patients of High Cost Prescribers n=543	*P*-value
			0.405
URTI	29 (33.3%)	138 (25.4%)	
Pharyngitis	14 (16.1%)	79 (14.5%)	
LRTI	12 (13.8%)	63 (11.6%)	
Sinusitis	8 (9.2%)	62 (11.4%)	
Otitis Media	5 (5.7%)	28 (5.2%)	
UTI	6 (6.9%)	54 (9.9%)	
SSTI	2 (2.3%)	47 (8.7%)	
Other	11 (12.6%)	72 (13.3%)	

In comparing the characteristics of the physicians (Table 32), it was found that physicians in both the low cost prescribing group and the high cost prescribing group were similar in terms of their age, gender, years of training, location of training, type of practice (group versus solo), numbers of patients seen both in total and for infections, and their antibiotic prescribing rate. However the low cost prescribing physicians prescribed antibiotics more appropriately (72% appropriate prescriptions versus 56%; p=0.007). However when the reasons for inappropriate prescriptions were analyzed, no differences were seen between the two groups of physicians with respect to specific categories of inappropriateness (i.e. medical indication, wrong drug, or lower line available).

Table 32. Comparison of physician and practice characteristics between low and high cost prescribers.

Physician Characteristics	**Low Cost Prescribers** n=13	**High Cost Prescribers** n=53	***P*-value**
Mean Age (Years)	43.3	45.9	0.336
Proportion of Male Physicians	42.9%	62.3%	0.190
Mean Years Since Med School Graduation	18.7	19.3	0.832
Proportion of Canadian Med School Graduates	85.7%	83.0%	0.809
Proportion in Group Practice	92.9%	92.5%	0.959
Mean Total Patients Seen in 2 Days	49.2	63.7	0.125
Mean # of Acute Infection Patients	11.4	14.6	0.243
Mean Prescribing Rate for Infections	60.4%	65.4%	0.419
Proportion of Appropriate Prescriptions	72.0% (59/82)	56.2% (276/491)	**0.007**

4.1.11 Least Appropriate Versus Most Appropriate Prescribing Physicians

Physicians assigned to the least appropriate prescribing group (n=17) had a mean rate of appropriate prescriptions of 32.2%, compared to a mean prescription appropriateness rate of 76.0% among the most appropriate prescribing physicians (n=53) (Table 33). Upon examination of certain patient characteristics, those patients seen by the least appropriate prescribers tended to be older (P=0.009) and a greater proportion were male (P=0.006). As well, more patients of the least appropriate prescribing group were covered by a drug plan (P<0.001). However the presenting complaints and the diagnoses made by the two groups of physicians were similar (Table 33 and Table 34).

Table 33. Comparison of patient characteristics seen by least and most appropriate prescribers.

Patient Characteristics	**Patients of Least Appropriate Prescribers** n=217	**Patients of Most Appropriate Prescribers** n=732	***P*-value**
Mean Age (Years)	33.0	29.0	**0.009**
Proportion of Male Patients	100 (46.1)	262 (35.8)	**0.006**
Proportion With Drug Plan	98 (62.8)	260 (59.0)	**<0.001**
Presenting Complaints			0.705
Upper Respiratory Illness	79 (40.3)	268 (39.5)	
Lower Respiratory Illness	31 (15.8)	137 (20.2)	
Ear Symptoms	9 (4.6)	39 (5.8)	
Flu Symptoms	20 (10.2)	51 (7.5)	
Urinary Symptoms	15 (7.7)	45 (6.6)	
GI Symptoms	3 (1.5)	13 (1.9)	
Other	39 (19.9)	125 (18.4)	

Table 34. Comparison of diagnoses made by least and most appropriate prescribers.

Diagnoses	**Patients of Least Appropriate Prescribers** n=217	**Patients of Most Appropriate Prescribers** n=732	***P*-value**
URTI	63 (29.0)	213 (29.1)	0.955
Pharyngitis	36 (16.6)	127 (17.3)	
LRTI	24 (11.1)	83 (11.3)	
Sinusitis	20 (9.2)	60 (8.2)	
Otitis Media	22 (10.1)	79 (10.8)	
UTI	18 (8.3)	50 (6.8)	
SSTI	9 (4.1)	44 (6.0)	
Other	25 (11.5)	76 (10.4)	

When physician characteristics were examined between the two physician groups, it was discovered that the least appropriate prescribers were, on average, older (P=0.006) and had been out of medical school longer (P=0.033) (Table 35). As well, a greater proportion of least appropriate prescribers were male (P=0.019) compared to their most appropriate prescribing counterparts. There were no differences between the two groups in terms of proportion who had attended medical school in Canada, were part of a group practice at the time the study took place, and average number of total patients seen in two days of regular practice.

Table 35. Comparison of physician and practice characteristics between least and most appropriate prescribers.

Physician Characteristics	**Least Appropriate Prescribers** n=17	**Most Appropriate Prescribers** n=53	***P*-value**
Mean Age (Years)	50.0	43.6	**0.006**
Proportion of Male Physicians	14 (82.4%)	26 (50.0%)	**0.019**
Mean Years Since Med School Graduation	22.8	17.7	**0.033**
Proportion of Canadian Med School Graduates	14 (82.4%)	44 (84.6%)	0.825
Proportion in Group Practice	15 (88.2%)	48 (92.3%)	0.605
Mean Total Patients Seen in 2 Days	56.4	61.7	0.542
Mean # of Acute Infection Patients	12.8	14.1	0.603
Mean Prescribing Rate for Infections	72.6%	60.2%	**0.033**
Mean Rate of Appropriate Prescriptions	32.2%	76.0%	**<0.001**

4.2 Community Oral Antibiotic Use in the Province of Newfoundland - NLPDP

Data from the Newfoundland and Labrador Prescription Drug Program (NLPDP) indicate that, since the 1994/1995 fiscal year, the number of antibiotic prescriptions have declined by approximately 24%; 169,110 antibiotic prescriptions were dispensed under the auspices of the program in 1994/1995 compared to 129,337 in 1999/2000 (Table 36). Figure 4 demonstrates that the drop in number of antibiotic prescriptions does not directly correlate with decreases in the number of claimants eligible for the program. Although

Table 36. Number of prescriptions (percent) covered by the provincial drug plan separated by antibiotic category and fiscal year.

Antibiotic Category	94/95	95/96	96/97	97/98	98/99	99/00
Cephalosporins	22,658	24,477	23,991	22,278	20,548	20,279
	(13.4)	(14.2)	(15.4)	(15.2)	(15.2)	(15.7)
Macrolides	19,816	20,108	18,424	16,880	17,046	18,150
	(11.7)	(11.7)	(11.8)	(11.6)	(12.6)	(14.0)
Penicillins	100,095	100,454	88,046	80,730	70,846	63,796
	(59.2)	(58.3)	(56.3)	(55.3)	(52.6)	(49.3)
Quinolones	17,434	18,752	18,458	18,852	19,513	20,578
	(10.3)	(10.9)	(11.8)	(12.9)	(14.5)	(15.9)
Sulfonamides	443	369	230	227	194	153
	(0.3)	(0.2)	(0.1)	(0.2)	(0.1)	(0.1)
Tetracyclines	7,926	7,295	6,401	6,350	5,807	5,397
	(4.7)	(4.2)	(4.1)	(4.3)	(4.3)	(4.2)
Other	738	734	727	787	853	984
	(0.4)	(0.4)	(0.5)	(0.5)	(0.6)	(0.8)
Total	169,110	172,189	156,277	146,104	134,807	129,337
	(100)	(100)	(100)	(100)	(100)	(100)

the number of low income families did decrease between 97/98 and 98/99 (by approximately 2500), dispensed antibiotic prescriptions began to substantially decrease between 95/96 and 96/97. Overall there were 787 fewer seniors covered by the program in 98/99 as compared to 94/95. Therefore, within the time frame of data collection, overall enrollment of low income seniors in the NLPDP decreased by 2%, enrollment of low income families decreased by 9% and total numbers of prescriptions decreased by 24%.

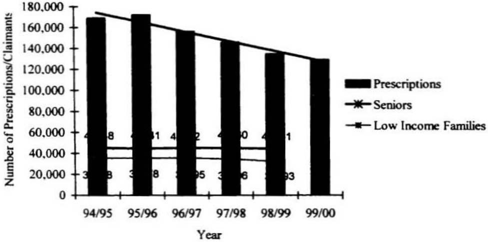

Figure 4. Number of claimants (seniors and low income families) and total prescriptions covered by NLPDP (claimant data for 99/00 was unavailable).

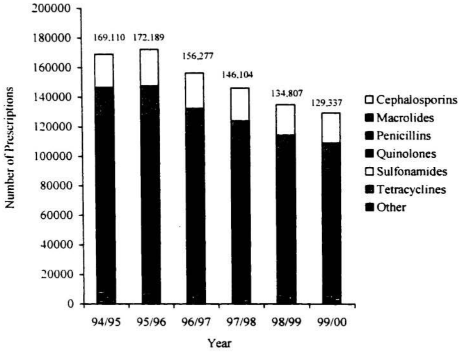

Figure 5. Graphical representation of the proportions of total antibiotic prescriptions in Newfoundland comprised by each antibiotic category for the years 94/95 to 99/00.

In 94/95 the penicillin group of antibiotics comprised 59.2% of total prescriptions. This proportion decreased to 49.3% in 99/00, representing a decrease of almost 10%. However the contribution to total prescriptions that cephalosporins and macrolides made both increased by 2.3%. Quinolones comprised 10.3% of overall antibiotic prescriptions in 94/95. This proportion increased to 15.9% in 99/00. Therefore the greatest proportional changes occurred for penicillins (-9.9%) and quinolones (+5.6%)

The most commonly dispensed antibiotic in the NLPDP was amoxicillin, accounting for 37.9% of total prescriptions in 94/95 and falling to 31.8% of prescriptions in 99/00. Among the penicillin group of antibiotics, the greatest reduction in numbers of dispensed prescriptions occurred for ampicillin, falling from 10.3% of all antibiotics dispensed in 94/95 to 4.0% in 99/00. Among the macrolides, the greatest number of prescriptions were for erythromycin (11.6% in 94/95 and 9.5% in 99/00). Cephalexin was the most commonly prescribed cephalosporin (6.3% in 94/95 and 7.4% in 99/00). Among the quinolone group, ciprofloxacin accounted for the greatest number of prescriptions (6.2% of total prescriptions in 94/95 and 11.2% in 99/00). Therefore ciprofloxacin represented the greatest proportional increase in prescriptions (+5%), while ampicillin accounted for the greatest proportional decrease (-6.3%).

4.3 Community Oral Antibiotic Use in Canada and USA – IMS Market Databases

Evaluation of oral antibiotic prescribing databases derived from Canada revealed that the numbers of dispensed antibiotics gradually increased between 1992 and 1995, and then declined to pre-1993 levels in 1996 (Table 37). Between 1995 and 1996, the number of dispensed antibiotics in Canada decreased by 4% in the absence of a concomitant decrease in the Canadian population (Figure 6). Overall number of antibiotic prescriptions fluctuated between 1992 and 1996 in the USA (Table 37).

In 1992, penicillins accounted for the greatest proportion of prescriptions in both Canada and the USA (Figure 7 and Figure 8). In 1996, this was still the case, but the proportion of penicillin prescriptions decreased by approximately 4% in both Canada and the USA. This was the greatest proportional decrease of all drug classes between 1992 and 1996. Conversely the greatest proportional increase in this same time period occurred with the macrolides, increasing by 3% in Canada and almost 5% in the USA (Table 37). For the remaining drug classes, the proportions among total prescriptions remained relatively constant.

Table 37. Estimated number of prescriptions (percent) dispensed in Canada and the USA

Antibiotic Category	1992	1993	1994	1995	1996
Cephalosporins					
Canada	2,674,949 (11.8)	3,242,477 (12.8)	3,241,440 (12.7)	3,362,834 (12.9)	3,301,757 (13.2)
USA	52,922,000 (20.2)	60,489,000 (21.2)	58,148,000 (21.2)	60,940,000 (21.4)	56,463,000 (20.7)
Macrolides					
Canada	3,038,702 (13.4)	3,572,139 (14.1)	3,765,399 (14.7)	4,158,899 (16.0)	4,142,327 (16.6)
USA	30,786,000 (11.8)	34,791,000 (12.2)	34,562,000 (12.6)	40,857,000 (14.3)	44,410,000 (16.3)
Penicillins					
Canada	10,448,417 (46.1)	11,618,207 (45.9)	11,535,020 (45.2)	11,419,606 (43.9)	10,559,343 (42.3)
USA	109,491,000 (41.9)	119,925,000 (42.0)	111,376,000 (40.7)	112,431,000 (39.4)	101,789,000 (37.3)
Quinolones					
Canada	1,203,975 (5.3)	1,376,645 (5.4)	1,509,160 (5.9)	1,569,859 (6.0)	1,658,520 (6.6)
USA	13,467,000 (5.2)	14,058,000 (4.9)	14,148,000 (5.2)	14,569,000 (5.1)	14,779,000 (5.4)
Sulfonamides					
Canada	2,594,576 (11.5)	2,824,004 (11.1)	2,767,885 (10.8)	2,795,932 (10.7)	2,585,074 (10.4)
USA	23,272,000 (8.9)	24,560,000 (8.6)	24,100,000 (8.8)	24,861,000 (8.7)	23,658,000 (8.7)
Tetracyclines					
Canada	1,978,868 (8.7)	1,935,348 (7.6)	1,865,751 (7.3)	1,792,811 (6.9)	1,607,447 (6.4)
USA	20,912,000 (8.0)	21,024,000 (7.4)	20,221,000 (7.4)	19,804,000 (6.9)	18,746,000 (6.9)
Other					
Canada	716,253 (3.2)	769,928 (3.0)	855,281 (3.3)	940,001 (3.6)	1,087,780 (4.4)
USA	10,626,000 (4.1)	10,894,000 (3.8)	11,391,000 (4.2)	11,893,000 (4.2)	12,872,000 (4.7)
Total					
Canada	22,655,740 (100)	25,338,748 (100)	25,539,936 (100)	26,039,942 (100)	24,942,248 (100)
USA	261,476,000 (100)	285,741,000 (100)	273,946,000 (100)	285,355,000 (100)	272,717,000 (100)

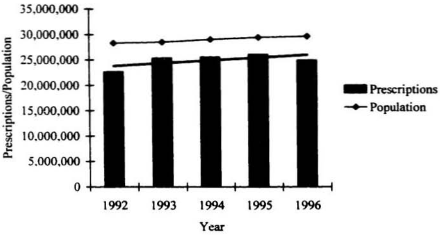

Figure 6. Population of Canada and estimated total dispensed prescriptions from 1992 to 1996.

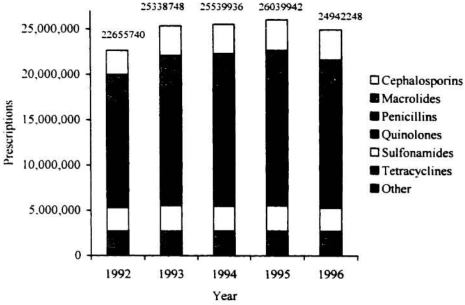

Figure 7. Graphical representation of the proportions of total antibiotic prescriptions in Canada comprised by each antibiotic category for the years 1992-1996.

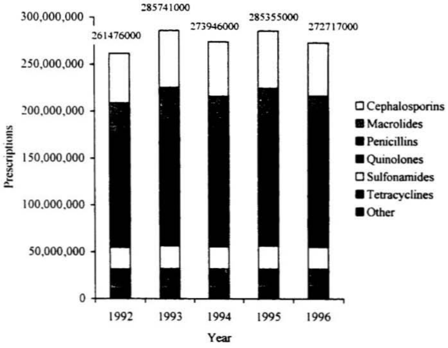

Figure 8. Graphical representation of the proportions of total antibiotic prescriptions in the USA comprised by each antibiotic category for the years 1992-1996.

Table 38. Estimated annual rates of antibiotic prescriptions per 1000 per year by drug class in 1996 for Canada and the USA.

	Estimated Annual Rate Per 1000 Canada	Estimated Annual Rate Per 1000 USA
Cephalosporins	**111**	**213**
Cefaclor	44	28
Cephalexin	40	98
Macrolides	**140**	**167**
Erythromycin	89	68
Clarithromycin	42	54
Penicillins	**356**	**384**
Amoxicillin	229	263
Penicillin V	59	59
Quinolones	**56**	**56**
Ciprofloxacin	37	41
Norfloxacin	16	3
Ofloxacin	3	11
Sulfonamides	**87**	**89**
TMP/SMX	86	87
Tetracyclines	**54**	**71**
Tetracycline	24	22
Doxycycline	17	36
Other	**37**	**49**
Metronidazole	17	19
Nitrofurantoin	11	20
Clindamycin	6	6
TOTAL	**842**	**1028**

In 1996, the most commonly dispensed antibiotic in both Canada and the USA was amoxicillin, accounting for 27% and 26% of total prescriptions respectively. The estimated annual rate of amoxicillin prescriptions per 1000 persons per year was 229 in Canada and 263 in the USA (Table 38). In the USA, the second and third most commonly dispensed oral antibiotics were cephalexin and erythromycin. However, in Canada, the second most commonly dispensed antibiotic was erythromycin followed by Penicillin V. Overall 1028 oral antibiotics were dispensed per 1000 persons per year in the USA, while 842 prescriptions per 1000 persons per year were dispensed in Canada (Table 38).

Figure 9 and Table 39 demonstrate a comparison of the proportion of oral antibiotic prescriptions dispensed in the community, by each antibiotic drug class, for each of the three previously discussed sources of prescribing information (i.e. oral antibiotic use in the community of St. John's and databases from NLPDP (97/98) and IMS (1996)). For all four areas of study, penicillins account for the greatest proportion of total prescriptions, ranging from 55% (NLPDP) to 37% (USA). The least amount of cephalosporins were used by the St. John's GPs (9%), while this same drug class accounts for 21% of prescriptions in the USA. For the most part, proportions of each antibiotic drug class of total prescriptions are relatively similar between St. John's GP prescribing and the rest of Canada.

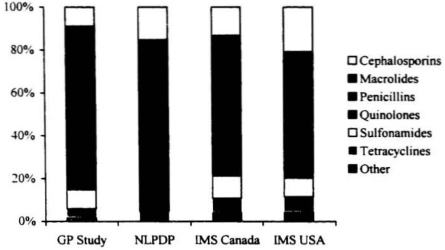

Figure 9. Graphical representation of the proportions of each antibiotic drug class of total prescriptions, comparing oral antibiotic prescribing in the community of St. John's (GP Study), and as determined by NLPDP (97/98) and IMS antibiotic prescribing databases (1996).

Table 39. Proportions of each antibiotic drug class of total prescriptions, comparing oral antibiotic prescribing in the community of St. John's (GP Study), and as determined by NLPDP and IMS antibiotic prescribing databases.

	GP Study	NLPDP	IMS Canada	IMS USA
Cephalosporins	8.8%	15.2%	13.2%	20.7%
Macrolides	19.9%	11.6%	16.6%	16.3%
Penicillins	50.0%	55.3%	42.3%	37.3%
Quinolones	6.6%	12.9%	6.6%	5.4%
Sulfonamides	8.8%	0.2%	10.4%	8.7%
Tetracyclines	4.0%	4.3%	6.4%	6.9%
Other	2.0%	0.5%	4.4%	4.7%

4.4 Antibiotic Use in Acute Care for the Treatment of Community-Acquired Pneumonia

4.4.1 Characteristics of the Study Population

In the two study time periods, a total of 569 patients were eligible for this study. Of these patients, 226 (40%) were admitted during the 95/96 fiscal year and 343 (60%) were admitted during the 98/99 fiscal year. Assessment of several demographic and clinical variables determined that there were no differences between the patients admitted in 95/96 and 98/99 (Table 40). Therefore all 569 patients were combined for analysis. Overall approximately 43% of patients were treated at the Health Sciences Centre (HSC), 42% were treated at St. Clare's Mercy Hospital (SCMH) and the remaining 16% were admitted at the Salvation Army Grace General Hospital (SAGGH). Overall the mean age (± SD) of the patients was 67 ± 18 years. No difference in age was noted across time periods of study. Approximately 59% of total patients were male. The majority of patients lived in private residences, as opposed to nursing homes, prior to admission to hospital. Most patients were admitted to hospital following presentation to the emergency department with CAP symptoms, regardless of study period. Patients admitted in 95/96 spent, on average, 1day longer in hospital compared to patients admitted in 98/99.

Table 40. Characteristics of patients admitted with community-acquired pneumonia (number (percent) of patients unless indicated).

Characteristic	1995/1996	1998/1999	Total	*P Value*
Age (Years) Mean ± SD	66.6 ± 17.8	67.2 ± 17.8	67.0 ± 17.8	0.696
Gender (Male)	131 (58.0)	203 (59.2)	334 (58.7)	0.773
Nursing Home Resident	20 (9.2)*	42 (12.2)	62 (11.1)	0.266
Referral from ER	203 (94.0)**	313 (91.3)	516 (92.3)	0.171
Hospital Site				0.628
HSC	96 (42.5)	146 (42.6)	242 (42.5)	
SCMH	90 (39.8)	146 (42.6)	236 (41.5)	
SAGGH	40 (17.7)	51 (14.9)	91 (16.0)	
Total	226 (100)	343 (100)	569 (100)	
Length of Stay Median ± IR	8.0 (5.0-11.0)	7.0 (5.0-11.0)	8.0 (5.0-11.0)	
Severity of Illness				0.177
Risk Class I	28 (12.4)	32 (9.3)	60 (10.5)	
Risk Class II	47 (20.8)	68 (19.8)	115 (20.2)	
Risk Class III	47 (20.8)	64 (18.7)	111 (19.5)	
Risk Class IV	80 (35.4)	118 (34.4)	198 (34.8)	
Risk Class V	24 (10.6)	61 (17.8)	85 (14.9)	

*data not available for 9 patients in 1995/1996; **data not available for 10 patients in 1995/1996.

Table 41. Age and gender of patients in the study population admitted to hospital with community-acquired pneumonia.

Age Category	Patients Admitted with Community-Acquired Pneumonia No. (% of 569)		
	Total	**Male**	**Female**
≤ 25 Years	19 (3.3)	10 (1.8)	9 (1.6)
26-50 Years	93 (16.3)	58 (10.2)	35 (6.2)
51-75 Years	218 (38.3)	121 (21.3)	97 (17.0)
≥ 76 Years	239 (42.0)	145 (25.5)	94 (16.5)
Total	569 (100)	334 (58.7)	235 (41.3)

Table 41 illustrates the age distribution and gender of all patients admitted with CAP. For those patients under the age of 25 years, there were equal numbers of males and females. However, after the age of 25 more males than females were treated for CAP in hospital, although these differences were not statistically significant.

4.4.2 Comorbid Conditions

The numbers and percent of patients presenting with various comorbid conditions are presented in Table 42. The most common comorbid condition that was manifested in the sample of patients was coronary artery disease (37% of patients). Thirty one percent (31%) of patients had chronic obstructive pulmonary disease, 30% were smokers and 17% of patients had asthma. The mean number of comorbid conditions documented in all study patients was approximately 2.

Table 42. Comorbid conditions of patients admitted with community-acquired pneumonia (number (percent) of patients unless indicated).

Comorbid Condition	Total
Alcoholism	37 (6.7)
Asthma	92 (17.0)
Cerebrovascular Disease	50 (9.3)
COPD*	169 (31.2)
Chronic Renal Failure	50 (9.4)
Congestive Heart Failure	125 (23.2)
Coronary Artery Disease	201 (37.0)
Diabetes Mellitus	114 (21.1)
Interstitial Lung Disease	58 (10.9)
Liver Disease	9 (1.7)
Neoplastic Disease	107 (20.0)
Neurological Condition	34 (6.3)
Oral Steroids	105 (19.7)
Smoking	164 (30.0)
Mean # Comorbid Conditions	2.3

*COPD = Chronic Obstructive Pulmonary Disease. Percentages are calculated from numbers of patients in which the information was known/available.

4.4.3 Presenting Complaints

The number and percent of patients presenting with various complaints associated with CAP upon admission are presented in Table 43. The majority of patients manifested some type of respiratory complaint upon admission. Approximately 7% of patients admitted with CAP had none of the recorded respiratory complaints.

Table 43. Presenting complaints of patients admitted with community-acquired pneumonia (number (percent) of patients).

Presenting Complaint	Total
Cough	432 (77.6)
Dyspnea	370 (67.9)
Sputum Production	314 (56.9)
Pleuritic Chest Pain	161 (30.6)

4.4.4 Physical Examination and Laboratory Findings

Results of the physical examination findings in CAP patients are presented in Table 44. For the vast majority of patients, recorded temperatures were within normal range, as was pulse rates and systolic blood pressure. However approximately 23% of admitted patients had greater than or equal to 30 breaths per minute.

Table 45 illustrates the laboratory and radiographic findings in the admitted patients. Sixty five percent (65%) of patients had an x-ray result which indicated that infiltrate was found in only one lobe of their lungs, while 28% of patients had infiltrate

Table 44. Physical examination findings of patients admitted with community-acquired pneumonia (number (percent) of patients unless indicated).

Physical Examination Findings	Total
Temperature	
Mean ± SD	37.6 ± 1.1
<35 or ≥40 degrees	10 (1.8)
Respiratory Rate	
Mean ± SD	25.3 ± 6.0
≥30 breaths/min	125 (22.5)
Pulse	
Mean ± SD	95.0 ± 18.6
≥125 beats/min	35 (6.3)
Systolic Blood Pressure	
Mean ± SD	128.6 ± 25.0
<90 mm Hg	15 (2.7)
Altered Mental Status	126 (22.9)

Table 45. Laboratory and radiographic findings in patients admitted with community-acquired pneumonia (number (percent) of patients unless indicated).

Laboratory/Radiographic Findings	Total
Blood Urea Nitrogen	
Mean ± SD	8.7 ± 7.6
(≥11 mmol/L)	106 (19.0)
Hematocrit	
Mean ± SD	0.49 ± 2.76
< 30%	53 (9.6)
Po2*	
Mean ± SD	73.6 ± 35.7
<60 mm Hg	112 (31.1)
Chest Radiograph	
(1 lobe infiltrate)	358 (65.0)
Chest Radiograph	
(>1 lobe infiltrate)	156 (28.3)

*Partial pressure of arterial oxygen

in both lungs. Therefore no infiltrate was found on x-ray for 7% of patients admitted with CAP.

Results from sputum and blood culture reports are presented in Tables 46 and 47. Approximately 60% of admitted patients had a blood culture done and 45% had sputum samples taken. In cases in which a sputum culture was taken, approximately 35% of cultures were positive for some type of growth, while only 10% of blood cultures depicted growth. *Streptococcus pneumoniae* was most commonly identified for both sources of samples. Of those sputum samples that were positive for growth, 27% harboured *Streptococcus pneumonia*. Twenty-two percent (22%) of positive sputum samples grew *Haemophilus influenzae*. Among the positive blood cultures, approximately half were positive for *Streptococcus pneumonia*.

Table 46. Identified pathogens on sputum cultures in patients admitted with community-acquired pneumonia (number (percent) of patients).

	Total
Positive Sputum Culture	83 (34.6)
Identified Pathogen	
Streptococcus pneumonia	22 (26.5)
Candida albicans	14 (16.9)
Haemophilus influenzae	18 (21.7)
Staphylococcus aureus	3 (3.6)
Gram-negative bacilli	6 (7.2)
*Miscellaneous Pathogens**	20 (24.1)

*Includes light growth coliforum, Morexalla catarrhalis, Pseudomonas aerugenosa, Serratia marcessens, Acinetobacter anitratus, Group A haemolytic Streptococci, gram-negative cocci, Enterobacter cloacae, coagulase negative Staphlococci and others

Table 47. Identified pathogens on blood culture in patients admitted with community-acquired pneumonia (number (percent) of patients).

	Total
Positive Blood Culture	31 (9.5)
Identified Pathogen	
Streptococcus pneumonia	16 (51.6)
Gram-positive cocci	4 (12.9)
Coagulase-negative staphloccoci	4 (12.9)
Staphylococcus aureus	3 (9.7)
*Miscellaneous Pathogens**	4 (12.9)

*Includes E coli, non-haemolytic Streptococci and Klebsiella pneumoniae

4.4.5 Pneumonia Severity Index (PSI) Scores

The mean Pneumonia Severity Index (PSI) score for all patients was 88. The number and percent of patients in each risk class group are presented in Table 48. Approximately 31% of all patients admitted with CAP were at low risk for death within 30 days due to CAP, as determined by their assignment to risk classes I and II (Table 48). Half of admitted patients were at higher risk for death; 35% of patients were assigned to risk class IV and 15% of patients were assigned to risk class V.

Table 48. Pneumonia Severity Index (PSI)* of patients admitted with community-acquired pneumonia (number (percent) of patients unless indicated).

	Total
Mean PSI Score ± SD	87.9 ± 43.0
Risk Class I	60 (10.5)
Risk Class II	115 (20.2)
Risk Class III	111 (19.5)
Risk Class IV	198 (34.8)
Risk Class V	85 (14.9)

*PSI classes I and II = score ≤ 70; PSI class III = score between 70-90; PSI class IV = score between 91-130; PSI class V = score >130. Patients in classes IV and V are at considerable risk for death.

4.4.6 Length of Stay

The overall unadjusted median length of stay for all patients was 8 days (Table 49). The median length of hospital stay for patients in risk class I was 5 days while the median length of stay was 7 days for patients in risk classes II and III. Patients in risk classes IV and V both had a median length of stay of 9 days.

Table 49. Median (and interquartile range) length of stay (days) of patients admitted with community-acquired pneumonia (unadjusted and stratified by pneumonia risk class).

		Total
Unadjusted	Median	8.0 (5.0-11.0)
Risk Class I	Median	5.0 (4.0-7.0)
Risk Class II	Median	7.0 (5.0-10.0)
Risk Class III	Median	7.0 (5.0-11.0)
Risk Class IV	Median	9.0 (6.0-13.0)
Risk Class V	Median	9.0 (6.5-15.0)

*PSI classes I and II = score ≤ 70; PSI class III = score between 70-90; PSI class IV = score between 91-130; PSI class V = score >130. Patients in classes IV and V are at considerable risk for death.

4.4.7 Types of Antibiotics Used

Upon admission to hospital, the majority of patients initially received intravenous (IV) antibiotics only (n=384; 67.5%). Of the remaining patients, 19% received a combination of IV and oral antibiotics, while 13% received oral antibiotics only. Interestingly 6 patients (1%) received no antibiotics upon admission or during their hospital stay.

Of those 384 patients who received IV antibiotics only as their initial empiric treatment, 297 (77%) received single agent therapy and 87 (23%) received two IV antibiotics. The antibiotic treatments used in those patients initially treated with IV antibiotics only (either as monotherapy or in combination) are displayed in Table 50.

The most common treatment regime for patients receiving IV therapy only was treatment with a non-pseudomonal third generation cephalosporin only, accounting for 35% of treatments. The next most common treatment options for IV therapy only were a second generation cephalosporin only (29%) and a non-pseudomonal third generation cephalosporin plus a macrolide (8%).

Table 50. Initial empiric antibiotic treatments for patients admitted with community-acquired pneumonia and treated with IV antibiotics only (n=384).

Initial Antibiotic Treatments	**Total N (%)**
Non-Pseudomonal 3rd Gen. Cephalosporin Only	136 (35.4)
2nd Gen. Cephalosporin Only	112 (29.2)
Non-Pseudomonal 3rd Gen. Cephalosporin + Macrolide	29 (7.6)
2nd Gen Cephalosporin + Macrolide	27 (7.0)
Macrolide Only	21 (5.5)
Non-Pseudomonal 3rd Gen. Cephalosporin + Other	16 (4.2)
Quinolone Only / with Other	11 (2.9)
Penicillins Only	8 (2.1)
Pseudomonal 3rd Gen Cephalosporin Only	6 (1.6)
2nd Gen. Cephalosporin + Other	5 (1.3)
Pseudomonal 3rd Gen Cephalosporin + Other	2 (0.5)
Pseudomonal 3rd Gen Cephalosporin + Macrolide	1 (0.3)
All Other Treatment Combinations	10 (2.6)

One hundred and seven (107) patients (19%) were initially treated with a combination of IV and oral antibiotic therapy. Table 51 displays the number of prescriptions written for each treatment regime for those patients concomitantly treated with initial oral and IV antibiotics. Almost half of the treatments (49%) were for a second generation cephalosporin plus a macrolide. A non-pseudomonal third generation cephalosporin plus a macrolide accounted for 37% of treatments.

Table 51. Initial empiric antibiotic treatments for patients admitted with community-acquired pneumonia and treated with both IV and oral antibiotics (n=107).

Initial Antibiotic Treatments	Total N (%)
2nd Gen. Cephalosporin + Macrolide	52 (48.6)
Non-Pseudomonal 3rd Gen. Cephalosporin + Macrolide	40 (37.4)
2nd Gen. Cephalosporin + Other	4 (3.7)
Non-Pseudomonal 3rd Gen. Cephalosporin + Other	4 (3.7)
Quinolone Only / with Other	4 (3.7)
Pseudomonal 3rd Gen. Cephalosporin + Macrolide	1 (0.9)
Pseudomonal 3rd Gen. Cephalosporin + Other	1 (0.9)
All Other Treatment Combinations	1 (0.9)

Table 52. Initial empiric antibiotic treatments for patients admitted with community-acquired pneumonia and treated with oral antibiotics only (n=72).

Initial Antibiotic Treatments	Total N (%)
Macrolide Only	26 (36.1)
Quinolone Only / with Other	17 (23.6)
2nd Gen. Cephalosporin Only	13 (18.1)
2nd Gen. Cephalosporin + Macrolide	8 (11.1)
Non-Pseudomonal 3rd Gen. Cephalosporin Only	2 (2.8)
Penicillins Only	2 (2.8)
2nd Gen. Cephalosporin + Other	1 (1.4)
All Other Treatment Combinations	3 (4.2)

Table 52 presents the types of antibiotic treatments administered to patients initially treated with oral antibiotics only upon admission to hospital. Thirty six percent (36%) of patients received a macrolide only. A further 24% received either a quinolone only or a quinolone in combination with some other antibiotic. Eighteen percent (18%) of patients received single therapy with a second generation cephalosporin.

Table 53. Antibiotic choice for patients previously receiving intravenous therapy only and switched to oral therapy (number (percent) of prescriptions (n=320)).

Antibiotic Class		Total
Cephalosporins		**183 (57.1)**
	Cefuroxime	177 (55.3)
Macrolides		**77 (24.1)**
	Erythromycin	41 (12.8)
	Clarithromycin	35 (10.9)
Penicillins		**17 (5.3)**
	Penicillin V	11 (3.4)
Quinolones		**30 (9.4)**
	Ciprofloxacin	30 (9.4)
Sulfonamides		**1 (0.3)**
	TMP/SMX	1 (0.3)
Other*		**12 (3.8)**
	Clindamycin	10 (3.1)

* Other includes clindamycin and metronidazole.

Of those patients who initially received only IV antibiotic therapy and were subsequently switched to oral therapy, 254 patients (89%) were administered one oral antibiotic, while 33 patients (11%) were treated with two oral antibiotics. Table 53 demonstrates that, in patients switched from IV only antibiotics to oral antibiotics, approximately half of the oral antibiotics chosen were from the cephalosporin drug class (57%). Almost all of these prescriptions were for cefuroxime. When a macrolide was used, similar numbers of prescriptions for erythromycin and clarithromycin were administered.

The mean number of antibiotics used to treat each patient for their entire hospital stay was 1.8.

4.4.8 Agreement of Antibiotic Choice with Recommended Guidelines

4.4.8.1 Appropriateness of Initial Empiric Antibiotic Therapy

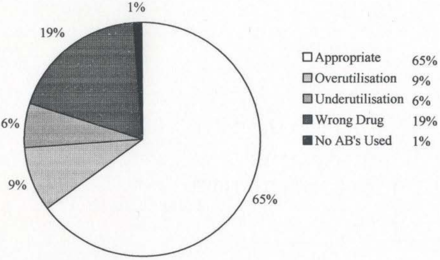

Figure 10. Overall appropriateness of initial empiric antibiotic therapy (IV and oral) in patients admitted to hospital with community-acquired pneumonia.

An assessment of the agreement of initial empiric antibiotic choice (IV and oral) with recommended Canadian treatment guidelines in patients admitted with CAP revealed that 65% of initial antibiotic treatment courses were in exact accordance with the guidelines (Figure 10). In 19% of patients the antibiotic treatment regimen was incorrect in that the wrong drug was prescribed. Overutilisation (combination therapy in which one of the antibiotics was appropriate) was documented in 9% of patients, while underutilisation was discovered in 6% of patients. Interestingly no antibiotics were prescribed for 6 patients (1%).

In order to provide a more detailed investigation of antibiotic choice, assessment of guideline agreement was evaluated by severity of disease, as indicated by PSI risk classes. This analysis revealed that guideline agreement was very low in patients in the lower risk classes (Tables 54 and 55). Only 22% of patients assigned to risk class I received an initial empiric antibiotic course which was in complete agreement with the prescribing guidelines. Thirty three percent (33%) of risk class I patients received combination therapy in which an extra antibiotic was prescribed, thus resulting in overutilisation of antimicrobial therapy. However, by combining these two assessment categories, 55% of patients in risk class I received at least one initial antibiotic (IV or oral) which was in accordance with recommended guidelines. In the remaining patients for which their initial course of antibiotic treatment was in disagreement with prescribing guidelines, 43% of patients received treatment with the wrong drug, while one patient did not receive any antibiotic treatment while in hospital.

For cases in which overutilisation was discovered, the vast majority of prescribed extra antibiotic was for a cephalosporin, primarily cefuroxime, used in combination with a macrolide. For the patients in which the wrong drug was prescribed, prescriptions were mostly for cefuroxime as single therapy or a non-pseudomonal third generation cephalosporin as monotherapy.

Table 54. Guideline agreement of initial empiric antibiotic choice (IV or oral) for patients assigned to risk class I (n=60).

Guideline Agreement	Total No. (%; 95% CI)
In Agreement	13 (21.7; 13.1-33.6)
Overutilisation	20 (33.3; 22.7-45.9)
Overall Agreement	33 (55.0; 42.5-66.9)
Wrong Drug	26 (43.3; 31.6-55.9)
No Antibiotics Used	1 (1.7; 0.3-8.9)

Table 55. Guideline agreement of initial empiric antibiotic choice (IV or oral) for patients assigned to risk class II (n=115).

Guideline Agreement	Total No. (%; 95% CI)
In Agreement	40 (34.8; 26.7-43.9)
Overutilisation	6 (5.2; 2.4-10.9)
Overall Agreement	46 (40.0; 31.5-49.1)
Underutilisation	15 (13.0; 8.1-20.4)
Wrong Drug	52 (45.2; 36.4-54.3)
No AB's Used	2 (1.7; 0.5-6.1)

For patients assigned to PSI risk class II, a similar trend in disagreement with prescribing guidelines was seen (Table 55). Only 35% of patients in risk class II received initial antibiotic treatment that was in complete agreement with prescribing guidelines. Five percent (5%) of patients received extra antibiotic (clindamycin). The wrong drug was prescribed in 45% of cases (ceftriaxone, a third generation cephalosporin), while underutilisation and lack of antibiotic therapy were found in 13% and 2% of patients respectively. In those cases in which underutilisation was identified, patients received therapy with a macrolide only.

Table 56. Guideline agreement of initial empiric antibiotic choice (IV or oral) for patients assigned to risk classes III, IV and V (n=394).

Guideline Agreement	Total No. (%; 95% CI)
In Agreement	318 (80.7; 76.5-84.3)
Overutilisation	25 (6.3; 4.3-9.2)
Overall Agreement	343 (87.1; 83.3-90.0)
Underutilisation	19 (4.8; 3.1-7.4)
Wrong Drug	29 (7.4; 5.2-10.4)
No AB's Ordered	3 (0.8; 0.3-2.2)

As prescribing guidelines are the same for patients in the remaining risk classes, patients in risk classes III, IV and V were combined for analysis. Guideline agreement of initial empiric antibiotic choice for patients in risk classes III, IV and V was substantially better than patients in the lower risk groups (Table 56). Eighty one percent (81%) of patients were treated with antibiotics in a manner which was in complete agreement with prescribing guidelines recommendations. When overutilisation of antibiotics occurred (6% of patients), the vast majority of extra antibiotic used was either ciprofloxacin or clindamycin. Seven percent (7%) of patients were prescribed the wrong drug (ciprofloxacin) and, in 5% of patients, only a macrolide was used, whereas the guidelines state that macrolides should be in combination with either a cephalosporin or TMP/SMX.

4.4.8.2 Appropriateness of Secondary Oral Antibiotic Choice

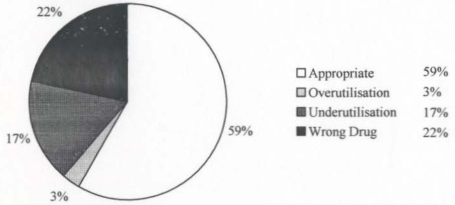

Figure 11. Overall appropriateness of secondary oral antibiotic therapy in patients admitted to hospital with community-acquired pneumonia and who initially received IV therapy only.

Among those patients who initially received IV antibiotic therapy only and were subsequently switched to oral therapy, the chosen oral antibiotic was in complete agreement with prescribing guidelines for 59% of patients (Figure 11). Twenty-two percent (22%) of patients received oral prescriptions which were for the wrong drug, 17% of patients received suboptimal amounts of antibiotic and 3% received extra antibiotic.

For patients assigned to risk class I, the overall level of agreement for oral antibiotics, when switched from IV, was quite low in that only 26% of prescriptions were in complete accordance with the recommended guidelines (Table 57). In 65% of patients, the wrong drug was prescribed; these patients were primarily prescribed cefuroxime in monotherapy.

Table 57. Guideline agreement of oral antibiotic choice (when switched from intravenous antibiotics) for patients assigned to risk class I (n=31).

Guideline Agreement	**Total** No. (%; 95% CI)
In Agreement	8 (25.8; 13.7-43.2)
Overutilisation	3 (9.7; 3.3-24.9)
Overall Agreement	11 (35.5; 21.2-53.1)
Wrong Drug	20 (64.5; 46.9-78.8)

Table 58. Guideline agreement of oral antibiotic choice (when switched from intravenous antibiotics) for patients assigned to risk class II (n=59).

Guideline Agreement	Total
	No. (%; 95% CI)
In Agreement	34 (57.6; 44.9-69.4)
Overutilisation	3 (5.1; 1.7-13.9)
Overall Agreement	37 (62.7; 50.0-73.9)
Underutilisation	11 (18.6; 10.7-30.4)
Wrong Drug	11 (18.6; 10.7-30.4)

The total number of oral prescriptions in complete agreement with guidelines for those patients in risk class II equalled 58% (Table 58). Disagreement with prescribing guidelines equally occurred for underutilisation (using a macrolide as monotherapy) and wrong drug prescriptions (ciprofloxacin and penicillin).

Table 59. Guideline agreement of oral antibiotic choice (when switched from intravenous antibiotics) for patients assigned to risk classes III, IV and V (n=199).

Guideline Agreement	Total
	No. (%; 95% CI)
In Agreement	128 (64.3; 57.5-70.6)
Overutilisation	3 (1.5; 0.5-4.3)
Overall Agreement	131 (65.8; 59.0-72.1)
Underutilisation	37 (18.6; 13.8-24.6)
Wrong Drug	31 (15.6; 11.2-21.3)

Among the patients with more severe disease (risk classes III, IV and V), guideline agreement for secondary oral antibiotic prescriptions was approximately 64%

(Table 59). For the most part, the reason for the discrepancy between what was prescribed and what the guidelines recommend was equally due to using a macrolide singularly and using a drug not included in the guidelines. When the wrong drug was used, the antibiotic chosen was primarily ciprofloxacin followed by penicillin.

4.4.9 Factors Associated with Incorrect Antibiotic Prescribing

Results from the previous analysis were confirmed in a logistic regression analysis determining factors associated with initial empiric prescription events (IV or oral) that were deemed to be in disagreement with prescription guideline recommendations. The results from the regression model are presented in Table 60. Patients assessed to be in risk group I were almost five times more likely, and patients in risk group II were ten times more likely, to receive initial empiric antibiotic treatment that was in disagreement with the guidelines, as compared to patients in risk group V. Site of admission also influenced guideline disagreement in that patients admitted to SAGGH were four times more likely to receive initial empiric treatment not in accordance with recommended guidelines as compared to patients admitted to HSC. No other patient or clinical factors were identified as influencing appropriateness of initial antibiotic treatment.

Table 60. Logistic regression model of guidelines disagreement of initial empiric antibiotic prescription events (IV or oral) (n=569).

Characteristics	N (%)	Unadjusted OR§ (95% CI)	Adjusted OR† (95% CI)
Risk Group			
I	27 (45.0)	5.50 (2.44-12.40)*	4.99 (2.16-11.53) *
II	69 (60.0)	10.09 (4.84-21.05)*	9.87 (4.65-20.92)*
III	17 (15.3)	1.22 (0.54-2.76)	1.20 (0.52-2.76)
IV	23 (11.6)	0.88 (0.41-1.91)	0.80 (0.37-1.75)
V	11 (12.9)	1.00 (Referent)	1.00 (Referent)
Hospital Site			
SAGGH	45 (49.5)	3.76 (2.24-6.29)*	4.15 (2.30-7.48)*
SCMH	52 (22.0)	1.09 (0.70-1.68)	1.30 (0.80-2.13)
HSC	50 (20.7)	1.00 (Referent)	1.00 (Referent)

§OR = Odds ratio obtained from bivariate logistic regression analysis.
† OR = Odds ratio obtained from multivariable logistic regression model, adjusted for all other variables listed in the column.
*p<0.0001

4.4.10 Effect of Antibiotic Appropriateness on Length of Stay

A linear regression analysis assessing the effects of several clinical variables, in addition to appropriateness of initial antibiotic treatment, demonstrates that severity of disease, as indicated by PSI risk classes, accounted for 9.2% of the variation in length of stay for patients admitted with CAP (Table 61). Other important clinical variables such as the presence of COPD, interstitial lung disease and a positive blood culture account for a further 2.9% of the variation. However, when appropriateness of initial antibiotic treatment was added to the regression model, it had no effect on the measure of variation in length of stay. Therefore inappropriate initial antibiotic treatment did not prolong hospital stay.

Table 61. Linear regression model of length of stay for patients admitted with community-acquired pneumonia.

Independent Variables	Coefficient	*P-value*	R^2
Pneumonia Risk Class			
II	0.196	0.003	
III	0.271	<0.0001	
IV	0.423	<0.0001	
V	0.330	<0.0001	0.092
COPD	0.110	0.020	
Interstitial Lung Disease	0.088	0.053	
Positive Blood Culture	0.106	0.015	0.121
Appropriate Initial Antibiotic Treatment	0.055	0.262	0.121

4.4.11 Effect of Antibiotic Appropriateness on Patient Outcome

In total, 10.7% of patients admitted with community-acquired pneumonia died during their hospital stay (n=61). None of the patients assigned to risk group I died while in hospital. For patients in risk groups II, III, IV and V, 2.6%, 6.3%, 13.6% and 28.2% of patients within each risk group, respectively, died in hospital (Table 62). The effects of initial antibiotic prescription appropriateness on survival was assessed using Kaplan-Meier survival analysis and a Cox proportional hazards regression analysis.

Table 62. Comparison of patients who died in hospital separated by risk groups (number (percent)).

Risk Group	Total
I	---
II	3 (4.9)
III	7 (11.5)
IV	27 (44.3)
IV	24 (39.3)
Total	61 (100.0)

Kaplan-Meier survival analysis confirmed the findings that disease severity, as determined by assignment to risk group classes, was the only factor which influenced survival, as measured by thirty day in-hospital mortality ($P<0.001$) (Figure 12). Interestingly adherence of initial empiric antibiotic prescribing to recommended guidelines was not associated with survival.

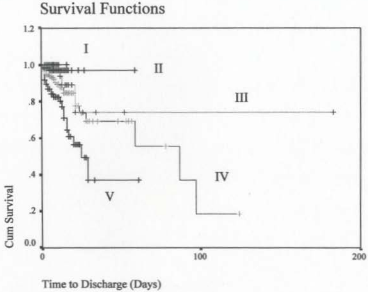

Figure 12. Kaplan-Meier survival curve for each risk group.

A Cox proportional hazards regression analysis determined that patients in risk group II were 7.7 times less likely to die as compared to patients in risk class V (0.04 – 0.44 CI; P=0.001). Similarly, the hazard ratio for patients in risk group III was 0.19 (0.07 – 0.50; P<0.01), and was 0.46 (0.27 – 0.81; P=0.007) for patients in risk group IV, as compared to risk group V patients. Like the Kaplan-Meier survival analysis, appropriateness of initial antibiotic treatment did not have a statistically significant influence on this analysis. Therefore inappropriate initial antibiotic prescription did not influence survival of patients admitted to hospital with CAP.

CHAPTER V – CONCLUSIONS

5.1 Antibiotic Prescribing in Community Practice

The epidemiology of community oral antibiotic use was elucidated through the evaluation of antibiotic prescribing administrative databases and a community-based chart review study of a representative sample of patients with infections in the community. This study was unique in its detailed population-based perspective, examining the combined issues of quantity, indications, factors influencing antimicrobial prescribing and appropriateness.

Overall trends in antibiotic prescribing were similar, but not exactly the same, between the three sources of prescribing information, namely the community chart review study, the Newfoundland prescription drug program (NLPDP) antibiotic prescribing database and prescribing information from Canada and the USA provided by IMS. Antibiotic prescribing trends in the USA differed from the Canadian sources of prescribing information (i.e. increased use of cephalosporins and less use of penicillins), but this is not surprising as geographical variations in treatment, without differences in clinical factors or measures of appropriateness, across various clinical scenarios is a common phenomenon.[111] The analysis of prescribing through the NLPDP database and the GP study differed somewhat, but this can be explained by differences in patient populations from which the prescribing information was derived. The limitation associated with using NLPDP data is that the NLPDP patient population consisted of low income and older patients, whereas the GP study was based on a representative sample from all of St. John's, including all ages and economic classes of patients. Therefore these two samples may not be entirely comparable. More importantly, though, is that the trends in antibiotic prescribing comparing the GP study and Canada as a whole were quite similar. Therefore the results from this study on appropriateness of prescribing and factors influencing the decision to prescribe an antibiotic may be generalizable to other urban communities in Canada. However several limitations should be noted. A limitation of using the IMS prescribing data is that it includes prescriptions written not only by GP's, but office-based specialists as well. Therefore comparing the prescribing trends identified in the GP study with prescribing trends identified in IMS databases would not be a comparison of exactly the same type of physicians making the antibiotic prescription decisions. A further limitation of comparing both the NLPDP and IMS databases with results from the GP study would be differences in the time frames of data collection. Specifically the NLPDP and IMS databases are longitudinal whereas the GP study is cross-sectional.

The fall in antibiotic use seen in the Newfoundland drug program from 1995 and onwards may have been due to the influence of the ongoing nature of our utilization review study of antibiotic prescribing in the community. Planning and physician recruitment for this study started in 1995/1996 and data was collected in 1997/1998.

Each physician who participated in this study was aware that his or her antibiotic prescribing practices would be evaluated at an unspecified time. Therefore it is possible that some of the fall in antibiotic use, as demonstrated in the NLPDP prescribing database, was the result of physician monitoring.

Nonetheless the level of inappropriate antibiotic use, revealed by our utilization review among the majority of GPs in St. John's, is of concern. Overall only 59% of all prescriptions analyzed in the study were considered to be appropriate, as defined by agreement with community antibiotic prescribing guidelines in patients defined according to the doctors' diagnoses. Prescriptions administered for respiratory tract infections tended to be less appropriate than those administered for non-respiratory illnesses. Inappropriate antibiotic prescriptions for respiratory tract infections tended to be inappropriate because of a lack of medical indication for the prescription. Conversely inappropriate prescriptions for non-respiratory infections were predominantly because of poor antibiotic choice (i.e. a wrong drug was used or a lower line/more narrow spectrum of antibiotic was available). Among those prescriptions which were considered inappropriate overall, regardless of diagnostic category, more "not indicated" prescriptions were administered to children, whereas the "wrong drug" or "lower line available" prescriptions were administered to adults.

It is likely that inappropriate prescriptions, because of the lack of a medical indication, in patients with respiratory tract infections was underestimated. Rather than accepting the doctors' diagnoses as being correct, we used a criteria-based decision tree to identify the probable etiology of respiratory tract infections. Presenting complaints, signs and symptoms of each adult patient were considered. In this analysis, greater than 80% of the respiratory infections were thought to be viral in nature, and thus did not require an antibiotic prescription, as determined by the decision tree. The physicians, based on their decision to not prescribe an antibiotic, thought that 44% of respiratory infections were viral.

Clearly this type of analysis has its limitations. Complete documentation of clinical findings in the patients' charts is necessary. It was assumed that if a particular finding was not noted in the chart then that finding was not present in the patient (elevated temperature/presence of fever, for example). Therefore this analysis falls victim to the same limitations of all chart review studies in that the extent of the information collected is based on how much the physicians have reported in the chart. To circumvent this problem, physician interviews were conducted in which physicians had the opportunity to provide any additional clinical information that may not have been previously recorded in the chart. These interviews took place within three days of seeing the patients and the charts were available for the physicians' perusal during the interview.

In the vast majority of cases, no further clinical information was provided by the physician, beyond what was already abstracted from the patients' charts.

In addition to inappropriateness when compared to guidelines and diagnostic mislabeling, inappropriate duration of antibiotic therapy was examined. Eighty six percent (86%) of UTI cases were treated for between 4 and 14 days, despite the fact that current recommendations suggest that uncomplicated acute urinary tract infections in females can be eradicated with proper antibiotic therapy in three days.[112, 113] The patients who formed the study sample were presenting to the doctor with acute infections. Therefore those patients who were making a repeat visit for a previous infection were excluded from the analysis. Therefore all patients diagnosed with UTIs in the study sample would most likely be suitable candidates for a short, three day course of antibiotic therapy.

Reasons why antibiotics were prescribed in clinical situations not requiring antibiotics were investigated, including the clarity of the medical indication and patient expectation. In 80% of prescription events, the physicians perceived the medical indication for the prescription to be clear or very clear. Nonetheless, when respiratory tract infections were considered separately, the clarity of the medical indication was less, when compared to non-respiratory infections in which confidence in the clarity of medical indication was 86%. The difference in the perception of medical indication between these two diagnostic groups may be a reflection of the problems associated with the assessment of respiratory infections. Even though research has shown that greater than 80% of respiratory infections are viral in nature,[74] it is obvious that many physicians practice a "better to be safe than sorry" approach. In this study, it is likely that the physicians assumed bacterial rather than viral etiology and prescribed an antibiotic in order to not miss treating a bacterial infection, an observation suggested by our criterion based decision tree. Clearly if the assessment of an infection is based on the assumption that it is probably viral (and not undeniably viral as would be confirmed through microbiological analysis), then the possibility still remains that the infection might be bacterial.

Patient or parent expectation also influenced the antibiotic prescription decision, particularly in those with respiratory tract infections. The demand for antibiotics by patients may be a result of the pervasive, yet wrong, belief held by the general public that antibiotics are an effective treatment for the common cold.

It is possible that many unnecessary or questionable antibiotic prescriptions are administered because of the perception that few serious side effects occur if inappropriately administered, combined with the perception that these drugs are inexpensive relative to other pharmaceuticals. These perceptions ignore the major public health problem of bacterial resistance to antibiotics and the fact that the national costs for antibiotics are substantial. In Canada, anti-infectives have ranked as the third most commonly prescribed pharmaceutical class in both 1998 and 1999 (source: IMS Health Canada), and consequently are associated with the problem of increasing drug expenditures in Canada. In the present study, the average antibiotic prescription cost was approximately $20. The total retail costs for all 604 prescriptions captured in the study equalled $10,888.30. This amount is derived from only two days of regular practice among 76% of the GPs in St. John's. Those antibiotic classes for which members are primarily still under patent have greater mean retail prescription costs (i.e. quinolones). Therefore quinolone prescription costs, for example, contributed to 23% of total costs among those prescriptions captured in the study. However the penicillin group of antibiotics which are, for the most part, considered to be relatively inexpensive drugs, contributed to 30% of total costs. Undoubtedly the high level of cost contribution represented by the penicillin class of pharmaceuticals is due to the substantial volume with which these prescriptions are administered to patients in the community.

It is of interest that prescription costs were, on average, almost $6.00 greater for those patients who were covered by some form of drug plan as compared to those patients who paid for their prescriptions without any form of reimbursement. However there were no differences in the diagnoses of these two patient groups. It is plausible to suggest that more expensive antibiotics were prescribed simply because the patient was able to seek reimbursement through some type of drug plan. In addition to this, when high cost prescribing physicians were identified and compared to their lower cost prescribing counterparts, it was discovered that a greater proportion of patients seen by the high cost prescribing physicians had a drug plan. No clinical differences existed between the patients of the high and low cost prescribing physicians in terms of presenting complaints, signs, symptoms and diagnoses. Further to this, it was found that the high cost prescribing physicians had a greater proportion of inappropriate prescriptions. Although one would intuitively expect the predominant category of inappropriate prescriptions to be "lower line available" (as the lower line drugs listed in the guidelines tend to be less expensive), the inappropriateness equally encompassed all categories thus indicating that problematic antibiotic prescribing associated with high cost prescribers is multi-faceted.

Other physician characteristics or prescribing habits have been identified as giving rise to potentially problematic prescribing. When physicians were categorized according to their rate of appropriate prescriptions, it was discovered that the least appropriate prescribing physicians tended to be older and male. These two characteristics are probably related in that the proportion of females attending medical school twenty to thirty years ago was far less than it is now. It is possible that the greater number of years since medical school graduation contributes to inappropriate antibiotic prescribing.

Specific areas of problematic antibiotic prescribing have been identified in this study. The current estimated annual rates of antibiotic prescriptions demonstrate that almost half of the study population receive antimicrobial therapy in a year. The overall quantity of antibiotic prescriptions could potentially be far less if physicians critically evaluated the likelihood of bacterial etiology for infections, particularly in relation to respiratory tract infections. Other areas of inappropriateness of prescriptions must also be improved. Our study has demonstrated that physicians err in prescribing longer than necessary durations of treatment for UTI, lack of medical indication, and mistakes in recommended drug choices. Therefore, with this information regarding the epidemiology of antibiotic prescriptions in community practice, interventions to encourage judicious use of antimicrobial therapy can accurately address current antibiotic prescribing problems.

5.2 Treatment of Community-Acquired Pneumonia

This study examined the antibiotic treatment of patients admitted to hospital with CAP. Previous studies addressing this same issue have uncovered a substantial amount of heterogeneity in the antimicrobial treatment trends across various geographical regions. The present study examined not only how antibiotics were used for this particular diagnosis, but also the appropriateness of antibiotic choice as compared to Canadian prescribing recommendations.

Two key issues arise from the present study. These issues are the requirement for a more critical evaluation of the need to admit low risk patients diagnosed with CAP and the associated level of antibiotic prescribing that is not in accordance with recommended Canadian prescribing guidelines.

Overall 31% of patients admitted to hospital with CAP were assigned to risk classes I and II. Fine and colleagues suggest that these low risk patients do not require hospitalization, as their risk for mortality within 30 days of admission due to CAP is less than 2%. Fine et al. recommend that these particular patients can be appropriately and effectively treated as outpatients.[110] In another Canadian study examining the treatment of CAP in Canadian hospitals, only 19.4% of admitted patients were assigned to risk classes I and II.[101] Therefore a large discrepancy exists between the severity of illness among patients admitted to hospital in St. John's as compared to the rest of Canada. A more critical evaluation of the need to admit these low risk patients in St. John's hospitals is necessary. Given the enormous difference in costs between treating patients in hospital and treating patients as outpatients, low risk CAP patients represent an important segment of the health care system in which acute care cost savings could potentially be achieved, assuming that adequate outpatient support services are available.

By assessing the appropriateness of antibiotic prescriptions used to treat admitted CAP patients, the present study has uncovered that the majority of the initial prescriptions which were not in agreement with the guidelines were administered to patients who were at very low risk for death within thirty days due to CAP. Of patients assigned to risk groups I and II, approximately one half received an initial empiric antibiotic which was not in agreement with the Canadian prescribing guidelines. Furthermore another 15% of the same low risk patients received extra antibiotics not suggested in the guidelines, in addition to correct recommended treatment. Therefore only 30% of patients assigned to risk classes I and II were appropriately prescribed initial empiric antibiotics as outlined by the recommended guidelines. However information on concomitant diagnoses in addition to CAP was not collected. Therefore it is possible that patients receiving extra antibiotics may have had a second diagnosis for which the extra antibiotic was administered and therefore would be potentially appropriate.

The problematic prescribing associated with low risk patients primarily resulted from the administration of cephalosporins in risk group I patients and 3rd generation cephalosporins or clindamycin in risk group II patients. However, if these patients were assigned to higher risk groups, most of these prescriptions would have been considered correct. Therefore it appears that physicians are assuming that all patients who are admitted to hospital must suffer relatively severe illnesses and be treated accordingly, with severe being defined based on the decision to admit rather than clinical criteria. Certainly sound clinical judgment on a per-patient basis always overrides any clinical practice guidelines. However a more critical evaluation of the necessity to admit low risk patients with CAP to hospital would result in substantial health care savings with regard to reducing costs associated with acute care bed utilisation and in-hospital drug costs.

Initial antibiotic prescribing for patients with more severe illness was commendable in that 87% of initial antibiotic treatment choices were in accordance with the recommend guidelines. Only 6% of patients received extra antibiotics in addition to recommended therapy, with the extra drugs primarily consisting of either ciprofloxacin or clindamycin. Although clindamycin is not listed in the guidelines as an appropriate agent for any patient, ciprofloxacin is recommended for patients admitted to the intensive care unit (ICU). Three percent (3%) of patients in the present study were mechanically ventilated and therefore were cared for in the ICU, however none of these patient received treatment with ciprofloxacin. Therefore the cases in which this particular drug was used may have resulted from physician overestimation of the severity of disease.

Less adherence to recommended prescribing guidelines was found when treatment was switched from IV to oral therapy, in that only 59% of the secondary oral prescriptions were in accordance with the guidelines. Again, overall guideline agreement was less for patients in risk class I (36%) as compared to patients in risk classes III, IV and V (66%). Like the inappropriate initial antibiotic prescriptions for low risk patients, the inappropriateness of secondary oral prescriptions resulted from the use of agents that are recommended for more severely ill patients (i.e. cephalosporins). The inappropriateness of oral prescriptions administered to sicker patients was equally the result of using a macrolide as monotherapy and the use of a wrong drug, with ciprofloxacin, again being the most common incorrectly prescribed agent followed by penicillin.

Even though problematic antibiotic prescribing was identified in this present study, it did not appear to affect length of hospital stay or patient outcome in terms of mortality. Three explanations can account for this finding. Firstly the Canadian antibiotic prescribing guidelines for the treatment of CAP have not been validated. That is to say the recommendations are based on expert opinion, but it has never been proven that adherence to these guidelines results in better patient outcome or reduced length of hospital stay. The results of this study certainly support the notion that further evaluation of the prescribing guidelines is required.

Secondly the use of in-hospital mortality as a measure of patient outcome, albeit it very objective and not prone to error, may not have been the best measure for patient outcome. Subtle differences in time to subjective improvements in respiratory symptoms and time required to return to normal daily activities (i.e. employment) were not measured in this study. Perhaps if these outcome measures were assessed in a prospective manner, differences in patient outcome accounted for by differences in adherence to antibiotic prescribing guidelines may have been revealed.

Finally the type of inappropriateness of empiric therapy most likely accounted for the lack of influence of antibiotic prescribing appropriateness on length of stay and in-hospital mortality. The majority of antibiotic treatments which were considered to be in disagreement with the prescribing guidelines were cases in which low risk patients were treated as being more severely ill than what the PSI score would indicate. The therapy these patients received, albeit inappropriate according to guideline criteria, still provided good coverage for their infection. Because of this, most patients treated with inappropriate therapy probably experienced the same course of illness as patients treated with appropriate empiric therapy and thus no differences in length of stay or in-hospital mortality were evident between these two groups of patients.

Patients admitted to hospital in St. John's for CAP spend more time in hospital as compared to lengths of stay reported in other studies. A recent Canadian study examining lengths of stay for twenty hospitals across Canada reported a median length of stay for community-acquired pneumonia patients of 7.0 days.[101] In our study, the median length of stay was 8.0 days. When examining median lengths of stay by risk groups, St. John's patients consistently spent exactly one day longer in hospital than other Canadian hospitals. Comparing patient outcomes, as measured by mortality, only 10% of patients admitted in St. John's died in hospital, whereas 14% of patients admitted to other Canadian hospitals died within thirty days of admission.[101] Although this may indirectly suggest that the longer lengths of hospital stay may result in better patient outcome, previous studies have refuted this claim.[114, 115] This difference in outcome is more likely due to lower proportions of sicker patients admitted to hospital in St. John's; patients in risk groups IV and V accounted for only 50% of total patients whereas in other Canadian hospitals, these same high risk patients accounted for 65% of total patients.[101] Perhaps if physicians in St. John's admitted less numbers of low risk patients, overall rates of mortality CAP at St. John's hospitals would be more in line with national figures.

In conclusion the present study has determined that a greater proportion of low risk CAP patients is admitted to hospital in St. John's, as compared to other Canadian hospitals, and a high proportion of these low risk patients receives aggressive antibiotic therapy. A validated prediction rule assessing thirty day mortality due to CAP supports the notion that these low risk patients may not necessarily need to be admitted to hospital. Because of this, a more critical evaluation of the necessity to admit these patients is recommended. Problematic prescribing with regard to lack of adherence to Canadian antibiotic prescribing guidelines was also noted, particularly for low risk patients. The problematic prescribing did not appear to affect length of hospital stay or patient outcome, although these outcome measures may not have been sensitive enough to detect differences among those patients who were appropriately treated with antibiotics and those who were not. As well the prescribing guidelines used in this analysis have not been validated. Nonetheless it is important to encourage hospital physicians to closely examine their antibiotic prescription choices such that agents which should be reserved for more sicker patients are not used in less severely ill patients.

CHAPTER VI – DISCUSSION

This study on antibiotic prescribing in both community practices and in acute care settings has detailed a disconcerting level of inappropriateness in prescribing, as defined by discordance with recommended prescribing guidelines, as well as an overall unnecessary high level of antibiotic use. Although these studies have provided valuable insight into the wide-reaching extent of unnecessary and inappropriate antibiotic use within two specific sectors of health care delivery, researchable interventions to instigate improvements in antibiotic prescribing within the studied environments were outside the scope of this research project. The information revealed in this body of research undoubtedly is valuable to developing successful interventions to change prescribing behaviour or may be used as an impetus for developing antibiotic prescribing policies. It is necessary to first identify specific problems such that interventions and policies designed to change behaviours, in this case antibiotic prescribing, can be focussed and therefore potentially give rise to desired improvements in physician practice patterns.

Nonetheless a simple question is yet to be answered. What can be done about problematic antibiotic prescribing? The problems associated with antibiotic prescribing are multifaceted, involving both health care professionals and the general public. Therefore a multi-faceted approach to a solution is warranted. In light of this, several recommendations are proposed, including the development of evidence-based and validated antibiotic prescribing guidelines, implementation of a strategy for the successful dissemination and adoption of these guidelines utilising a computer-based decision support system, initiation of an antibiotic prescription monitoring program, utilisation of a detailing or mentoring program by respected opinion leaders, continual surveillance of local bacterial resistance patterns and implementation of a public education campaign in which prudent antibiotic use is promoted.

Of paramount importance is the development of evidence-based and scientifically validated antibiotic prescribing guidelines. The potential usefulness of clinical practice guidelines in processes of care and patient management has been demonstrated in previous studies.[116] However just because guidelines have been shown to be useful, does not necessarily mean that guidelines are used. Hayward and colleagues surveyed Canadian physicians about their attitudes toward clinical practice guidelines. The majority of physicians had positive attitudes toward clinical practice guidelines, indicating that they are a convenient source of advice and good educational tools. However only 40% of surveyed physicians had changed their practice in the year before the survey as a result of referring to guidelines.[117] In recent years physicians have been inundated with a myriad of clinical practices guidelines, some of which are even of questionable scientific merit.[118, 119] As Jonathan Lomas points out, "Ironically, the recognition standards routinely required of research studies are rarely found in the consensus reports that make the synthesis of such studies popularly available."[120] Therefore it is plausible to suggest that lack of adoption of some clinical practice guidelines may be because the guidelines are not scientifically validated and therefore are not seen as useful and applicable to daily practice.

In this study the Anti-infective Guidelines for Community-acquired Infections[1] and the community-acquired pneumonia treatment recommendations outlined by the Canadian Community Acquired Pneumonia Consensus Conference Group[2] were used as tools to assess appropriateness of antibiotic prescriptions. Although both of these sources of prescribing guidelines were formulated by expert opinion from numerous sources, neither of these tools have been scientifically validated. A recent assessment of various Canadian clinical practice guidelines determined that the Anti-infective Guidelines for Community-acquired infections in particular were sub-optimal with regard to scientific rigour of development, and scored slightly above average for context and content (reliability, applicability, flexibility and clarity).[119] This may have accounted for the suboptimal level of adherence to prescribing guidelines discovered in the present study. Because neither set of guidelines have been subject to rigorous scientific evaluation for efficacy, it has not been unequivocally proven that prescribing in the recommended manner is useful and therefore warranted, even though both tools were formulated from expert opinion. Therefore it is imperative that guidelines which withstand scientifically rigorous evaluation are developed so that physicians can have utmost confidence that aligning their antibiotic prescribing practices with the guidelines is the best approach for their patients and is beneficial from all perspectives.

Once evidence-based and validated antibiotic prescribing guidelines have been developed, a second recommendation is to ensure that an effective strategy is in place to facilitate the adoption of the antibiotic prescribing guidelines in daily practice by physicians.[121, 122] Such strategies are necessary to make certain that the disseminated guidelines will impact prescribing behaviour. Simply providing a printed version of guidelines has been previously shown to have a very weak influence on prescribing behaviour or physician practice patterns..[122-127] Therefore simply distributing the prescribing guidelines does not ensure that physicians will incorporate them into their daily practice. Although this second recommendation is perhaps a costly venture, easy access to antibiotic prescribing guidelines could be ensured through the implementation of a computer-based prescribing decision support system. This type of intervention could feasibly be operated in both community practices and hospitals. With this type of system, antibiotic prescribing protocols or guidelines would be central to the program. Information specific to the patient would be entered into the program, resulting in patient-specific recommendations for treatment.[128, 129] The purpose of implementation of this type of computer-based decision support system would be to improve quality of care with regard to antibiotic treatment by potentially reducing excessive or inappropriate antibiotic prescriptions.

A precedent for the usefulness of a computer-based decision support system for antibiotic prescribing has been reported.[130, 131] Evans and colleagues implemented a point-of-care computer-assisted management program for the treatment of infections in an acute care centre. With this system, patient-specific information such as diagnosis, white cell count, temperature, surgical data, chest radiographs and reports from pathology, serology and microbiology are incorporated together to determine the appropriate antibiotic treatment. As well, other factors such as allergies, drug-drug interactions, toxicity and cost are also considered in the computer program. A recommendation for choice of antibiotic treatment in addition to route of administration, dose, frequency and duration are provided. Physicians can override the suggestions, but must explain the rationale for their own antibiotic choice.[131] Evaluation of this computer-based decision support system has revealed that improvements in antibiotic prescribing have occurred since its implementation. For example less adverse drug reactions, susceptibility mismatches, and overdosing occurred after the system was in place. As well overall fewer doses of antibiotics were administered, reductions in antibiotic drug costs occurred, and patients treated with antibiotics spent fewer days in hospital.[131] Therefore improvements in antimicrobial use have been documented following the implementation of a computer-based decision support system.

A third recommendation with regard to improving antibiotic prescribing practices is to incorporate an antibiotic prescription monitoring program for both community practices and in hospital. This type of intervention, typically referred to as physician profiling, would involve the comparison of the physicians' individual antibiotic prescribing behaviour to some sort of prescribing gold standard, evolved from either antibiotic prescribing guidelines or a "benchmark" that has been previously established. In this manner, differences between actual antibiotic prescribing patterns of individual physicians and recommended practices would be noted. Periodic reporting of the monitoring results to the individual physicians would be provided and presumably this feedback would serve as the impetus for change in those physicians prescribing antibiotics in a less than satisfactory manner.

Previous studies have shown that individual monitoring or feedback is a moderately effective intervention giving rise to change in physician practice patterns.[132] This type of intervention has been previously attempted with regard to antibiotic prescribing in both hospitals and community practice, also giving rise to encouraging results. In a study conducted by de Silva and colleagues, an ongoing program of peer review of antibiotic prescriptions in an acute care facility was found to significantly reduce inappropriate prescribing of third generation cephalosporins and aminoglycosides (the two targets of the intervention), in that the percentage of mean monthly costs of inappropriate prescriptions fell from 41% to 7% after a prescription monitoring system was implemented.[133] Two feedback studies focussing on antibiotic prescribing have been conducted in community practices. Pitts and Vincent's study involved a one time general feedback on antibiotic prescribing for sore throats following a two month audit period.[134] The prescribing data for individual doctors was presented in addition to a proposed policy on antibiotic prescribing for sore throats. Although overall variation in antibiotic prescribing rates had not changed after the audit, the choices in antibiotics used to treat sore throats had improved; substantially more patients were treated with either penicillin or erythromycin thus increasing the appropriateness of the prescriptions.[134]

A Canadian study also demonstrated positive effects from a feedback program involving antibiotic prescribing.[135] The goal of this particular program was to reduce antibiotic prescription costs by providing individualized feedback to primary care physicians. Choices in antibiotic therapy were compared with recommendations for treatment outlined in the Ontario Anti-infective Guidelines for Community-acquired Infections.[1] Given that cost of therapy was an important consideration in the development of the guidelines (i.e. with efficacy and safety being equal, the less expensive antibiotic would be listed as a first line agent for treatment before more expensive choices), it was hypothesized that individual feedback on antibiotic prescribing would encourage the physicians to prescribe more first line agents, thus reducing prescription costs.[135] After the implementation of the feedback program, the authors found that there were no changes in the median antibiotic prescription costs among those physicians who had received prescribing feedback. However the control physicians, for which no feedback was provided, increased their average prescriptions costs by over $3.00.[135] A post-study survey indicated that 82% of participants would readily participate in similar future programs.[135] Therefore the feedback intervention was not only successful, but favourably received by the participants as well.

All of the above cited references utilising a feedback or audit on antibiotic prescribing included some type of educational component. The educational component was delivered either at a seminar or by an informational mail-out. Although informational mail-outs or seminars in isolation have not been shown to result in changes in prescribing behaviour, their inclusion in physician profiling programs appears to be useful. With regard to antibiotic prescription monitoring, the educational component of future audit programs could perhaps incorporate both seminars and printed mail-outs outlining the recommended guidelines for antibiotic prescribing. The monitoring program could potentially serve as a means to determine whether the guidelines were effectively disseminated in addition to serving as an intervention on its own.

A fourth recommendation to improve antibiotic prescribing is the commencement of a detailing or mentoring program for physicians by respected opinion leaders. This type of program is typically modelled after the detailing programs in use by private industry, in which sales representatives visit physicians in a one-on-one meeting to inform the physicians about various aspects of pharmaceuticals. The academic detailing program should be nonpunitive, concise and endorsed by the local medical association. The first successful academic detailing programs focussed on antibiotic prescribing were published almost twenty years ago.[136, 137] Schaffner and colleagues demonstrated that a short, single visit by a physician colleague can reduce prescribing of contraindicated antibiotics and oral cephalosporins.[137] In follow-up studies, Ray and colleagues demonstrated that the effectual changes in antibiotic prescribing from the detailing program were long term with the positive changes in antibiotic prescribing lasting up to two years after the physician visits.[138] Interestingly the variation in prescribing behaviour in response to the educational visit could not be explained by medical demographics of the participating physicians (i.e. type of practice, year since graduation, board certification, receptivity to the educational visit).[139] As the authors point out, this finding suggests that no particular group of physicians are refractory to an educational visit.[139]

Since these earlier studies, other investigators have also published the results of successful academic detailing interventions involving antibiotic prescribing.[140-142] A common aspect of these studies involves the use of a focussed antibiotic prescribing message delivered by an opinion leader. In one of these published reports, a pilot study was initiated to determine the exact nature of problematic antibiotic prescribing in order to formulate the focussed academic detailing message.[140] Therefore the results of the current study on antibiotic prescribing in St. John's, NF could be used to develop focussed academic detailing messages as well. Specifically, messages outlining the need for a more critical evaluation of bacterial versus viral etiology in respiratory tract infections (and therefore the need for antibiotic treatment), improved drug choice for the treatment of non-respiratory infections, and decreased length of treatment for urinary tract infections would serve as useful messages to be imparted to general practitioners in the community. For acute care physicians treating patients admitted to hospital with community-acquired pneumonia, the current study has revealed the need for a more critical evaluation of severity of disease (and therefore the need to admit patients to hospital) and improvement in drug choices for both initial empiric treatment and when patients are switched to oral medications.

In order to ensure that antibiotics are as effective as possible, it is important that local resistance patterns are regularly monitored. Therefore a fifth recommendation is to establish a program in which pathogens giving rise to local nosocomial and community-acquired infections are routinely collected, isolated and monitored to measure their resistance patterns. With this approach, resistance would be measured from a clinical perspective based on the number of infected patients as opposed to a laboratory one based on the number of isolates.[143] This type of program would require the local coordinated effort of physicians, patients, microbiologists and infectious diseases specialists, and could be overseen by the local public health department. A bacterial pathogen resistance surveillance program would serve to keep local antibiotic prescribing guidelines up to date, as resistance is a continual evolutionary process. Furthermore regular surveillance of local bacterial resistance patterns could potentially allow researchers to determine if implemented antibiotic prescribing policies or interventions are effective and successful by cross referencing data on resistance patterns with antibiotic prescribing data.[143]

The final recommendation to improve antibiotic prescribing, specifically affecting general practitioners, is to launch a public education campaign in which prudent antibiotic prescribing is promoted. Physicians are ultimately the individuals who decide whether or not an antibiotic should be given and, if so, which one. However public pressure has been implicated in confounding the antibiotic prescribing decision. In the present study, patient pressure or expectation for an antibiotic prescription (as perceived by the physician) was an influencing factor in many of the cases in which an antibiotic was prescribed, particularly for respiratory tract infection diagnoses. Therefore to singularly implement interventions or policies that focus on changing physicians' attitudes and behaviours toward antibiotic prescribing negates the role that the patients play in prescription decision-making. If this were the case and physicians were the only ones to change, in the absence of public education, patients would continue to expect or demand antibiotics and possibly become very dissatisfied with physicians for not providing a prescription. Patients would perhaps become confused about why prescriptions were given in the past, but not during current visits.

An example of a current Canadian public education campaign promoting the message of decreased antibiotic use in the community is the "Do Bugs Need Drugs?"

campaign launched in the Edmonton area in the province of Alberta (http://www.dobugsneeddrugs.org). This particular campaign is comprehensive in the dissemination of its message, targeting healthcare professionals, the general public, teachers, parents and children. Three key messages have been emphasized: 1) the importance of handwashing to stop the spread of infections, 2) the difference between bacterial and viral infections and the uselessness of antibiotics in the treatment of infections caused by viruses, and 3) the prudent use of antibiotics being an important step in preventing bacterial resistance. The goal of the campaign is to increase public awareness about the seriousness of bacterial resistance and how inappropriate use of antibiotics contributes to this public health problem.

Because this study has identified antibiotic prescribing problems that are multi-faceted, a multi-faceted approach to a solution for these problems is required. Changing antibiotic prescribing to reduce excess of prescriptions and to make necessary prescriptions in line with current recommendations most likely will not entirely fix or reverse the current problems with bacterial resistance. However changing current practices to more appropriate future prescribing trends will undoubtedly contribute to the prevention of further resistance from developing. Given the prevalence of bacterial infections and the distinct possibility, in some cases, for the infection to result in death, it is imperative that we preserve the power that antimicrobial agents have over bacterial pathogens. Antibiotic utilisation studies are the first step toward this goal. By identifying how antibiotics are prescribed in various health care settings, problematic prescribing can be aptly identified. Subsequently, interventions or policies directed towards changing prescribing behaviour in response to the identified problems can be implemented. As a result the development of adverse consequences originally stemming from problematic antibiotic prescribing can be stymied, leading to future retention of the power that antibiotics have over bacterial pathogens.

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CHAPTER VIII – APPENDICES

Appendix I - Point Scoring System for Pneumonia Severity Index (PSI) Score*

Step I of Pneumonia Severity Index Scoring System:

1) Is the patient more than 50 years of age?

2) Does the patient have a history of any of the following coexisting cc..ditions?
   - Neoplastic disease
   - Congestive heart failure
   - Cerebrovascular disease
   - Renal disease
   - Liver disease

3) Does the patient have any of the following abnormalities on physical examination?
   - Altered mental status
   - Pulse ≥125/minute
   - Respiratory rate ≥30/minute
   - Systolic blood pressure <90 mm Hg
   - Temperature <35°C or ≥40°C

If "no" is the appropriate answer for all of the above questions, then the risk score equals zero and the patient is assigned to Risk Class I.

If "yes" is answered to any one or more of the above questions, then move to Step II of the scoring system.

Step II of Pneumonia Severity Index Scoring System:

Characteristic	Points Assigned
Demographic Factor	
Age - Men	Age (yr)
- Women	Age (yr) - 10
Nursing Home Resident	+10
Coexisting Illnesses	
Neoplastic Disease	+30
Liver Disease	+20
Congestive Heart Failure	+10
Cerebrovascular Disease	+10
Renal Disease	+10
Physical Examination Findings	
Altered Mental Status	+20
Respiratory Rate ≥30/min	+20
Systolic Blood Pressure <90 mm Hg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125/min	
Laboratory and Radiographic Findings	
Blood Urea Nitrogen ≥11 mmol/L	+20
Glucose ≥14 mmol/L†	+10
Hematocrit <30%	+10
Partial Pressure of Arterial Oxygen <60 Hg	+10

* Adapted From Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marie TH, and Kapoor, WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. NEJM 1997; 336: 243-250.

† Because patient information on glucose concentration was not available for data abstraction, patients with diabetes, as noted in the chart, were assigned points in the same manner as patients with a glucose concentration of 14 mmol/liter.

Risk Class I =	0 Points
Risk Class II =	≤70 Points
Risk Class III =	71-90 Points
Risk Class IV =	91-130 Points
Risk Class V =	≥131 Points

Appendix II - Antimicrobial Treatment Guidelines for Community-Acquired Pneumonia*

Non-Severe Patients + Patient Previously Well and/or < 65 Years Old (Risk Class I):

Macrolide
Tetracycline

Non-Severe Patients + Comorbid Illness and/or > 65 Years Old (Risk Class II):

2nd Generation Cephalosporin ± Macrolide
Trimethoprim/Sulphamethoxazole ± Macrolide
Penicillin plus beta-lactamase inhibitor ± Macrolide

Severe Patients - Hospital Ward (Risk Class III or IV or V):

2nd or 3rd Generation Cephalosporin ± Macrolide ± Rifampin

- in penicillin-allergic patients:

Trimethoprim/Sulphamethoxazole + Macrolide

Severe Patients - Intensive Care Unit (Risk Class III or IV or V):

Macrolide ± Rifampin + 3rd Generation Cephalosporin with antipseudomonas activity

OR:

Imipenen/Cilastatin

OR:

Ciprofloxacin

*Adapted from Mandell et al. Antimicrobial treatment of community acquired pneumonia in adults: A conference report. Can J Infect Dis 1993; 4: 25-28.