USE OF ADMINISTRATIVE HEALTHCARE CLAIMS TO EXAMINE THE EFFECTIVENESS OF TRIMETHOPRIM-SULFAMETHOXAZOLE AND FLUOROQUINOLONES IN THE TREATMENT OF COMMUNITY-ACQUIRED PYELONEPHRITIS

BY

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A Thesis
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Use of Administrative Healthcare Claims to Examine the Effectiveness of Trimethoprim-Sulfamethoxazole and Fluoroquinolones in the Treatment of Community-Acquired Pyelonephritis

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A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

For Kyle and Holly

Abstract

Practice guidelines for the treatment of community-acquired pyelonephritis recommend initial treatment with one of trimethoprim-sulfamethoxazole (TMP-SMX) or a fluoroquinolone. However, increasing resistance among uropathogens to TMP-SMX has prompted some authors to recommend fluoroquinolones over TMP-SMX despite their higher cost and the potential for selection of antibiotic-resistant strains.

This study uses an observational retrospective cohort design to examine treatment and outcome of community-acquired pyelonephritis in adult females. Administrative healthcare claims from Manitoba Health were used as the source of data. These included, medical, hospital, and pharmaceutical claims submitted to Manitoba Health from April 1, 1995 to March 31, 2000. Specific hypotheses relate to: patient-specific variables which result in receipt of a fluoroquinolone versus TMP-SMX for treatment of pyelonephritis, the comparative effectiveness of these two treatments, and how patient-specific variables affect comparative treatment outcomes.

The study cohort consisted of 1,084 women with a recent episode of pyelonephritis, of whom 60.2% received TMP-SMX and 39.8% received a fluoroquinolone. Increasing age, presentation to an emergency room, rural residence, recent antibiotic use, recent hospitalization, and higher income were significantly associated with receipt of a

fluoroquinolone. Approximately 19% of subjects receiving either treatment experienced treatment failure. Short duration of treatment (less than 10 days), recent antibiotic use, recent urinary tract infection (UTI) were significantly associated with treatment failure. Initial treatment with TMP-SMX significantly increased the risk of treatment failure in young women only.

Despite recent increases in the prevalence of resistant pathogens, TMP-SMX results in successful treatment outcome in greater than 80% of subjects. Thus, treatment with TMP-SMX for 10 to 14 days, after obtaining a urine culture continues to be an appropriate treatment selection. The effect of age on comparative treatment outcomes requires further study, as the findings in this regard were in direct opposition to current theory.

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Chapter 1.

Introduction

The current study uses administrative healthcare claims to examine the effectiveness of two recommended treatments for acute community-acquired pyelonephritis; trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones. Pharmaceuticals are the most rapidly increasing component of healthcare costs in Canada (1) and thus, the effectiveness of their use is of concern, as are methods to monitor their effectiveness at the population level.

Prior to marketing, a drug's efficacy is established using randomized controlled trials (RCT). However, these pre-market studies typically include only a small number of highly select subjects in a controlled environment, therefore, the results they achieve may not reflect those obtained in "real world" practice. Efficacy is a measure of the optimum benefit which may be derived from a drug under ideal conditions, while effectiveness is a measure of drug benefit under conditions of everyday practice. Drugs which exhibit equal efficacy under the ideal conditions of a RCT, may exhibit differences in effectiveness under conditions of everyday practice. Thus, it is desirable to establish the effectiveness of "real world" drug use, and implement methods to encourage effective drug use. This is

a formidable undertaking and will involve careful assessment of drug use for a variety of indications by large numbers of people. As the number of research questions related to the effectiveness of drug use will naturally exceed the funds available for studying them, it is prudent to focus on drugs which exert a high demand on the healthcare system due to high use, and/or high cost.

Antibiotics were chosen for this study as they are one of the most commonly prescribed drug classes (2,3). Studies of antibiotic use in community practice in Australia, the United Kingdom, and the USA have reported increasing use of new broad spectrum antibiotics (2-4). Although differences in quantity and type of antibiotic use were noted between countries, inappropriate and/or unnecessary use of antibiotics, particularly broad spectrum ones, presents a problem due to their potential for promoting antibiotic resistance. Studies indicate the proportion of common community-acquired pathogens exhibiting resistance to antibiotic agents has increased in the last decade (5-8). Therefore, the increase in use of broad spectrum antibiotics may be warranted due to resistance to older, narrow spectrum agents. However, it is unclear to what extent increasing antibiotic resistance accounted for the increase in use of broad spectrum antibiotics.

A study of antibiotic usage trends in Manitoba, Canada was undertaken using pharmaceutical claims from January 1, 1995 to December 31, 1999, to determine current prescribing practices and identify areas of concern for further study. While total antibiotic consumption decreased during this time period, use of new and/or broad spectrum antibiotics increased. The increasing use of fluoroquinolones was of particular interest. The introduction of fluoroquinolones in the late 1980s was a significant advance,

allowing out-patient treatment of infections previously managed in hospitals, or infections with pathogens resistant to older agents (9). Fluoroquinolones are the most broad spectrum antibiotics currently available for oral use, however, they are costly compared to older agents, and inappropriate use may result in a loss of effectiveness due to the promotion of antibiotic resistance.

Recent increases in the proportion of uropathogens exhibiting resistance to trimethoprim-sulfamethoxazole (TMP-SMX) have raised questions about the suitability of TMP-SMX for treatment of urinary tract infections (UTI), and may partially account for the increased use of fluoroquinolones. In the USA, the proportion of uropathogens resistant to TMP-SMX increased from 8 to 16 % from 1992 to 1996 (7). In Canada, in 1998, approximately 19% of uropathogens exhibited resistance to TMP-SMX in contrast to approximately 2% to fluoroquinolones (10). Thus, the effectiveness of TMP-SMX for treatment of UTI is questionable, however, much may depend on the site of infection. The implications of inadequate treatment of infections with antibiotic-resistant pathogens is greater in pyelonephritis, as it is an invasive infection compared to cystitis. Thus, urine cultures are recommended when pyelonephritis is suspected, although physicians must treat empirically pending urine cultures (11, 12). Several patient-specific variables have been identified as risk factors for infection with antibiotic-resistant pathogens, including recent antibiotic use, recent hospitalization, recent UTI, diabetes and increasing age. Patient status with regard to these variables may influence physicians' decisions whether to prescribe fluoroquinolones, and may be expected to affect response to treatment. This study attempts to determine the patient factors which influence the decision to prescribe

fluoroquinolones over TMP-SMX for treatment of acute pyelonephritis, and examines the comparative effectiveness of these two treatments.

To establish the effectiveness of drug treatment, as opposed to efficacy, it is necessary to observe outcomes of treatment under conditions of everyday practice. In keeping with this perspective, the present study uses an observational retrospective cohort design. Use of administrative healthcare claims from the province of Manitoba, Canada offered several advantages as a data source for this purpose. Like all Canadians, Manitoba residents enjoy universal health care coverage. Therefore, records of healthcare utilization for the entire population are available for study, which facilitates highly generalizable data. In addition, use of healthcare claims is non-intrusive, thereby eliminating the possibility of a Hawthorne effect (13). Furthermore, loss to follow-up is minimized since only subjects' claims need be followed up, rather than the subjects themselves, and finally, large numbers of subjects may be studied at minimal cost.

As acute uncomplicated UTI is predominantly a disease of young women, this patient population was the focus of this study. Specifically, all non-pregnant, non-institutionalized Manitoban women aged 18 to 65 years who experienced a new episode of community-acquired pyelonephritis initially treated with TMP-SMX or a fluoroquinolone were eligible for the study.

A number of hypotheses were developed for the study, however, they all related to two major themes; (i) what patient-specific variables result in receipt of initial treatment with a fluoroquinolone? and (ii) what is the comparative effectiveness of these two treatments for pyelonephritis, and how do patient-specific variables affect the comparative effectiveness? Variables examined included subject age, in addition to

patient status regarding diabetes, recent antibiotic use, recent hospitalization, recent UTI, residence (urban or rural), income, and location of physician visit (office or emergency room). Women who experienced new episodes of pyelonephritis were identified by diagnosis codes recorded on claims for physician visits. The effectiveness of the two treatments was assessed based on their ability to resolve the infection without the need for further treatment (as determined by the presence or absence of additional healthcare claims related to treatment of pyelonephritis).

The method and use of administrative healthcare claims to answer questions of drug effectiveness was as much of interest in this study as the actual drug-disease question to which it was applied. Thus, descriptions of the claims-data and the method used to define subject variables from the data is detailed, and requires careful reading. Descriptions of the data-fields from various components of the Manitoba Health database are provided in table format for easy referral. In addition, the discussion of findings has much to do with limitations imposed by use of healthcare claims on this and future studies of drug therapy effectiveness.

Chapter 2.

Literature Review

2.1 Measuring Drug Effectiveness

In 1996, drugs accounted for 14.4% of health care expenditures in Canada (1). The cost for this drug use was estimated to be 10.8 billion dollars; equivalent to expenditures for physician services. There is evidence to suggest that in recent years, the cost of drugs has exceeded that of physician services (1). This is of concern since increasingly expensive drug treatments are being made available with little knowledge of their contribution to improved population health. Many of these newly marketed drugs are new therapeutic modalities, of which, some may be indicated for conditions with no currently available treatment, while others are intended to augment or replace existing treatments. Still other newly marketed agents are modifications of currently available treatments, possibly offering an enhanced pharmacokinetic or safety profile. Others may offer no such benefits and are considered merely "me too" drugs. In an environment of finite wealth it is imperative that healthcare dollars not be spent on ineffective, sub-optimal or inefficient treatments. How then, can we determine that drug expenditures are providing the most optimal outcomes possible?

Prior to market approval, new drug entities are required to demonstrate both safety and efficacy in clinical trials. These randomized controlled trials (RCT) are considered to provide the most rigorous comparative assessments of drug efficacy. The randomization of treatment allocation minimizes the potential for bias due to unequal distribution of known and unknown predictors of outcome. Depending on the indication for which these drugs are marketed, the control treatment may be a placebo (in indications where no currently available treatments exist) or active control (ideally the best alternative treatment). As a demonstration of treatment efficacy only therapeutic equivalence compared to alternative treatment need be demonstrated or, in the case of no currently available treatment, superiority to placebo. Thus, there are few data available from pre-market studies on which to base therapeutic decisions in clinical practice regarding the merits of one treatment over another.

Pharmaceutical manufacturers necessarily have a stake in demonstrating the best efficacy and safety profile possible. Therefore, the chosen comparator in pre-market RCT may not reflect the best alternative treatment available in the most appropriate dosage regimen. In addition, these comparisons are carried out using a highly select group of motivated, relatively healthy patients, under highly controlled circumstances, overseen by similarly motivated physicians/researchers. Results obtained in these ideal circumstances may not mirror those observed in everyday practice. For example, Andrade *et al.* reported rates of discontinuation of antihyperlipidemics in everyday practice which were significantly higher than those observed in RCT (14). Thus, benefits observed in RCT represent the optimum benefit which may be derived from a treatment; referred to as treatment *efficacy*. Furthermore, pre-market studies are necessarily of limited duration,

resulting in little data on the consequences of long term use and a focus on short-term outcomes rather than long-term benefits of therapy. At point of market approval, pharmaceuticals have been tested in a limited number of select patients, and duration of treatment is similarly limited. It has been suggested that adverse events occurring in less than 1 in 1000 patients are not characterized prior to market approval (15). In addition, the ability to predict long-term consequences of drug treatment, both adverse and beneficial, are poor due to the necessarily limited duration of testing. Estimations of adverse events are likely to be low, given the tendency to exclude patients more likely to experience adverse events (elderly, those with co-morbid illness and concomitant medications). Thus, information regarding adverse effects, drug-drug and drug-food interactions, and drug effectiveness is limited at time of drug approval and marketing.

Once marketed, drugs become used by a much more heterogeneous population of patients and physicians than in pre-market studies. In addition, these drugs may be used in indications for which they were never approved, either intentionally through "off-label" use, or unintentionally through lessened precision in diagnosis, since diagnostic technologies used during clinical trials may not be routinely available in everyday practice. The benefit derived from a treatment when used under conditions of everyday practice is referred to as treatment *effectiveness*.

The difference between the efficacy and effectiveness of a drug is related to the conditions of treatment. Treatment conditions encompass such patient, physician, and environmental concerns as: acceptability of treatment and related compliance, presence of co-morbid conditions, use of concomitant medications, diagnostic abilities, and cost of therapy. Thus, pre-market studies leave unanswered questions regarding both a drug's

safety and effectiveness. In Canada, official mechanisms exist for continued monitoring of drug safety. Post market surveillance of adverse drug events is coordinated in Canada by the Canadian Adverse Drug Reaction Monitoring Program, and is accomplished through spontaneous reporting by healthcare practitioners, the public, and drug manufacturers. Recently, small numbers of reports of rare adverse events resulted in discontinued and curtailed use of grepafloxacin and trovafloxacin respectively. Unfortunately, no official mechanisms exist to ensure a drug, once marketed, is used appropriately and demonstrates effectiveness and efficiency relative to alternate therapies. This situation is not confined to Canada. In the US, researchers, citing the difficulty in having such research funded, have called for a shared responsibility between the public and private sectors to collect information on drug effectiveness (16).

Effective drug use by a population has many components. The first concerns whether a drug, or class of drugs, is being used in indications for which it is known to be efficacious. For example, it is commonly accepted that antibiotics are often prescribed for conditions of largely viral etiology (2, 17-20). Such use would constitute an ineffective use of these agents. Monitoring patterns of drug utilization, especially those drug classes with high usage or high cost, may provide insight as to where to focus further research efforts. Secondly, an examination of general effectiveness is needed; that is, an examination of the extent to which a drug is producing desirable outcomes in everyday clinical practice. Such studies should include a wider range of patients than those in pre-market studies to facilitate the examination of patient and disease factors that may modify effectiveness. In addition, studies of comparative effectiveness between treatment modalities are required. Drugs whose equivalent efficacy has been demonstrated in RCT

may exhibit differences in effectiveness when used in everyday practice. When considerable cost differences exist between treatments, the idea of efficiency of drug use, or cost effectiveness, is raised. Without data on comparative effectiveness, healthcare decisions may be made arbitrarily based on cost, irrespective of improved outcome (21, 22). Finally, equity of the distribution of the drug therapy may be considered, that is, are all persons eligible to receive the drug, able to receive the drug. The ability of all persons in a population to receive a drug may relate to access to pharmaceutical services from a geographic perspective or to economic determinants. New or costly therapies are often de-listed from drug payment plans creating a situation of unequal access through differential ability to pay. Examining all these facets of effective drug use at the population level will ensure inclusion of a wide range of patient types, and will facilitate the study of subject specific variables which may affect average effectiveness.

Since effectiveness is defined as the benefit of treatment in everyday practice, it follows that a determination of drug effectiveness requires observation of everyday practice. Observational studies of drug use have derived study methodologies from the field of epidemiology. Cross-sectional studies are appropriate for determining the burden of illness, associated patterns of drug utilization, and the equity of drug distribution. Case-control and cohort studies are appropriate for examining the association between treatment and outcome. Case-control studies are best used to study adverse effects of drugs while cohort studies may be used to study beneficial drug effects. Both prospective and retrospective designs may be used.

While population based observational studies of drug effectiveness are expected to have increased external validity compared to RCT, such studies are prone to bias and

confounding. The extent to which these factors operate will be determined by study design, the type of research question, and data sources. Particularly troublesome in observational studies of comparative effectiveness is confounding by indication, due to the lack of randomization to treatment. Confounding by indication results when treatments are either more or less likely to be employed over an alternate therapy, based on factors related to the clinical status of the patient. On the assumption that these factors may be quantifiable, they may be controlled for in the analysis through the use of stratification, or multiple regression utilizing propensity scores or co-morbidity indices. Unfortunately, even if such factors are quantifiable such data may not be available, depending on the data source. In addition, some determinants of treatment allocation, such as a decisions based on a physician's clinical experience, may not be quantifiable. A variety of data sources may be utilized for studies of drug use and drug effectiveness; all exert their own particular limitations. These sources include: surveys, medical records and healthcare claims. The drug and/or disease state under investigation will dictate the type of data required, which in turn may dictate the data source utilized. Following is a description of the benefits and limitations inherent in these data sources.

2.1.1 Data Sources for Effectiveness Studies

Although a more obtrusive method of data collection than review of medical records or healthcare claims, surveys may yield data not available by other means. Surveys may take the form of personal interview, or mailed or administered questionnaires. Mailed questionnaires can be an efficient means of collecting data from a large number of patients or providers for a variety of observational studies. Such surveys may be

prospective or retrospective and may be used to identify and/or quantify subjects with the condition, treatment, or outcome of interest.

Physician surveys are commonly used to determine physician practice patterns. In the US, office based physicians are surveyed routinely as part of the National Ambulatory Medical Care Surveys (NAMCS). These surveys, based on a national probability sample, record details of actual patient/physician encounters for pre-determined periods of time. Results of such surveys may provide information regarding where to focus further research efforts. For example, data may be used to estimate the burden of illness. Disease states which exert a high demand on the healthcare system may be targeted for further research, to determine the effectiveness of current treatment. Alternatively, examining physician prescribing patterns may provide the impetus for further research. This may include identifying agents or classes of agents with rapidly changing patterns of use, high usage, high cost, or which appear to be used unnecessarily or inappropriately. Thus, whether drugs are being utilized for indications in which they are known to be efficacious may be determined. Several researchers have used the NAMCS to document inappropriate use of antibiotics; specifically the use of antibiotics for infections of viral etiology (2, 18). Aparasu *et al.* used data from the NAMCS to estimate the prevalence of inappropriate prescribing of psychotropic medications in an elderly population (23). While the NAMCS reflect actual treatment decisions, other survey methodologies have been used to describe physicians' prescribing patterns. Commonly, these physician surveys describe a hypothetical situation and request that physicians describe their likely treatment approach. The first approach describes what physicians actually do, while the

latter describes what physicians say they would do. The latter method has also been used to document the inappropriate use of antibiotics (17, 19, 20).

Patient surveys may also be useful data sources for studies of the association between treatment and outcome. This may include identification of subjects with the condition of interest. Robinson *et al.* compared patient survey data to administrative data regarding the existence of several health conditions (24). Agreement was high between the two sources of data for chronic conditions such as diabetes and hypertension, however, there was less agreement for episodic conditions such as previous myocardial infarction and stroke. The researchers indicated that this was likely due to the limited time frame of administrative data available. Heliovaara *et al.* compared self-reported disease from patient surveys to the results of a health examination (25). Agreement was highest for diabetes and hypertension and lowest for respiratory, musculoskeletal and mental disorders. The authors cited the episodic nature of musculoskeletal and respiratory illnesses, and the social stigma surrounding mental illness, as possible reasons for the underreporting by patients of these conditions. The authors of both studies indicated that the nature of the condition and the research question posed will dictate the method for identifying subjects with the condition of interest.

For examinations of treatment outcomes, patient surveys may be particularly beneficial in determining subjective treatment outcomes. Outcomes such as functional status and related quality of life may be of foremost concern to patients, and thus, patient reports are excellent sources of such data. A variety of surveys of overall health are available for this purpose; for example, the Sickness Impact Profile and the Medical Outcome Study Short Form (26, 27).

Although patient and/or provider surveys may be used to efficiently gather data related to both treatment and outcome, selection and information biases may make them poor choices in some instances. In all surveys the potential for selection bias due to self-selection by the respondents exists. For example, physicians who most feel there is literature support for their treatment decisions may be more likely to volunteer information regarding their own treatment decisions. There is generally no way to determine how non-respondents differ from respondents with respect to the question of interest. Characterization of respondents, with a concomitant decrease in the generalizability of results may be necessary. Similarly, results of patient surveys are influenced by those who choose to respond to them (28). Unsolicited mailings received by patients may result in poor response rates. In addition, differences in comprehension and literacy levels exist which may influence the demographics of respondents and thus the generalizability of results (28). Long surveys may be felt to be particularly burdensome to some, enhancing selection bias. In addition, information bias related to disease state or drug exposure may lead to misclassification of study subjects. Information regarding disease states gathered from patients is naturally limited by information provided to them by caregivers. In addition, surveys which attempt to elicit retrospective data related to drug exposure or disease states may be open to information bias, due to poor recall. The importance of recall bias in a study may be dependent on many factors, such as: time since event (disease or drug use), drug class under study, and the length of time a drug was used (29). In addition, the obtrusive nature of data collection may result in a possible Hawthorne effect (13).

Review of medical records, for drug use or disease of interest, may be a very labour intensive method of subject identification, especially in large studies. However, they may be used as a source of additional data subsequent to subject identification by survey or healthcare claims review. Medical records contain a wealth of clinical data relevant to the study of treatment effectiveness, which may not be available from other sources, such as physiological measurements and diagnostic test results. In addition medical records have been used to validate data derived from patient surveys and/or healthcare claims (24, 30, 31). In this way misclassification, which might be expected due to poor recall or coding errors, may be minimized. However, several researchers have documented missing data related to disease state, drug use, and treatment outcome in medical records. In a comparison of medical claims to pharmacy claims data, West *et al.* indicated 11% of medical records in a Health Maintenance Organization (HMO) lacked documentation of non-steroidal anti-inflammatory drug (NSAID) use (32). Similarly, in a comparison of pharmacy records with out-patient clinic records, 26% of drugs dispensed in pharmacies had no corresponding documentation in the medical record (33). Liesenfeld *et al.* examined the completeness of medical charts for diabetic patients and reported a lack of data related to diabetes control in 8% of insulin dependent diabetics and 26.4% of non-insulin diabetics (34). Burns *et al.* reported a lack of documentation in hospital medical records of functional status (35).

For population-based studies, the review of large numbers of patient charts can be labour intensive and costly. In addition, access to patient charts is not always feasible. Complete review of patient charts may be an achievable goal for researchers working within the confines of a hospital or HMO, however, accessing medical records in general

private practice may prove difficult. As with survey data, differential access to patient charts, based on patient and/or physician consent, may introduce considerable selection bias.

In recent years there has been a growing interest in utilizing administrative databases for healthcare research, due to their availability and ability to capture healthcare utilization for large numbers of people at relatively low cost. Administrative databases contain data collected primarily for purposes of monitoring utilization and payment of providers. The ability to use patient identifiers to link to other data sources, thus increasing the knowledge of subject characteristics, makes such databases powerful research tools. Possible sources of administrative data for health service research include: disease registries, departments of vital statistics, US Medicaid data, Health Maintenance Organizations (HMO), and Canadian provincial Ministries of Health. Studies of the burden of disease, descriptions of patterns of care, and the assessment of treatment effectiveness have been undertaken using data derived from such sources (36-41).

The use of administrative data has many advantages. The scope of this previously collected data allows researchers to examine large cohorts of individuals, attaining sufficient statistical power at relatively low cost. The longitudinal nature of the data allows the results of retrospective follow-up studies to be available in a timely manner. In addition, large numbers of subjects may be screened to identify those with rare exposures or disease states (42). Furthermore, the use of administrative data avoids many of the selection and information biases, which plague more traditional observational studies (43). For example, access to complete records of all persons utilizing health services eliminates self-selection by study subjects. However, it must be recognized, that all

persons with the condition of interest may not seek, or may be unable to access, health services. Recall bias, especially in long term follow-up studies is minimized through the use of healthcare claims and Hawthorne effects are eliminated through the non-intrusive examination of healthcare claims (43).

Limitations of healthcare databases present unique challenges to researchers. These limitations may vary in importance depending on the patient population from which the data was gathered, and upon the research question to be answered. Commonly recognized limitations include: the scope of the database, the lack of researcher control over data collection, and the unknown reliability and validity of available data (42).

Limitations in "scope" may refer to the ability to reliably identify individual subjects, the size and type of patient population from which the data are collected, and the type and extent of data collected. To be able to construct personal healthcare histories, within and between databases, unique patient identifiers are required for all persons eligible for coverage. Databases lacking unique patient identifiers may construct probabilistic matching of records based on several patient variables such as date of birth, first name, and family identifiers. The patient population eligible for coverage is an important consideration with regard to the external validity of study results. Bright *et al.* reported that US Medicaid data does not represent a typical cross-section of Americans, as approximately 70% of Medicaid recipients were eligible through enrollment in welfare programs, and the reminder eligible due to disability or age over 65 years (44). In addition, most of the healthcare utilization was by those over 65 years of age (37%) and the disabled (35%), while younger, healthier claimants accounted for only 26% of claims (44). Medicaid records include a number of healthcare services (hospitalization,

outpatient physician visits, and pharmaceuticals), however, due to the non-representative nature of the population, generalization of study results to the US population should be undertaken with caution (44, 45). Health Maintenance Organizations (HMO) in the US, such as Kaiser Permanente and the Group Health Cooperative of Puget Sound also maintain healthcare databases. However, the clientele served by these organizations also may not be representative of the general U.S. population.

In Canada, universal health care is provided. Provincial Ministries of Health are responsible for administering healthcare payment programs and maintaining records of healthcare utilization, such as physician and hospital care. However, differences exist between provinces with regard to coverage of pharmaceutical costs and recording of pharmaceutical usage. Miller reported that 9 out of 10 Canadian provinces maintained pharmaceutical databases (46). However, only two provinces (Manitoba and Saskatchewan) recorded claims for pharmaceuticals for the total population. The remainder of the provinces recorded pharmaceutical use only for subsets of the population, such as the elderly or those on social assistance. Both Manitoba and Saskatchewan have the capability to link physician, hospital, pharmaceutical, vital statistic, and cancer and psychiatric registry data, using unique patient identifiers. Thus, the potential for healthcare research utilizing these data sources is great. However, despite the extent of healthcare information available for the population of these two provinces, certain elements of healthcare are still unavailable. Lifestyle choices (e.g., tobacco/ alcohol use, diet/exercise) and family history, that may have a large impact on health, are not captured in the databases. In addition, clinical data, which may be required

to determine severity of illness or extent of treatment response, is lacking in most available healthcare databases.

Use of administrative data is constrained by concerns of data quality. The quality of administrative data is commonly assessed by an estimation of its reliability and/or validity. Reliability refers to the reproducibility of data. That is, do two or more sources agree on the true value of a variable. Roos *et al.* suggested that, "using several independent sources of information is basic for reliability studies" (47). Validity is considered to be a measure of how well the data reflect the "truth". For example: (i) does a subject with a claim for a physician visit with a diagnosis code for diabetes really have the disease in question? (ii) did a subject with a claim for 21 amoxicillin capsules really receive this drug, in this amount, on the day in question? Validity of data may be assessed by the same method as reliability; by comparing two sources of data. However, in this case the comparator data is considered to reflect the truth; it acts as a gold standard. The choice of what constitutes the truth may be somewhat arbitrary, and as such, whether the reliability or validity of data in a database is being evaluated is open to debate. Alternate sources of data, which have been used to assess the reliability and validity of administrative data, include patient charts (both hospital and out-patient clinic), self-reports, prospectively collected clinical data, and enrollment in a disease specific education program (30, 48-50). As previously indicated, administrative data have even served as the gold standard in studies designed to examine the validity of self reports (24, 30, 31).

The reliability and/or validity of variables within a dataset may vary by variable type. Roos *et al.* indicated that the highest degree of reliability is expected for variables that are

unambiguous and least likely to be affected by professional disagreement (47). Demographic data have been shown to be more reliable than diagnostic or procedural data. For example, in an assessment of the reliability of data contained in the Manitoba Mental Health Medical Information System (MHMIS), Robinson and Tataryn compared three types of data contained in the database (demographic, diagnostic, and date specific), to information recorded in patient charts (51). Demographic data were the most reliable, with gender and date of birth concordant in 100% and 83.6% of cases respectively. The reliability of diagnostic data was less, and varied depending on whether truncated diagnostic codes were used. Diagnostic data was concordant in 76.4% and 82.9% of cases using five and three digit ICD-9-CM[a] codes respectively. Date specific data such as the opening and closing of psychiatric case files, were concordant in 67.1% and 68.9% of cases respectively. In a comparison of data contained in the Saskatchewan Hospital Separation Database (SHSD) and patient charts, Tennis *et al.* reported discharge dates were concordant in 94.2% while diagnostic data (rheumatoid arthritis) was concordant in 83.3% of cases (30).

Studies using patient charts to determine the validity of diagnostic codes on administrative claims may rely solely on physicians' notation of disease status within the chart, or may use more rigorous criteria, such as that used by Tennis *et al.* to validate the diagnosis of rheumatoid arthritis in the SHSD (30). Hospital charts with a discharge diagnosis of rheumatoid arthritis were examined and the validity of the diagnosis was

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[a] The International Classification of Disease 9th revision Clinical Modification (ICD-9-CM) codes are commonly used in administrative data to describe diagnoses. These codes may be recorded to the five digits (which offer the most precise description of a diagnosis) or may be truncated at three or four digits (less precise descriptions of diagnoses).

assessed by determining if each subject met the American Rheumatism Association (ARA) criteria for rheumatoid arthritis (RA). Documentation of five or more of the ARA criteria in a subject's chart was taken as evidence of true RA. Using this method, the agreement between hospital charts and the SHSD was low, with only 50.7% agreement. The lack of agreement was thought to be due to poor documentation in hospital charts.

For studies using diagnostic information to construct study cohorts, the reliability and validity of diagnostic codes are of particular importance. Diagnosis codes truncated at three digits have been shown to be more reliable than those recorded to four or five digits (51, 52). Commonly, physician claims for out-patient visits allow for submission of only one diagnosis code, while claims for hospitalization allow for the submission of many. Hospital codes are commonly sequenced by degree of importance to that particular episode of hospitalization. Understanding the limitations of the ICD-9-CM system of classification and the methods used to record diagnoses in the database is important in the construction of study cohorts.

Validity of diagnostic data may be compromised by coding errors in the database (52). This miscoding may be due to unintentional random error, incomplete coding or over-coding (52). Unintentional random error may be due to keypunch errors, misinterpretation of physicians' notes by medical records personnel, or mis-sequencing of multiple codes into hospital discharge databases. Mis-sequencing may not be problematic when the objective is to identify all subjects with a particular disease state. However, mis-sequencing of codes will create problems when the study requires information regarding the reason for admission. Incomplete coding may be a result of limited space or a desire to maintain patient confidentiality. Patients may present to

physicians' offices with more than one complaint, yet only one diagnosis may be submitted as the reason for the visit. Thus, diagnostic codes for chronic conditions may cease to be submitted in favour of more recent complaints. This may cause problems in studies where the objective is to determine the burden of illness. This practice may be expected to limit case ascertainment for chronic conditions (e.g., diabetes or hypertension) when the study period is of short duration. Hospital claims databases commonly allow for submission of multiple diagnoses. However, even this extended capability may not completely eliminate under-coding. This point was highlighted in a study by Iezzoni, who found a lower death rate among diabetic patients compared to non-diabetics (53). This counterintuitive finding was explained by the tendency to record only the most severe conditions for hospitalized patients.

For hospitalized patients it may not be possible to distinguish which conditions were present at admission (co-morbidities) and which conditions arose in hospital (complications) (52). For example, infections are a common complication of hospitalization, yet it may be unclear from a hospital claim whether a code for pneumonia indicated a reason for admission, or a complication of hospitalization. In addition, more than one code may be used to describe the same condition. For example, Motheral and Fairman suggested visits for subjects presenting with angina might be coded based on symptoms, manifestations or pathophysiology as chest pain, ischemic heart disease, or coronary artery disease (42). In addition, non-specific disease codes exist, which make discerning actual disease states problematic. For example, the ICD-9-CM code 599.0 (urinary tract infection-site not specified) may be used, rather than the more specific 595.0 (cystitis) or 590.0 (acute pyelonephritis). Over-coding may result when the

submission of a disease code for a hospitalization or physician visit occurs, when the result of the visit was to rule out the condition of interest. The possibility of over-coding due to incentives for reimbursement has also been suggested (52).

Due to the many factors which may influence the presence or absence of diagnostic codes in healthcare databases, and the construction of cohorts resulting from their use, validation of this data is suggested. As noted earlier, comparisons with independent data sources, such as patient charts and survey data, may be used to validate administrative data. However, Romano and Luft noted that many researchers can not obtain primary data, as physicians and hospitals may not allow access to patient charts for research purposes (52). This problem is likely to become more acute with increasing regulation regarding patient confidentiality. Several authors have offered alternate methods for validation of diagnoses, such as examining additional administrative data for the existence and time sequencing of associated treatments, (e.g., surgical procedures and pharmaceutical use) (47, 52). However, procedural or pharmaceutical treatments should preferably have only one indication, and consideration should be given to possible "off label" use of pharmaceuticals. Thus, the presence of diagnosis codes in combination with claims for appropriate drug treatments may provide researchers with assurance regarding the validity of diagnostic codes. However, this method may result in underestimation of the burden of illness, since not all persons with illness receive pharmaceutical treatment. For example, conditions such as hypertension, diabetes and hyperlipidemia may be managed by diet and exercise alone. Patients with ischemic heart disease may rely on medications purchased without prescription (e.g., nitroglycerin) that may not be captured

by pharmaceutical databases. Study objectives will necessarily determine the methods used to validate data.

Each data source has its own particular strengths and limitations. As previously indicated, the research question will necessarily dictate the data required, which will suggest the appropriate data source. Macklan *et al.* indicated that limitations inherent in each data source may be addressed by the use of complimentary sources of data (54). The following section examines how the research question, and associated outcome of interest, influenced the choice of data sources in earlier studies. Treatment effectiveness, or treatment outcome, was assessed in a variety of ways, which influenced the data source utilized.

2.1.2 Examining Treatment Outcomes

Health outcomes have been described in the negative context of the 5 D's (death, disease, disability, discomfort and dissatisfaction) however, Lohr defined outcomes more positively as, "the end result of treatment in terms of palliation, control of illness, cure, or rehabilitation" (55). Added to this list may be the prevention of illness. Observational studies provide an opportunity to examine a wider range of outcomes than may practically be studied in pre-market RCT. For example, knowledge of treatment outcome may be expanded from such short-term clinical or physiologic endpoints as symptomatic relief and changes in physiological measurements to long term quality of life measures and changes in subsequent healthcare utilization. The specific outcome examined is necessarily dictated by the drug-disease under study, however, the range of outcomes which may be examined is large.

Kozma *et al.* developed the Economic, Clinical and Humanistic Outcomes (ECHO) model to aid in the planning of studies of treatment effectiveness (56). As stated by Kozma *et al.* "The ECHO model should assist health services researchers in planning, conducting and evaluating pharmaceutical products and services from a multidimensional perspective." It stresses the importance of three distinct classes of treatment outcomes: clinical, economic and humanistic. Clinical outcomes are defined as medical events which occur as a result of treatment. Clinical outcomes may include mortality, emergency room (ER) visits, or hospitalizations. However, clinical indicators of patients' physical status such as blood glucose or serum lipids may be used as surrogates for clinical outcomes. Humanistic outcomes include functional status and quality of life, while economic outcomes include costs per successful outcome or utility measures, such as cost per quality adjusted life year. Kozma *et al.* stress consideration of all outcomes when evaluating treatments, yet recognize that the weight of importance attached to each type of outcome will depend on the drug and/or disease under study, and the perspective of the person asking the question. Similarly, Mullin *et al.* suggested that in determining the outcome to be examined, the outcome endpoint must be justifiable, and noted that the drug and/or disease state under study will naturally suggest useful outcomes (57). For example, Mullin *et al.* suggested that the study of a humanistic outcome, such as quality of life, has limited usefulness in acute conditions, such as infectious diseases, for which highly efficacious therapies exist.

When examining outcomes of the treatment of infectious diseases, cure is a desirable and expected outcome. Since symptoms of infectious disease are presumed to prompt patients to seek treatment, cure may be further assumed if patients do not subsequently

return for further treatment. Thus, healthcare claims may be used to indirectly identify successful treatment outcome. That is, a lack of further healthcare claims may indicate successful treatment. For example, Berman *et al.* examined outcomes of children treated for otitis media (39). Data source used was the Colorado Medicaid claims database. The study cohort was defined based on the existence of a claim for a physician visit for otitis media (based on ICD-9-CM codes) and receipt of an antibiotic within 48 hours of physician visit. Successful treatment outcome was defined as a lack of claims for additional antibiotic treatment within 24 days after initial antibiotic treatment. Similarly, MacDonald *et al.* examined treatment outcomes of subjects receiving a prescription for any antibiotic as recorded by the Medicines Monitoring Unit in Dundee, Scotland (58). As indication for treatment was unavailable in the database, after identifying subjects based on receipt of an antibiotic, medical records were examined to identify the specific indication for treatment. Successful treatment outcome was defined as no subsequent record of receipt of an antibiotic within 30 days of initial treatment, unless prescribed for an alternate indication. In the above studies no attempt was made to control for confounding by indication through an assessment of severity of illness.

Froom *et al.* utilized survey data to compare antibiotic treatment to no treatment for acute otitis media (59). Physicians from nine countries were asked to record data on up to 15 consecutive episodes of otitis media, to determine the effect of antibiotic treatment on infection resolution. The initial survey requested such patient demographics and clinical data as age, symptoms, tympanic membrane findings, and history of recurrent otitis media. Patient survey was used to determine treatment outcome. Two months after initial treatment the parents of the young patients were surveyed to determine if the episode has

resolved (yes, no, or uncertain). Although data which may have been used to control for confounding by indication (severity) was gathered from physicians, none of these variables was used in the analysis.

In chronic conditions for which there is no cure, and for which the purpose of treatment is to prolong life, mortality may be the primary outcome of interest. However, since death is a relatively rare event, large numbers of patients, or long follow-up periods may be required. In addition, studies may preferentially include patients most likely to experience the outcome of interest. For example, Gambassi compared the effectiveness of angiotensin converting enzyme (ACE) inhibitors and digoxin in preventing mortality, in the very old with heart failure (60). The outcomes of approximately 20,000 eligible residents of long term care facilities in five states in the US were examined. Data sources were the Medicaid and the Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) databases. Data related to mortality and drug exposure were elicited from the Medicaid database. The SAGE database contains clinical data such as, symptoms, functional status, and cognition. Clinical data derived from the SAGE database, in addition to data related to the existence of other disease states and concomitant drug use, was used to control for confounding by indication (severity). Krumholz *et al.* examined the effectiveness of ASA in preventing early mortality following a myocardial infarction in approximately 10,000 patients in four US states (61). Subjects who were recently hospitalized subsequent to a myocardial infarction (MI) were identified from Medicaid claims data. Outcome of interest (30 day mortality) was also obtained from Medicaid records. However, drug exposure, patient demographics and data related to confounding variables (history of heart failure, presence of chest pain, duration

of symptoms, laboratory results) were abstracted from hospital medical records. Data on confounding variables collected from medical records may be used to control for confounding by severity.

Chronic conditions for which there is no cure, and for which mortality is rare, require alternate outcomes relevant to the drug and/or disease of interest. For disease states in which symptoms of disease result in healthcare utilization, the utilization of healthcare services, has been used as a measure of treatment effectiveness. Healthcare claims databases provide an efficient means to measure this treatment outcome. In a study of the use of inhaled corticosteroids for the treatment of asthma, Blais *et al.* examined their effectiveness in preventing hospital readmissions (38). The healthcare claims database of Saskatchewan, Canada was used to identify the cohort of interest, and determine exposure status and outcome. In addition, severity of illness was assessed using data available from the database (e.g., use of other anti-asthma medications, number of previous hospitalizations). Utilization of healthcare services has also been used to assess the effectiveness of several agents in the treatment of gastro-oesophageal reflux disease (GORD) (41). Eggleston *et al.* used the Mediplus UK database to determine exposure status and to quantify the use of healthcare services within six months of being treated for an initial episode of GORD (41). No attempt was made to control for the severity of illness. However, only those subjects with a first episode of GORD were eligible, thus the possibility of more aggressive treatment for those with recurrent disease was not a factor in this study.

Studies of disease states in which death is a relatively rare event, and physical symptoms and the seeking of healthcare services may not be used as a measure of

treatment success, may utilize relevant physiologic markers as outcome measures. O'Connor identified a cohort of subjects receiving niacin or lovastatin for treatment of dyslipidemia from a HMO claims database (62). Medical records were then abstracted to identify outcome (serum lipid levels) in addition to confounding variables (age, gender, cardiovascular risk factors, diabetes, smoking history), in order to compare the effectiveness of these two treatments. Similarly, Beggs *et al.* identified a cohort of subjects receiving one of three antihyperlipidemics from a prescription database in New Zealand (63). A random sample of the cohort was selected and a survey was then sent to each subject's treating physician requesting relevant data. Data requested included the outcome of interest (lipid levels), in addition to data related to possible confounders (duration of therapy, dose, cardiac risk factors, diabetes, smoking history). In both of these studies, possible bias existed, since only a fraction of subjects identified had follow-up lipid levels recorded in the medical records.

In summary, there is a need to monitor many components of effective drug use. This may include studies of indications for use, associated treatment outcomes, and comparative outcomes between agents or classes of agents. Research efforts should naturally focus on drug classes which exhibit high usage and/or high cost. The exact research question posed will suggest appropriate methodologies and data sources. Antibiotics were chosen as the subject of the current study due to their frequent use in community practice (2, 3). In addition, the effectiveness of antibiotics is particularly interesting given the evolving nature of bacterial susceptibilities. Antibiotic resistance can be expected to change the relative effectiveness of antibiotics over time. For this reason, continuous monitoring of antibiotic effectiveness will be required. The following

section describes current knowledge regarding the use of antibiotics in community practice.

2.2 Antibiotic Use in Community Practice

In institutions, intravenous antibiotics account for a large proportion of the drug budget; in North America this figure is commonly between 20 and 30% (64-68). Concerns of increasing antibiotic resistance among nosocomial pathogens, coupled with evidence of inappropriate antibiotic use, has prompted surveillance and the development of control mechanisms in the institutional setting (69-74).

In the community, courses of therapy are less costly due to the use of oral agents, yet, considerable antibiotic use occurs in this setting. Antibiotics are frequently reported to be the second or third most commonly prescribed class of agents in community practice; accounting for a significant proportion of drug costs (2, 3). Again, evidence of increasing antibiotic resistance among community-acquired pathogens (5, 6, 8, 75) and suggestions of inappropriate antibiotic use (65, 76) have prompted efforts to curtail antibiotic use in this setting. However, to optimize antibiotic use in community practice requires an understanding of current antibiotic usage patterns (including quantity, indication, and appropriateness of use), as well as patterns of antibiotic resistance which may be affecting use.

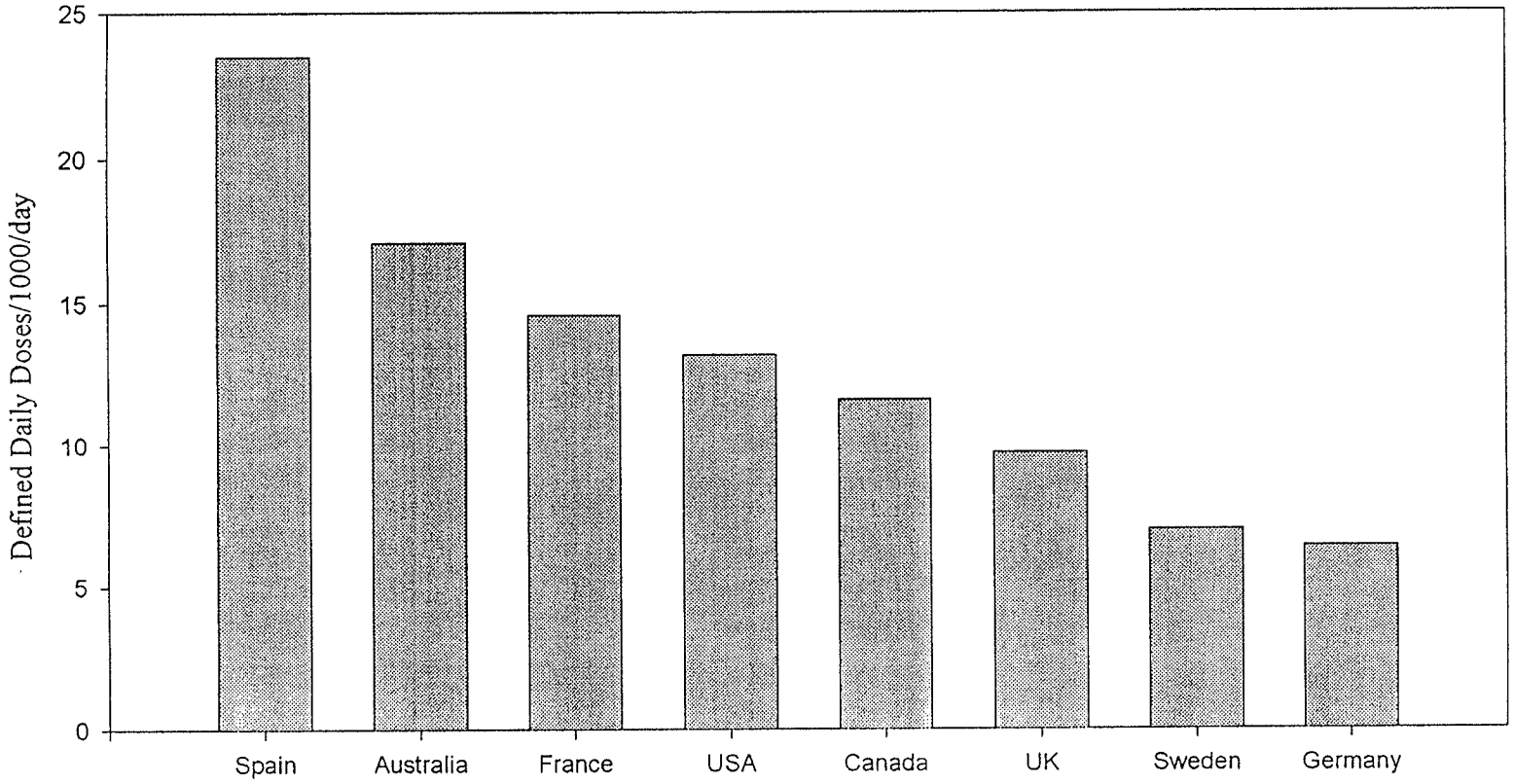
2.2.1 Quantifying Antibiotic Use

In 1983, a worldwide study of antibiotic use was commissioned by the Fogarty International Centre of the USA National Institutes of Health (NIH) (77). In order to quantify antibiotic use by country, data were gathered from many sources; market research companies, ministries of health, pharmaceutical manufacturers, and the World Health Organization. The data generated was categorized by source, as production and trade, or sales data. In developing countries, reliable sales data were not available, thus, production and trade figures were used to estimate antibiotic use. A more reliable measure of actual use are sales data, however, information on sales was only available in the more developed countries. Antibiotic usage in eight countries is shown in Figure 1, reported as defined daily dosage per 1000 persons per day (DDD/1000/day). The DDD is a technical unit of measurement defined by the World Health Organization as the usual adult daily dosage for the major indication for a specific agent (78).

In 1983, Spain and Australia were the highest users of antibiotics, at 23.5 and 17.1 DDD/1000/day respectively, while Sweden and Germany were relatively conservative users at 7.0 and 6.4 respectively (Figure 1). Canada and the USA were moderate users of antibiotics at 11.6 and 13.2 DDD/1000/day respectively. For the countries presented, more broad spectrum agents were used (e.g., cephalosporins, tetracyclines, aminopenicillins and trimethoprim-sulfamethoxazole) than narrow spectrum agents, (e.g., penicillin G, and erythromycin), however, the extent to which they favoured broad spectrum agents varied considerably. Germany, although the lowest overall consumer of antibiotics had the highest ratio of broad to narrow spectrum agents; conversely, Sweden also a country with relatively low antibiotic consumption had the lowest ratio of broad to

narrow spectrum use. The ratio of broad/narrow spectrum agents in Canada and the US was intermediate.

Figure 1. **Antibiotic use in eight countries; 1983**



Wyatt *et al.* (3) analyzed community consumption of oral antibiotics in Northern Ireland from 1983 to 1987. Data were gathered from the Central Services Agency in Northern Ireland, which records the number of doses for each drug dispensed by pharmacists or physicians. Annual prescription volume did not change appreciably over the five years; remaining fairly constant at approximately two million per annum. Broad spectrum penicillins (amoxicillin and ampicillin), trimethoprim-sulfamethoxazole, penicillin V, and erythromycin accounted for 70% of antibiotic use as measured by the number of dosing units dispensed per year. A dosing unit was defined as a single recommended adult dose for an agent. While total antibiotic consumption remained static, changes in the consumption of individual agents was observed. For example, ampicillin use decreased possibly in favour of amoxicillin, while TMP-SMX use decreased possibly in favour of trimethoprim alone, whose use increased almost 140% over 5 years. Further, oxytetracycline use decreased by approximately 20% while minocycline and doxycycline use increased by approximately 80% and 130% respectively. There was a noticeable trend toward increased use of newer or broad spectrum agents such as, amoxicillin-clavulanic acid, tetracyclines and various cephalosporins; many of which doubled in use over the five-year study.

In 1993 as part of a study of market penetration of new drugs in the United Kingdom, McGavok *et al.* (79) published usage data for cefuroxime axetil and ciprofloxacin in Northern Ireland. The Central Services Agency was once again used as the data source to quantify usage trends for these broad spectrum agents, shortly following their

introduction. Usage was not reported as a rate, but simply the number of defined daily dosages for the years 1988 to 1991. Ciprofloxacin use increased 205% (from 6,157 DDD in 1988 to 18,782 DDD in 1991) and cefuroxime use increased 210% (from 2,792 DDD in 1988 to 8,647 DDD in 1991).

McManus *et al.* (4) studied antibiotic use in community practice in Australia between 1990 and 1995 using several data sources. The database of the Drug Utilization Sub-Committee (which contained information on all government subsidized prescriptions, in addition to an estimate of non-subsidized prescriptions) was used to quantify antibiotic use. Total oral antibiotic consumption was demonstrated to be stable between 1990 (24.7 DDD/1000/day) and 1995 (24.8 DDD/1000/day), with amoxicillin (5.6), doxycycline (4.5), amoxicillin-clavulanic acid (2.9), and erythromycin (2.2) (measured as DDD/1000/day), observed to be the most commonly used agents. Over the study period the consumption of newer or broad spectrum agents (e.g., amoxicillin-clavulanic acid, cefaclor, roxithromycin) increased, while consumption of older or narrow spectrum agents (e.g., erythromycin, trimethoprim-sulfamethoxazole, amoxicillin) decreased.

Trends in oral antibiotic prescribing, among office-based physicians in the United States, were studied by McCaig and Hughes (2). Data were compiled from the National Ambulatory Medical Care Surveys (NAMCS) for the years 1980, 1985, 1989 and 1992. NAMCS are conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention and are based on a national probability sample. A select sample of these physicians was asked to supply specific data on a sample of patient visits, and as such the data reflect antibiotics prescribed rather than dispensed.

Prescribing rates were reported as the number of prescriptions per 1000 persons annually (Rx/1000/year). During the thirteen-year span, the estimated number of antibiotic prescriptions increased from 86 million in 1980 to 110 million in 1992, however, no increase in the actual prescribing rate was reported, overall or when patients were subdivided by age, race, and gender. The highest rates of antibiotic use were seen in children less than 15 years of age. Prescribing trends were tracked in terms of antibiotic class rather than individual agents in most cases. Broad spectrum penicillins (amoxicillin and ampicillin combined) were the most commonly used agents in all years studied and their use, as a class, increased over the 13-year span. However amoxicillin use increased from 50 Rx/1000/year in 1980 to 175 Rx/1000/year in 1992 while ampicillin use decreased from 55 Rx/1000/year in 1980 to 10 Rx/1000/year in 1992. Cephalosporin use increased from 30 Rx/1000/year in 1980 to 90 Rx/1000/year in 1992 becoming the second most commonly prescribed antibiotic agents, while the usage of narrow spectrum penicillins decreased from 75 Rx/1000/year in 1980 to 25 Rx/1000/year in 1992. No significant changes in prescribing rates were observed for trimethoprim-sulfamethoxazole, erythromycins or tetracyclines; approximate usage in 1992 was 25, 75 and 40 Rx/1000/year respectively.

Thus, several countries have published population based studies of antibiotic use in community practice. These studies, performed over varying time periods between 1980 and 1995, employed a variety of data collection methods and measurement systems. USA, Australia and Northern Ireland reported no increase in the rate of total antibiotic consumption. All countries reported increased consumption of newer or broad spectrum

agents (e.g., fluoroquinolones, second generation cephalosporins, roxithromycin) with a decline in the consumption of older or narrow spectrum agents (e.g., penicillin V, erythromycin, and tetracycline).

2.2.2 Indication for Antibiotic Use

Few population based studies are available describing antibiotic use by indication. McCaig and Hughes (2) reported the five leading diagnoses for which antibiotics were prescribed in community practice in the USA in 1992; five diagnoses accounted for 76% of total antibiotic prescriptions (otitis media (21%), upper respiratory tract infection (16%), bronchitis (15%), pharyngitis (12%) and sinusitis(12%)). The leading diagnoses for the prescribing of specific antibiotics included: amoxicillin (otitis media), cephalosporin (otitis media), penicillin (pharyngitis), erythromycin (bronchitis), and trimethoprim-sulfamethoxazole (otitis media).

Indications for antibiotic use in Australia were studied by McManus *et al.* using data from the Therapeutics Resource and Education Network for Doctors (TREND) database (4). The TREND database includes information on prescribed treatment from a survey of general practitioners in urban and rural New South Wales. In 1995, the most commonly prescribed agents for otitis media included, cefaclor (35.5%), amoxicillin (21%) and amoxicillin-clavulanic acid (20.5%). For bronchitis, treatment included amoxicillin (18.1%), roxithromycin (16.5%) and cefaclor (15.2%). Antibiotics prescribed for upper respiratory tract infections included amoxicillin (29.5%), cefaclor (10.2%) and amoxicillin-clavulanic acid (9.4%). Antibiotics most commonly prescribed for sinusitis

included doxycycline (20.7%), amoxicillin-clavulanic acid (18.1%) and cefaclor (15.1%).

Wang *et al.* (80) examined use of antibiotics in respiratory tract infections in children less than 5 years of age in Saskatchewan, Canada. Acute otitis media (43%), pharyngitis (17%) and acute upper respiratory tract infections (22%), were the most commonly diagnosed respiratory tract infections for which antibiotics were prescribed, in this patient population. Penicillins were the most commonly prescribed agents in all three of these diagnostic categories.

The available evidence would indicate that the majority of antibiotic use in community practice is for the treatment of respiratory tract infections, however, antibiotic usage, by diagnosis, varies by geographic location. In Australia, broad spectrum agents (e.g., cefaclor, amoxicillin-clavulanic acid) were commonly employed in the treatment of respiratory tract infections (4).

2.2.3 Appropriateness of Use

Addressing the appropriateness of antibiotic use within a country or region is perhaps the most difficult aspect of assessing antibiotic use; likely the reason why few such studies exist. In short, appropriate use may be considered adherence to treatment principles regarding effective treatment: i.e., treatments identified as producing optimal outcomes. Antibiotic use may be termed unnecessary where no antibiotic is indicated, and inappropriate where an antibiotic is indicated but an inappropriate agent is selected. However, what constitutes unnecessary use may be open to debate. While it is generally agreed that the use of antibiotics for the common cold is unnecessary, the necessity of antibiotics for otitis media and bronchitis may be controversial (81-83).

Several recent studies describe the unnecessary use of antibiotics. In a study of Kentucky (USA) Medicaid claims from 1993 to 1994, Mainous *et al.* (84) described antibiotic use by patients diagnosed with the common cold (ICD-9-CM 460.0). Sixty percent of these patients were identified as having received a prescription for an antibiotic. Antibiotics received included: amoxicillin (54%), second and third generation cephalosporins (14%), and erythromycin (11%). Gonzales *et al.* presented data on the treatment of colds, upper respiratory tract infections and bronchitis in adults in the USA (18). Data from the 1992 National Ambulatory Medical Care Surveys were used to determine the proportion of subjects receiving antibiotics for these largely viral infections (for which antibiotic therapy would be unnecessary). The proportion of subjects receiving antibiotics for colds (ICD-9-CM 460), upper respiratory tract infections (ICD-9-CM 465) and bronchitis (ICD-9-CM 466, 490), were 51%, 52% and 66% respectively. Similar antibiotic prescribing for these indications in children were reported by Nyquist *et al.* (85). Wang *et al.* (80) reported the proportion of children less than five years of age receiving antibiotics for colds (ICD-9-CM 460), acute upper respiratory tract infections (ICD-9-CM 465) and acute bronchitis (ICD-9-CM 466) to be 18%, 49% and 65% respectively. In Australia, McManus *et al.* (4) reported the receipt of antibiotics by 57% and 73% of urban and rural subjects respectively, for new cases of upper respiratory tract infections and pharyngitis (ICD codes not provided).

A study of the management of upper respiratory tract infections in Dutch family practice provided an interesting contrast (86). Data from the National Study of Illness and Procedures of the Netherlands Institute of Primary Health Care between 1987 and 1988 were used to examine antibiotic prescribing. The proportion of subjects receiving antibiotics at first physician contact for acute otitis media, acute upper respiratory tract infection and acute tonsillitis (ICD codes not provided) were 27%, 17% and 74% respectively. Similar results were reported from a study by Froom *et al.*, in which 31.2% of patients diagnosed with acute otitis media in the Netherlands received antibiotics, compared to 98.2% and 97.9% in Australia and USA respectively (59). Thus, the unnecessary use of antibiotics in the treatment of infections of largely viral etiology was common, although international differences in prescribing practices were evident.

There remains a lack of studies that examine the extent of inappropriate antibiotic use within a population. This may be due to the difficulty in defining inappropriate use. Inappropriate antibiotic treatment may be defined as: (i) selection of an agent inactive against the most likely causative organisms, (ii) use of a broad spectrum agent when an equally effective narrow spectrum agent is available, (iii) inappropriately long or short duration of treatment, and (iv) treatment which deviates from accepted practice or published treatment guidelines. A recent study by Gleason *et al.* (87) highlighted the problem associated with using published guidelines as a measure of appropriate use. Gleason *et al.* compared outcomes in community-acquired pneumonia in patients treated, or not, in accordance with American Thoracic Society (ATS) Guidelines. This multicentre, observational, prospective, cohort study of 864 subjects from the USA and Canada, reported 82.4% of patients over 60 years of age, with one or more co-morbid

conditions, were not treated in accordance with ATS guidelines. ATS guidelines recommended treatment with a second generation cephalosporin, trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid for this patient population. There were no differences in therapeutic outcome between those treated, or not treated, in accordance with the guidelines. However, adherence to ATS guidelines resulted in a 10-fold increase in cost of treatment, as well as an increased potential for the selection of organisms resistant to these new or broad spectrum agents.

Thus, the appropriateness of antibiotic use requires further investigation. There appears to be sufficient evidence of unnecessary use in viral infections (e.g., common cold) but little information is available regarding the appropriateness of antibiotic use in other indications.

2.2.4 Antibiotic Resistance in Community Practice

Antibiotic resistance presents a problem for many reasons, including the lack of development of new agents which affect novel bacterial targets. With respiratory tract infections accounting for the majority of community antibiotic use, increasing antibiotic resistance among respiratory pathogens assumes great importance. *Streptococcus pneumoniae*, a major respiratory pathogen, became increasingly resistant to penicillin in the last decade in the US, Canada, and Spain (5, 6, 8). Penicillin-resistant strains were more likely to be isolated in children and were also more likely to exhibit cross-resistance to macrolides, cephalosporins, tetracyclines and trimethoprim-sulfamethoxazole than were penicillin sensitive strains (5, 6). Rates of penicillin resistance varied considerably between centres in both Canada and the USA (5, 6). In 1998, in Canada, 21.3% of *S.*

pneumoniae isolated from the respiratory tract were resistant to penicillin, however resistance had decreased to 16.5% by 2000 (88).

Haemophilus influenzae has become increasingly resistant to aminopenicillins (e.g., amoxicillin) through production of TEM or ROB β-lactamases. A recent study reported the proportion of β-lactamase producing *H. influenzae* in the UK, USA and Spain to be 9.7%, 27.4% and 32.2% respectively (75). *E. coli*, a major pathogen in community-acquired urinary tract infections (UTI), have become increasingly resistant to trimethoprim-sulfamethoxazole (TMP-SMX), with US data indicating that resistance to TMP-SMX among *E. coli* increased from 9.0% in 1992 to 18.0% in 1996 (7). Similarly, a Canadian study reported that 19.2% of community-acquired uropathogens in 1998 were resistant to TMP-SMX (10).

Antibiotic use is thought to be a major factor in the development of antibiotic resistance, although the exact relationship remains unclear (89). The association between antibiotic use and antibiotic resistance patterns has been well studied in the hospital setting (90-93), but less so in the community. One recent community level study, performed in Finland, examined the temporal relationship between antibiotic use and resistance to erythromycin from the late 1980s to 1990s (94). Increased erythromycin resistance among group A streptococci (from 5% in 1988 to 13% in 1990), was demonstrated to have followed steady increases in macrolide consumption throughout the 1980s. Following national recommendations in 1991 to decrease consumption of macrolides, use decreased from 2.4 DDD/1000/day in 1991 to levels of 1.3 to 1.7 DDD/1000/day between 1992 and 1995. During this time erythromycin resistance among group A streptococci continued to increase to a high of 19.0% in 1993 followed by steady

yearly decreases to a low of 8.6% in 1996. These data provide evidence of the role of antibiotic use in the development of antibiotic resistance, and further illustrate the possibility of controlling antibiotic resistance through prudent antibiotic use.

2.2.5 Need for additional studies of antibiotic use

A 1983 study by the National Institutes of Health in the U.S. (NIH) reported large international disparities in antibiotic usage with Spain and Australia described as high and Germany and Sweden as conservative users of antibiotics (77). Canada and the USA were described as relatively moderate users. It is tempting to speculate on the results of this study and identify countries such as Spain and Australia as over-users of antibiotics, while designating Germany and Sweden as responsible antibiotic users. However, it is important to note that, geography, population demographics, economic conditions, nutritional status and access to health care can all affect morbidity patterns and hence antibiotic usage patterns. The quality of antibiotic prescribing in any country cannot be determined by these international comparisons alone. Each country must determine the appropriateness of its antibiotic use and work within its constraints to optimize that use.

Subsequent to the NIH study, several other population-based studies to quantify antibiotic use and assess longitudinal changes in antibiotic selection have been published (2-4, 95). In all cases, concerns over antibiotic misuse and increasing antibiotic resistance were cited as reasons for the studies. Developed countries for which data were available (USA, Australia and Northern Ireland) have reported no increase in overall antibiotic use (22-24). However, all countries exhibited a trend toward the use of newer and/or broad spectrum agents (newer tetracyclines, cephalosporins, fluoroquinolones, and

amoxicillin-clavulanic acid) while the use of older and/or narrow spectrum agents (penicillin V, ampicillin, nitrofurantoin and TMP-SMX) declined or remained unchanged. All three countries reported changes within antibiotic classes that appeared to be increased preferences for agents with similar spectra of activity but improved pharmacokinetic and/or safety profiles. Examples of this trend include, an increased use of amoxicillin coupled with a decreased use of ampicillin, an increase in minocycline and doxycycline use coupled with a decrease in the use of oxytetracycline or tetracycline, and an increase in trimethoprim use coupled with a decrease in the use of TMP-SMX. These changes reflect reasonable therapeutic choices (i.e., improved pharmacokinetics and/or safety) and are unlikely to impact antibiotic resistance trends, although they may have economic impact. Reasons for changes between antibiotic classes may be more complex. Increasing resistance to older agents, industry advertising or promotion, and a trend toward de-institutionalized care necessitating treatment with oral broad spectrum agents may all play a part. The extent to which these or other explanations accounted for changing prescribing patterns was not determined in these studies.

Temporal effects, variability in data collection systems, and units of measurement make it difficult to compare trends in antibiotic usage between countries. The use of the NAMCS in the U.S. generated data based on prescriptions written, with no knowledge of whether the prescriptions were actually filled. Conversely, use of pharmacy claims databases in Australia and Northern Ireland measured prescriptions dispensed, thus avoiding the possible errors and biases inherent in physician surveys. In addition, choice of units of measurement may affect study conclusions. For example, use of the DDD/1000/day is sensitive to changes in prescribed dosage. A trend toward the use of

higher doses of amoxicillin and cephalexin was observed in an earlier Australian study (95), possibly in response to increasing antibiotic resistance among *S. pneumoniae.* Use of the DDD/1000/day in the above study made a significant contribution to the finding of increased use of these agents, and to a lesser extent to the finding of increased rates of antibiotic use in general, between 1987 and 1989 (95). Thus, evidence provided by McManus *et al.* (4) suggesting increasing rates of total antibiotic consumption from 1985-1994 in Canada, the USA, and other countries (based on sales to retail and hospital markets translated into DDD/1000/day), may reflect increasing daily dosages rather than an increasing number of prescriptions.

Limited data exist describing indications for, and appropriateness of, antibiotic use in community practice. McCaig and Hughes reported the majority of antibiotic use was for the treatment of respiratory tract infections, many of which are of viral etiology (2). McManus *et al.* (4) quantified antibiotic use by indication and observed respiratory tract infections were commonly treated with new or broad spectrum antibiotics (e.g., amoxicillin-clavulanic acid, cefaclor and roxithromycin). The unnecessary use of antibiotics in viral infections has been well documented (2, 4, 17-20, 84-86) and is reported to result from real or perceived patient demand coupled with physician time constraints, and the belief patients will simply seek out antibiotics elsewhere (96). Perception, by physicians and patients, of antibiotics as innocuous, and diagnostic uncertainty may also be factors. In addition, Kunin (65) has written extensively of the powerful influence of pharmaceutical companies on the use of antibiotics. The extent of unnecessary use varied widely between countries but is deserving of improved control measures globally. Use of antibiotics in the treatment of viral infections confers no

benefit and exerts unnecessary pressure for the selection of antibiotic-resistant organisms; it also increases health care costs. These health care costs may be considerable when costs of medication, increased morbidity and mortality related to adverse drug reactions and antibiotic resistance are considered (97).

The extent of inappropriate use is largely unknown and is deserving of further study. Lack of study in this area may be a result of a lack of consensus regarding what constitutes appropriate use. At the most basic level, the appropriate agent is one that cures the patient with the minimum of adverse effects and cost. This requires knowledge of: likely etiologic agents, antibiotic efficacy, resistance patterns, patient-specific variables, and costs (both costs of treatment and costs of treatment failure). In other words, appropriate antibiotic use includes many of the facets of effectiveness.

In summary, the amount and type of antibiotic consumption varied between countries, yet all countries reported increased consumption of newer and/or broad spectrum antibiotics, and a decreased consumption of older and/or narrow spectrum antibiotics. In addition, antibiotic resistance among community-acquired pathogens has increased over the last decade, with rates of resistance varying both between and within countries. The increase in the proportion of community-acquired pathogens exhibiting antibiotic resistance may be responsible for an appropriate increase in the use of new broad spectrum antibiotics. However, the extent to which these agents are being used appropriately is unknown and requires further study. Since antibiotic use may differ substantially between countries, local data are required to identify areas of concern specific to that geographic location. Thus, an examination of antibiotic prescribing

practices was undertaken in Manitoba, Canada. The following section describes changes in antibiotic use in Manitoba, Canada between 1995 and 1999.

2.2 Antibiotic Use in Community Practice in Manitoba (A pilot study)

As previously indicated, determinants of antibiotic consumption are multifactorial, and include: patient expectation, diagnostic uncertainty, antibiotic-resistant patterns, pharmaceutical company promotion and the trend toward de-institutionalized care. These and other factors, such as political determinants of delivery of health care result in unique patterns of antibiotic usage determined by geographic and political boundaries. The lack of recent Canadian data prompted an examination of antibiotic usage trends in Manitoba, Canada. It was anticipated that results of this preliminary investigation would assist in directing further research, by uncovering unique patterns of antibiotic usage, warranting further investigation.

2.3.1 Materials and Methods

Manitoba is a province in central Canada with a population of approximately 1.1 million. All Manitoba residents are eligible for drug benefits through the Pharmacare program of Manitoba Health, unless provided through an alternate provincial or federal government drug plan. In 1992, in an attempt to optimize drug (including antibiotic) use and control increasing drug costs, Manitoba Health amended their Drug Benefits Formulary (98). These amendments restricted Pharmacare reimbursement for second-line antibiotics to those instances where their use met established criteria (Appendix A). Quantification of antibiotic use was facilitated by the introduction of the Drug Programs

Information Network (DPIN) in Manitoba in July 1994. The DPIN is a computer network allowing immediate on-line billing for pharmaceuticals eligible for payment through provincial government programs. These programs include, Pharmacare (PC), Social Allowance Health Services Drug Plan (SAHSDP) and Personal Care Home Drug Plan (PCHDP). Individual prescription claims for all Manitoba residents are recorded and sorted by program (PC, SAHSDP, PCHDP). A separate file within the DPIN system (Non-adjudicated) contains details of prescriptions for persons and/or pharmaceuticals not eligible for the former three programs. Ineligible persons include those covered by the Department of Indian Affairs, Department of Veterans Affairs and City of Winnipeg Social Services. Thus the DPIN results in a prescription database that reflects drug usage for the majority of Manitoba residents. The completeness and validity of the DPIN database has been estimated (99). An examination of prescription files from a sample of Manitoba pharmacies indicated that 90.5% of prescriptions filled in these pharmacies had a corresponding prescription claim in the DPIN. Completeness was greater for the PC component, (93%) and less for the Indian Affairs/Social Services component (84.5%). Furthermore, the validity of the DPIN data was demonstrated, with 92% of prescription claims matching the original prescription by drug name, quantity dispensed, and number of days supply. The DPIN does not record details of prescriptions provided free of charge through the Sexually Transmitted Disease Control and Meningitis Prophylaxis Programs and, therefore, slight under-reporting of antibiotic use was expected.

Monthly usage data, (defined as the number of prescriptions dispensed) for each oral antibiotic, excluding antifungals, antivirals, and antitubercular agents, were extracted from the DPIN database for the period January 1, 1995 to December 31, 1999. For the

purpose of this study, antibiotic prescriptions provided to residents of personal care homes were excluded. Monthly usage data from the Pharmacare, Social Allowance Health Services Drug Plan and Non-adjudicated files were combined, and usage was calculated and reported as prescriptions per 1000 persons per year (Rx/1000/Yr) based on quarterly usage for the non-institutionalized population. The non-institutionalized population was defined as the total Manitoba midyear population less the average number of residents of personal care homes, mental health facilities and correctional institutions for that year (100-106). Population figures beyond 1998 were unavailable and thus 1998 population data were used to calculate antibiotic usage for 1999. Linear regression analysis of usage trends was performed using annual usage data. Regression lines were fitted for individual antibiotics and for total antibiotic usage, and their slopes tested for significant differences in use.

2.3.2 Results

In 1999, penicillins were the most commonly used antibiotic agents, representing 46% of total antibiotic prescriptions, followed by macrolides (18%), sulfonamides (11%), cephalosporins (10%), fluoroquinolones (6%) and tetracyclines (5%) (Figure 2). During the study period, highest total antibiotic consumption occurred in the first quarter of 1995; 1083.9 Rx/1000/Yr. During this time period, the most commonly used agents, as measured by Rx/1000/Yr, were amoxicillin (399.2), erythromycin (157.3), TMP-SMX (138.6), and penicillin G/V (79.7). The rate of total antibiotic use decreased by 11.3% between 1995 and 1999. Total antibiotic use decreased by 7.5% from 1995 to 1996 decreasing a further 6.7% between 1997 and 1998. However, total antibiotic use

increased from 1997 to 1998 and 1998 to 1999 by 1.2% and 1.7% respectively. During the study period, antibiotics which experienced declining usage included: amoxicillin (-17.5%), erythromycin (-34.2%), TMP-SMX (-18.7%), penicillin V/G (-29.0%), and tetracycline (-32.0%). Antibiotics with increasing usage included; ciprofloxacin (58.6%), cefuroxime (94.5%) and azithromycin/clarithromycin (146.6%). Seasonal variation in usage was evident for the majority of antibiotics (See Figures 3 to 6). With the exception of cloxacillin, all antibiotics evaluated exhibited peak use in the winter quarters with lowest use occurring in summer quarters.

Changes in antibiotic usage, by agent or class of agents is reported in Table 1. The most commonly used antibiotics (amoxicillin, erythromycin, TMP-SMX, and penicillin V/G) exhibited significant decreases in use, while cephalosporins, fluoroquinolones and new macrolides (azithromycin/clarithromycin) exhibited significant increases in use. Changes in the use of cloxacillin and minocycline/doxycycline were not significant. Within the macrolide class of antibiotics, the decrease in erythromycin use was offset by the increased use of the new macrolides (azithromycin/clarithromycin), resulting in no significant change in overall macrolide consumption. Among second and third generation cephalosporins, significant increases in the use of cefuroxime and cefprozil were partially offset by a significant decrease in the use of cefaclor, resulting in only a modest increase overall. Within the fluoroquinolone class, significant increases in the use of ciprofloxacin and levofloxacin were partially offset by a significant decrease in the use of norfloxacin.

In addition, the change in usage of second-line agents (as defined by the Manitoba Drug Benefits Formulary [Appendix A]) over the study period was examined. Figure 7

illustrates the increase in the use of second-line agents as a percent of total antibiotic use from 1995 to 1999; rising from 14.4% of total use in 1995 to 23.8% in 1999 ($p<0.001$).

Figure 2. **Antibiotic use by class of agent in Manitoba, Canada, 1999**

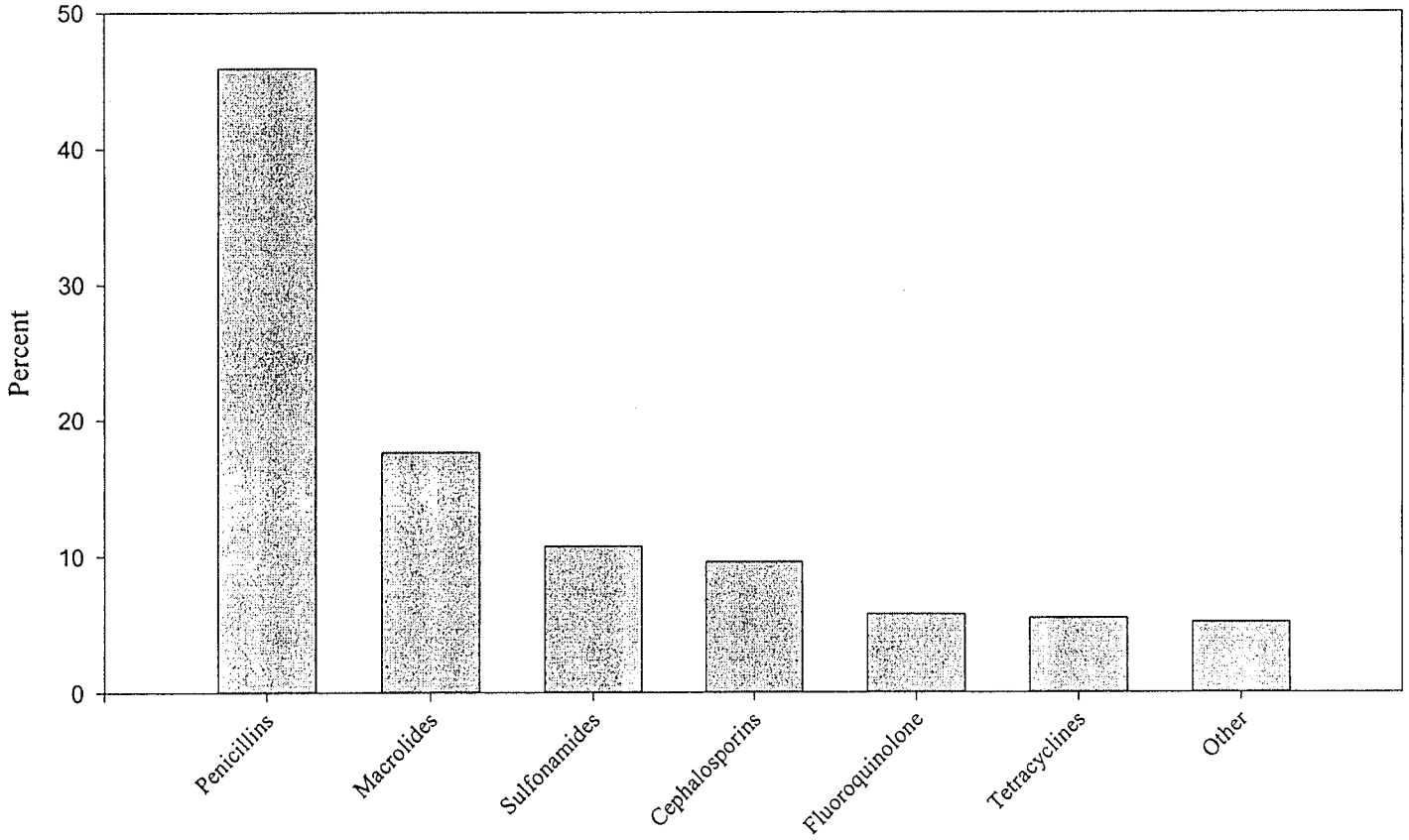
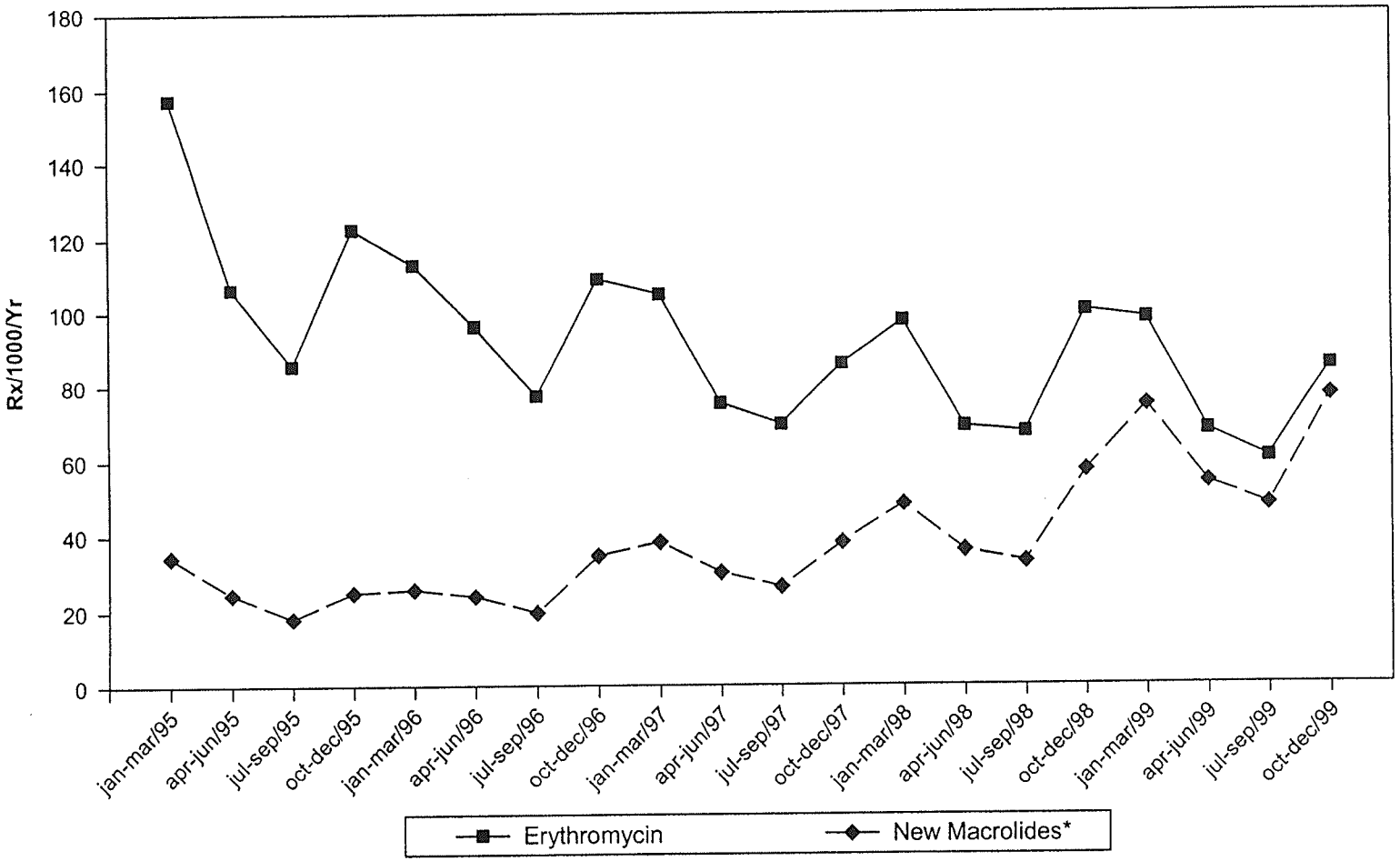


Figure 3. **Macrolide use in Manitoba, Canada 1995 to 1999**



***Clarithromycin and Azithromycin**

Figure 4. **Penicillin use in Manitoba, Canada 1995 to 1999**

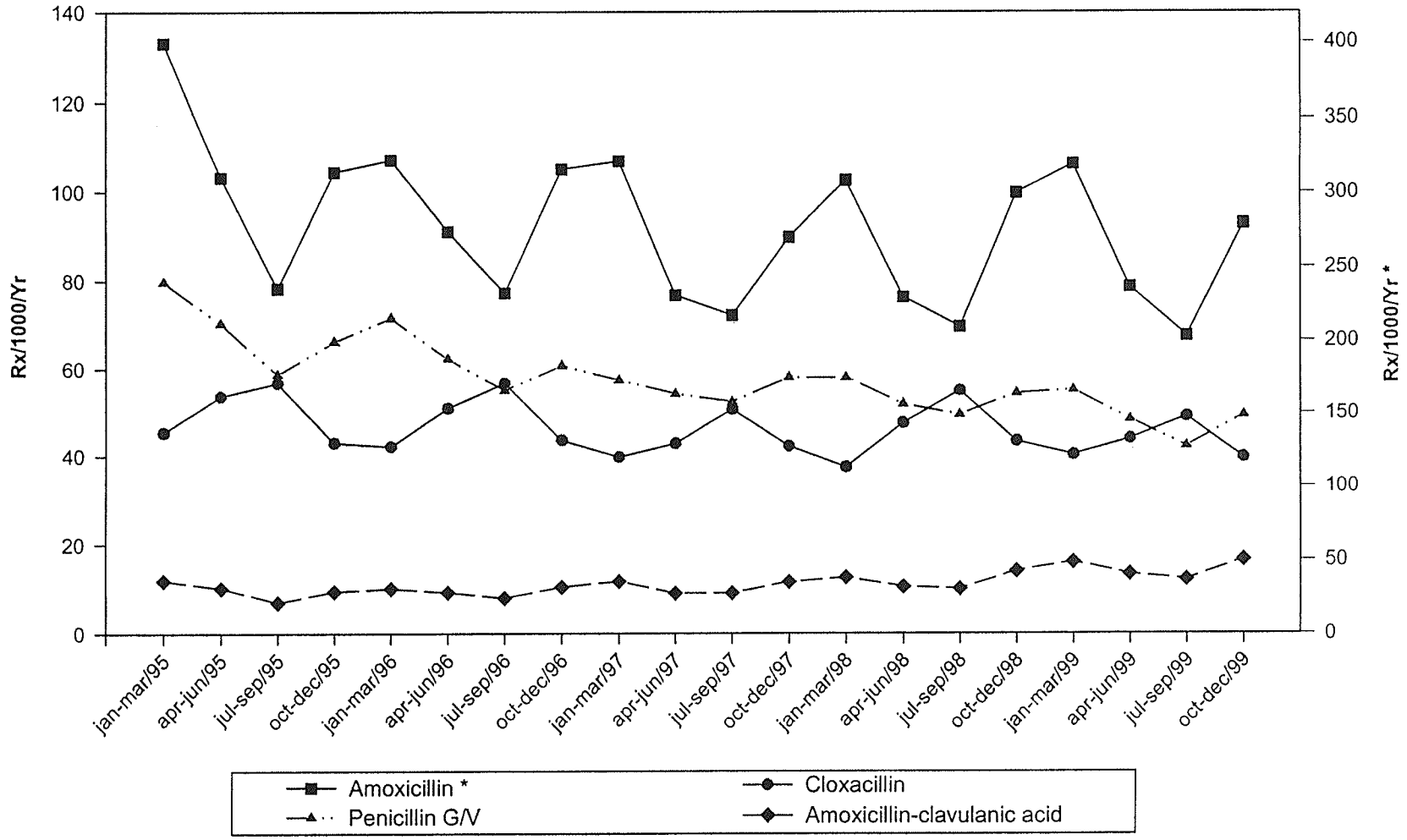
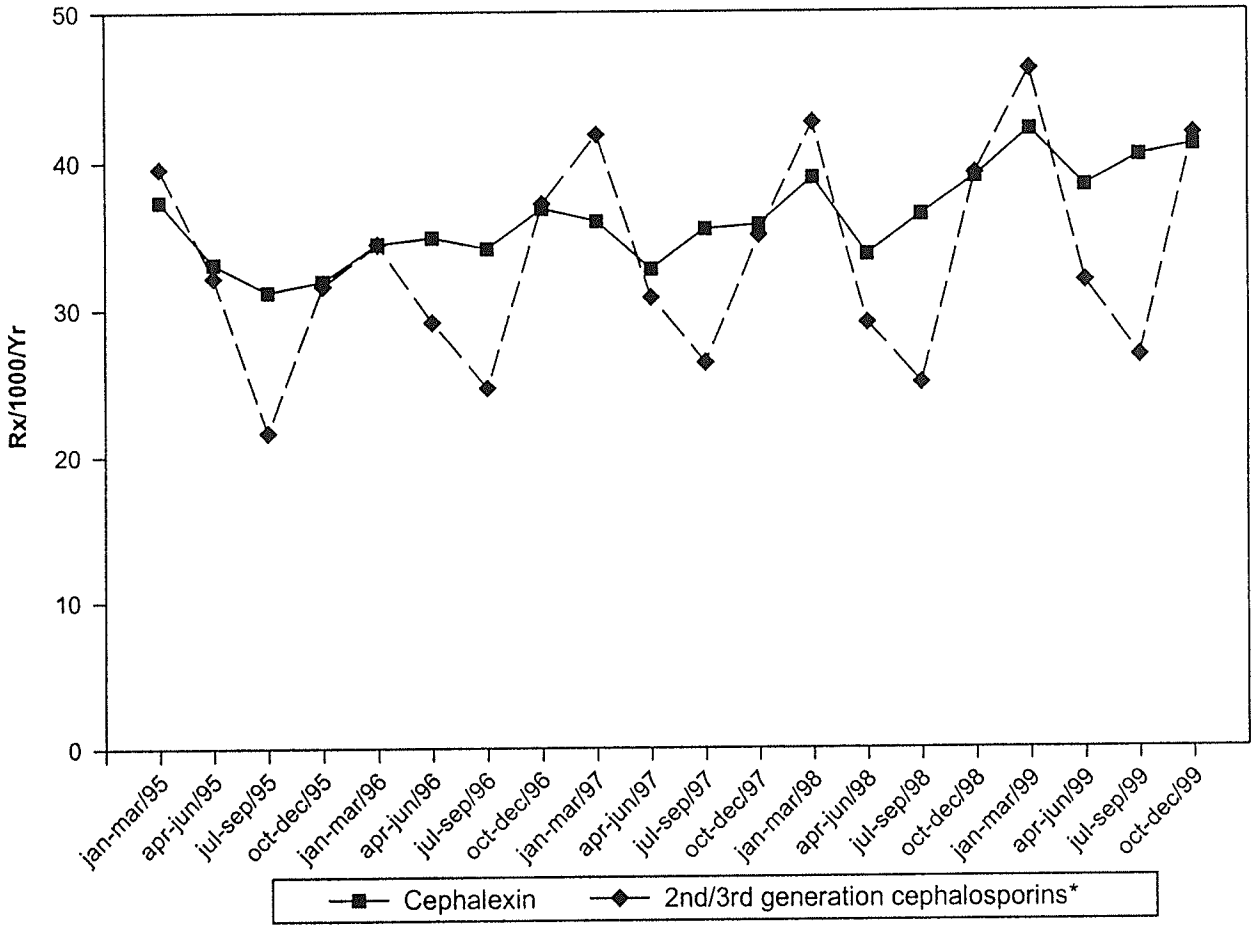


Figure 5. **Cephalosporin use in Manitoba, Canada 1995 to 1999**



*cefaclor, cefuroxime, cefixime, and cefprozil

Figure 6. **Sulfonamide and fluoroquinolone use in Manitoba, Canada 1995 to 1999**

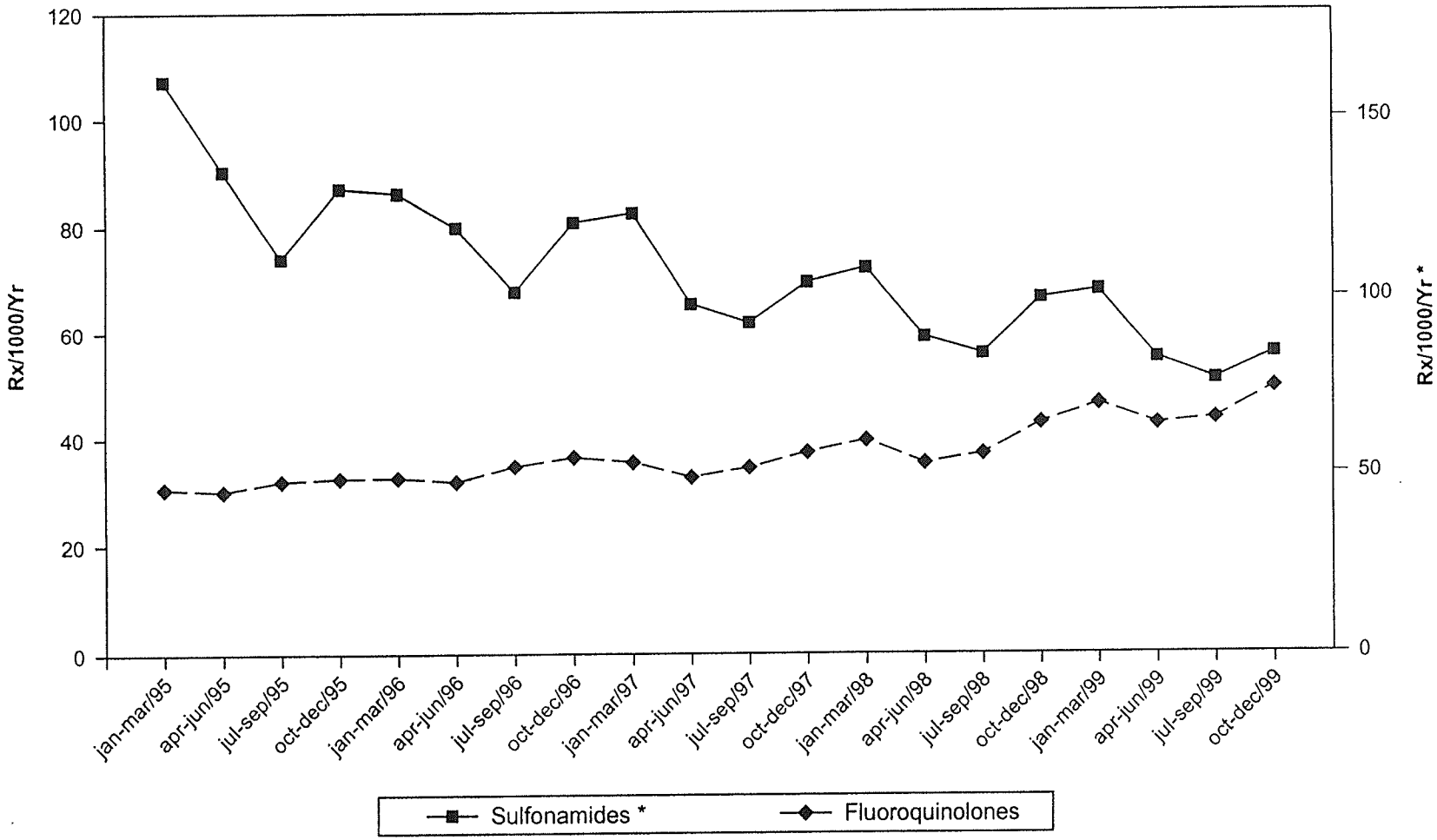


Figure 7. **Second-line antibiotic use as a percentage of total antibiotic use in Manitoba, Canada; 1995 to 1999**

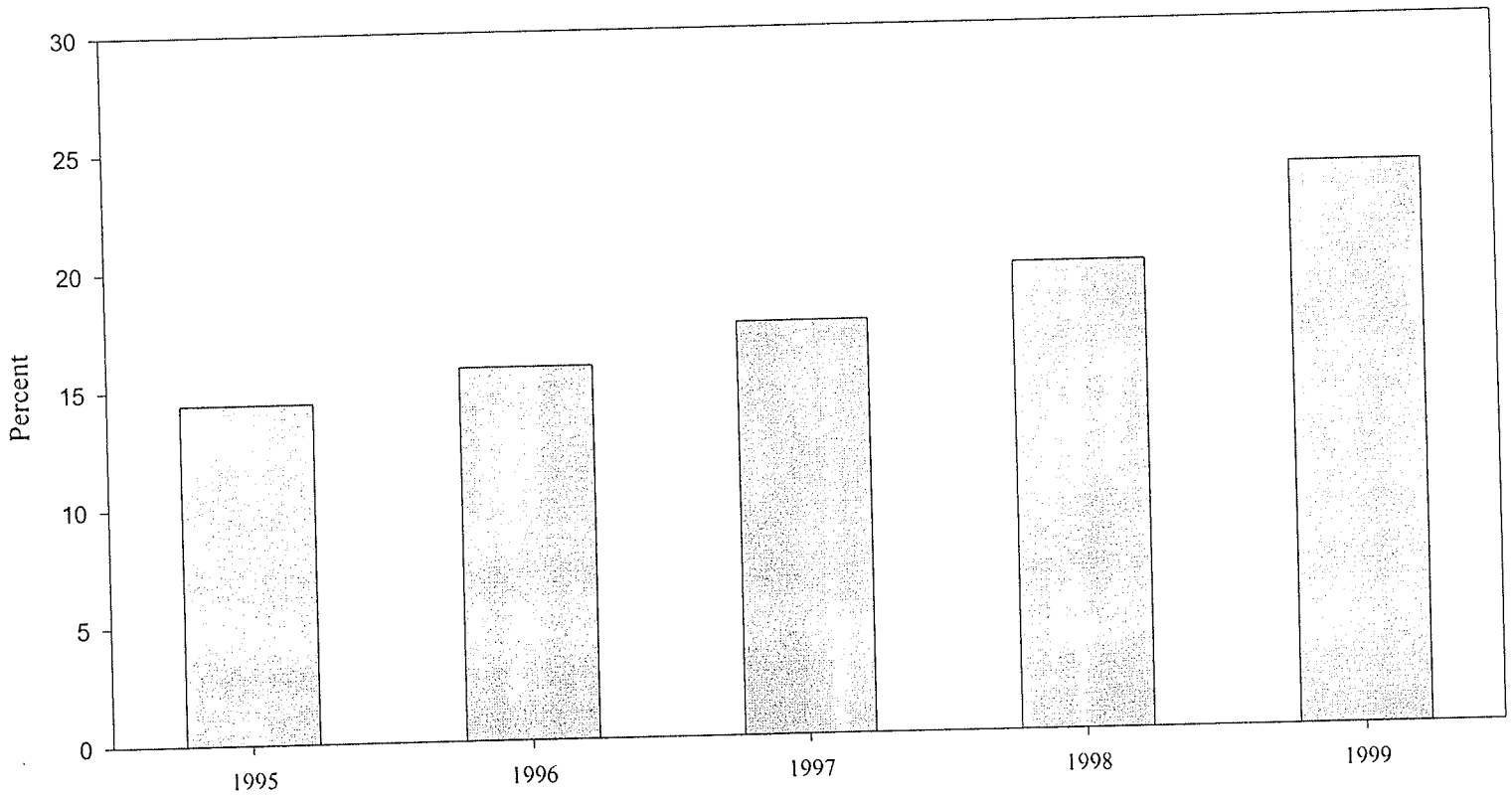


Table 1. **Changing antibiotic use in Manitoba, Canada; 1995 to 1999**

Antibiotic	a = intercept*	b = slope	95% CI	p
Amoxicillin	316.28	-13.41	-26.70 – -0.13	<0.05
TMP-SMX**	125.76	-9.17	-11.89 – -6.45	<0.005
Erythromycin	121.08	-9.59	-16.63 – -2.55	<0.05
Penicillin G/V	72.50	-4.88	-6.46 – -3.31	<0.005
Cloxacillin	50.84	-1.52	-3.09 – 0.06	NS
Cephalexin	31.39	1.60	0.49 – 2.70	<0.05
$2^{nd}/3^{rd}$ generation Cephalosporins	29.31	1.35	0.58 – 2.11	<0.05
Tetracycline	29.24	-2.15	-2.58 – -1.73	<0.001
Fluoroquinolones	26.89	3.31	1.38 – 5.24	<0.05
Minocycline/Doxycycline	20.41	0.68	-0.34 – 1.69	NS
Erythromycin-Sulfisoxazole	17.69	-2.79	-4.28 – -1.29	<0.01
Metronidazole	15.12	0.74	0.17 – 1.32	<0.05
Azithromycin/Clarithromycin	10.52	9.23	2.73 – 15.74	<0.05
Nitrofurantoin	9.97	0.37	0.10 – 0.64	<0.05
Amoxicillin-Clavulanic Acid	7.48	1.25	0.24 – 2.25	<0.05
Clindamycin	2.17	1.23	0.91 – 1.56	<0.005
Trimethoprim	1.62	-0.11	-0.33 – 0.12	NS
TOTAL	892.51	-24.90	-60.79 – 10.99	NS

* Rx/1000/Yr

**TMP-SMX = Trimethoprim-Sulfamethoxazole

2.3.3 Discussion

The formation of large medical and pharmaceutical claims databases are increasingly facilitating epidemiological studies of drug use. The introduction of the DPIN in Manitoba in 1994 provided Manitoba Health with the means to quantify drug use by Manitobans based on prescription claims for the majority of residents. In contrast to previous studies of antibiotic use from other developed countries (2-4, 95), which reported stable or increasing total antibiotic use, Manitoba's total antibiotic consumption declined over the study period. However, this reduction in antibiotic use was achieved only in the early years of the study. As expected, seasonal variation in antibiotic usage was evident with most agents exhibiting higher rates of use in winter quarters, excepting cloxacillin which exhibited higher use in summer quarters.

Decreases in total antibiotic consumption may be partly attributed to an increased awareness by patients and/or clinicians regarding the dangers of antibiotic misuse. In January 1997, the Canadian Infectious Disease Society, along with the Canadian Pharmaceutical Association and several other professional organizations launched a Canada-wide public awareness campaign regarding the dangers of antibiotic misuse. The observed decrease in the use of older and/or narrow spectrum agents (e.g. penicillin V, erythromycin, tetracycline) and the increase in the use of newer and/or broad spectrum agents (e.g., fluoroquinolones, clarithromycin/azithromycin) was consistent with antibiotic usage trends in other countries (2-4, 95).

Possible explanations for the increased use of newer and/or broad spectrum agents are numerous, including: (i) increasing antibiotic resistance in pathogens commonly

encountered in community practice may necessitate the use of broader spectrum agents, (ii) new agents may find use in treatment of newly recognized infections (e.g., clarithromycin for *Helicobacter pylori*), (iii) changes in healthcare delivery and the availability of new, potent, broad spectrum agents such as the fluoroquinolones may allow for out-patient treatment of moderate to severe infections previously managed in hospital, (iv) enhanced *in vitro* activity and/or improved pharmacokinetics and/or adverse effect profile, and (v) the novelty of prescribing new antibiotics and the availability of samples.

It is interesting to note that the majority of agents which exhibited increased use are scheduled second-line agents in Manitoba; agents whose widespread use is discouraged through reimbursement restrictions (Appendix A). To what extent these restrictions prevent inappropriate use is unknown. Additional studies are needed to address important questions such as: (i) for what indications and what patient populations (greater severity of illness, older, with co-morbidity) are new agents being used? (ii) are new agents improving patient outcomes? (iii) are current methods to control and optimize antibiotic use effective and to what extent is the increasing use of broad-spectrum agents warranted by antibiotic resistance to older agents?

A limitation of this study was the short time frame of the study period. Unfortunately, the recent introduction of the DPIN precluded the presentation of extensive longitudinal data. Determinations of antibiotic usage trends over time may be complicated by atypical results in short-term data. Further limitations of this study relate to the use of the DPIN as a data source. While there is no certainty that antibiotic prescriptions dispensed were actually consumed, prescriptions dispensed are expected to give a more accurate

indication of antibiotic consumption than studies which focus on numbers of prescriptions written (2). In addition, the DPIN database lacks a field which indicates the reason for a prescription. Linkage of the DPIN with the Physician Claims database may allow for studies of indication for use.

2.3.4 Direction of further research

The decrease in antibiotic consumption over the study period was encouraging, however several newer agents, or classes of agents, exhibited increasing usage; most notably the new macrolides (azithromycin/clarithromycin) and the fluoroquinolones. New macrolides have enhanced activity, and an improved pharmacokinetic/ pharmacodynamic and safety profile over that of erythromycin. This likely explains much of the increased use of new macrolides, since their increased use is matched with a comparable reduction in use of erythromycin (Figure 3). This change has significant economic implications due to the high cost of the new macrolides but is unlikely to impact resistance patterns unless the use of the new macrolides rises over the preceding erythromycin usage. In contrast, the increased use of fluoroquinolones raises concerns of possible future resistance to a valuable class of agents, and economic concerns due to the high cost of these agents.

Fluoroquinolones are the most broad spectrum oral antibiotics, effective against a broad range of gram-positive and gram-negative pathogens. The introduction of the fluoroquinolones in Canada in 1988, allowed for out-patient treatment of infections previously managed in hospitals, and infections with pathogens resistant to older agents. The potential loss of effectiveness of this valuable class of agents through increased

antibiotic resistance due to overuse is a significant concern. As indicated by McGavok *et al.* (79), the introduction of new agents is often met with enthusiasm, with resultant rapid increases in use. Birkett *et al.* (95) indicated that within 3 years of the introduction of fluoroquinolones in Australia, their use accounted for over 40% of the market share in the treatment of urinary tract infections, replacing the recommended treatment at the time, which was TMP-SMX. It has been over a dozen years since the introduction of fluoroquinolones to Canada, time enough for the initial enthusiasm to have waned. Yet fluoroquinolone use continues to increase. A possible explanation is increasing resistance to older agents. Gupta *et al.* (7) reported increasing resistance of urinary pathogens to TMP-SMX. However, to what extent, and in which patient population, use of fluoroquinolones is warranted due to resistance to older agents is unknown. These questions prompted the examination of the role of fluoroquinolones in the treatment of urinary tract infections. The following section summarizes the epidemiology, pathogenesis and current approaches to treatment of urinary tract infections in community practice.

2.3 Urinary Tract Infections in Community Practice

Urinary tract infections (UTI) are a commonly diagnosed and treated infection in community practice, with greater than 7 million episodes of UTI occurring annually in the USA (107). UTI are generally classified based on site of infection; upper (e.g., pyelonephritis) or lower (e.g., cystitis), and further classified as complicated or uncomplicated based on the existence of structural or functional abnormalities of the urinary tract. Lower tract disease is more commonly diagnosed than upper tract disease in community practice (107). Both the site of infection, and the presence or absence of complicating factors, have implications for disease management.

2.4.1 Pathogenesis and Etiology

The primary mode of acquisition of UTI is ascension of fecal flora (108). Pathogenic organisms selected from fecal flora, colonize the perineum, and those containing specific virulence factors may ascend the urethra to the bladder where multiplication and adherence to bladder sites results in the superficial infection, cystitis. In addition, bacteria may ascend the film of urine coating the ureters to infect the renal pelvis and parenchyma resulting in pyelonephritis, an invasive infection. Alternatively, UTI may be acquired via hematogenous spread, although this mode of infection is uncommon (108). The site of infection, lower (bladder) versus upper (ureters, kidney), is an important distinction in disease management.

Etiologic agents in acute uncomplicated UTI are predictable, with a small number of organisms being responsible for most cases. *Escherichia coli* is the most common causative pathogen, accounting for approximately 70-95% of cases, with *Staphylococcus*

saprophyticus, and Proteus spp. and Klebsiella spp. as lesser seen pathogens (107). Approximately 95% of cases of acute uncomplicated UTI are due to a single causative agent (108). In complicated infections *E. coli* continues to account for the majority of infections, although Enterobacter spp., Pseudomonas spp, and Enterococcus spp. are observed more frequently than in uncomplicated infections (108).

2.4.2 Epidemiology

Although UTI are commonly diagnosed, age and gender affect the risk of acquisition. Many studies have demonstrated variations in the risk of UTI, based on age, gender, and the presence or absence of comorbidities (109-115). In addition, several different incidence and prevalence measures have been used to quantify the risk of acquisition. Incidence is most correctly applied to reports of the number of episodes of symptomatic UTI experienced by a study population over a standard time period; most commonly one year. However, studies which employ the measure of cumulative incidence are common (116-118). In addition, studies examining the effect of patient variables (e.g., age, diabetes, pregnancy) on the risk of experiencing UTI have cited the prevalence of bacteriuria as opposed to the incidence of symptomatic UTI (110, 112, 119). Changes in the risk of experiencing UTI are inferred from changes in the prevalence of bacteriuria, although the exact relationship remains unclear.

The incidence of UTI in childhood is relatively low. Dickinson reported incidences of 1.7 and 3.1/1000/year for male and female subjects under 14 years of age respectively (109). Marild and Jodal reported an incidence of first-time UTI, for male and female children less than one year of age, of 7.7 and 9.7 /1000/year, however, by the age of six years, the incidence had fallen to less than 0.5 and 4/1000/year respectively (115). In

young adulthood the prevalence of bacteriuria increases for females, but not for males (108). Kunin and McCormack demonstrated the link between sexual activity and UTI in a comparison of bacteriuria between nuns and other working women (120). The prevalence of bacteriuria in working women was 12.8, 2.8, and 1.4 times greater than that of the nuns in the three age categories studied; 15 to 34 years, 35 to 54 years and 55+ years. Gaymans *et al.* reported an incidence of UTI among women greater than 15 years of age of 59/1000/year (121). Studies of the lifetime cumulative incidence of UTI in adult females illustrate the commonality of the experience (116-118). In a study by Foxman and Chi a self-reported history of UTI was evident in 39.6% of university students; mean age 21.9 years (117). In a similar study of older women, Berg *et al.* reported a lifetime history of UTI in 70% of adult females presenting to a University Health Service; mean age 30.2 years (118). A follow-up study of women who had presented to a University health service 10 years earlier (previous mean age 20.6 years) indicated that the lifetime history among these women for UTI was 63.2% (116).

The incidence of symptomatic UTI in young adult males is very low. Krieger *et al.* estimated the incidence of symptomatic UTI among male University students to be 5/10,000/year (113). Khan *et al.* demonstrated that, in contrast to young women, young men with UTI frequently have anatomic abnormalities which predispose them to UTI (114). Beyond middle age, the prevalence of bacteriuria has been shown to increase with age in both females and males (112). The increase has been attributed to altered hormone levels in females, and an increase in functional abnormalities in both sexes (122). Thus, UTI in young adult women are common and unlikely to be complicated by structural abnormalities, however, UTI in elderly women are more likely to be classified as

complicated infections. In young men UTI are infrequent, although the frequency increases with age. UTI in young men are commonly complicated by the existence of structural abnormalities. The following discussion of UTI will focus specifically on uncomplicated UTI in adult females.

In the normal female, sexual activity, diaphragm use, previous history of UTI, and antibiotic use in the previous 15-28 days (irrespective of reason for antibiotic use) have been identified as risk factors for the development of UTI (123-126). Pregnancy has been shown to increase the risk of bacteriuria with approximately one-quarter of these bacteriuric women developing pyelonephritis particularly in the third trimester (119). Due to the association of pyelonephritis with an increase in pre-term birth, routine screening for asymptomatic bacteriuria, and subsequent treatment if applicable, is suggested in pregnant women (127). Treatment of bacteriuria and UTI presents challenges in the pregnant patient due to contraindications for the use of certain classes of antibiotics in pregnancy (e.g., fluoroquinolones) (128). The prevalence of bacteriuria and incidence of UTI in women with diabetes has been shown to be greater than in non-diabetic women (110, 111), although this finding has not been universal (129). Glucosuria and the resultant increase in growth of pathogenic organisms has been suggested as a causative factor, however, bladder dysfunction resulting from diabetic neuropathy and cystopathy is considered to be of greater importance (130). For this reason UTI in the diabetic population may be considered a complicated infection. Nicolle *et al.* reported an association between hospitalization for pyelonephritis and native treaty status that could not entirely be explained by the increased prevalence of diabetes and pregnancy in the native population (131).

2.4.3 Diagnosis

Diagnosis of UTI may be made on the basis of history, clinical presentation, and laboratory findings. Upper tract infection is distinguished from lower tract infection by the presence of: fever, flank pain, nausea and/or vomiting, and costo-vertebral angle tenderness, with or without lower tract symptoms (dysuria, frequency, urgency). The diagnosis of UTI is confirmed by evidence of significant bacteriuria. However the definition of significant bacteriuria may vary. Traditionally, $>10^8$ colony forming units per litre (cfu/L) of a clean catch mid-stream urine is considered significant bacteriuria (132). However, there may be lower bacterial counts in women with acute cystitis ($>10^6$ cfu/L). Bacteria counts are higher in upper tract infection and the criteria for significant bacteriuria for the diagnosis of pyelonephritis is $>10^7$ cfu/L, when accompanied with clinical symptoms (132). In the absence of urine cultures, urinalysis may provide evidence for a presumptive diagnosis of UTI. Pyuria, defined as $>10 \times 10^6$ leucocytes/L of unspun urine, is exhibited in over 96% of symptomatic men and women with significant bacteriuria, and is thus suggestive of UTI (132). However, pyuria without infection is common. Jellheden *et al.* indicated a positive pyuria finding, as an indication of bacteriuria among symptomatic women, had a sensitivity of 84% but a specificity of only 35% (133). The finding of pyuria may be by direct microscopic examination of urine, or alternatively, by rapid diagnostic test using a leukocyte esterase dipstick, which is both sensitive (75-96%) and specific (94-98%) for detecting 10 x 10 leucocytes/L of unspun urine (133). Similarly, a rapid diagnostic test for the presence of nitrite (produced by reduction of urinary nitrate by bacteria) may also be used to make a presumptive

diagnosis of UTI. Jellheden *et al.* reported a positive nitrite test to be 89% specific but only 62% sensitive in finding significant bacteriuria in symptomatic women (133).

The need for additional diagnostic testing is dependent on history and clinical presentation. Young, otherwise healthy women with sudden onset symptoms of dysuria and frequency, suggestive of lower tract infection, may be presumed to have cystitis if tests for pyuria and/or nitrite are positive. A pretreatment urine culture is not recommended in this patient population since etiology and susceptibility of causative organisms are predictable (11, 12). In the presence of symptoms suggestive of upper tract infection, routine urine cultures are recommended due to the potential serious consequences of inappropriate treatment in this invasive infection (11, 12). Knowledge of site of infection also has implications for antibiotic selection and treatment duration. In research studies, the detection of antibody-coated bacteria (ACB) has been used to identify upper tract infection, however, this test may be an unreliable indicator of site of infection and is not routinely available for use in office practice (134). Thus, in clinical practice, distinction between upper and lower tract infection is based on presenting symptoms.

2.4.4 Treatment

Decisions regarding treatment of acute uncomplicated UTI in young women depend foremost on the site of infection. Due to the superficial nature of acute cystitis and the low propensity for complications, outpatient treatment is the norm. Studies of optimal treatment focus upon antibiotic selection and duration of treatment. In pyelonephritis, in addition to antibiotic selection and duration of treatment, the feasibility of outpatient

treatment has been the subject of study. Studies suggest that the majority of cases of community-acquired pyelonephritis may be treated on an out-patient basis (135-138). Out-patient treatment has been reported to result in satisfactory outcome at less than one-seventh the cost of in-patient treatment (135).

Since UTI are commonly encountered infections for physicians in community practice, treatment guidelines have been developed (11, 12, 139), although updating of such guidelines is necessary to reflect changing antibacterial susceptibilities and the introduction of new agents. The following sections discuss the results of randomized controlled trials (RCT) which have formed the basis for treatment guidelines.

As in most RCT that compare treatments for infectious diseases, diagnosis may be based on clinical or bacteriologic findings, or a combination of both. Similarly, treatment outcomes may be defined by bacteriologic (eradication of infecting organism) or clinical (resolution of signs and symptoms) endpoints, or a combination of both. Timing of follow-up has been fairly standard in most trials irrespective of site of infection. Response to treatment is usually assessed at five to nine days (early follow-up) and four to six weeks (late follow-up) after completion of treatment, in accordance with published recommendations for comparative studies of antibiotics in UTI (132). Bacteriologic outcome is commonly designated as: cure, relapse, re-infection or persistence. Relapse is defined as a recurrence of the initial infection by the same strain of the original organism, resulting from inadequate treatment of the initial infection, which usually occurs within one to two weeks after cessation of initial treatment (108). In contrast, a re-infection is a recurrence of infection with a different strain of the original organism, or a completely new organism, and is thought to result from the inability of treatment to eradicate

pathogenic bacteria from the vaginal and intestinal reservoir (108). Evidence that aminopenicillins were inferior in eliminating vaginal colonization, resulting in higher rates of re-infection, may have been a factor in the abandonment of aminopenicillins as first-line therapy of UTI (140-142).

2.4.4.1 Antibiotic Selection

Since etiologic organisms are comparable in both upper and lower tract infection, many of the concerns and controversies regarding antibiotic selection, related to the introduction of new agents and changing patterns of antibiotic resistance, are applicable to both. However, antibiotic comparison studies of cystitis are more numerous and site of infection may affect response to treatment, as evidenced by the tendency for lower cure rates in pyelonephritis studies (Tables 2 and 3). Comparative studies of treatment of acute uncomplicated UTI in females are discussed below. Comparisons between studies are complicated by differing methodologies related to: patient selection, definition of cure, inclusion/exclusion criteria, and duration of treatment. In addition, studies of UTI may include both upper and lower tract infections without a separate analysis by site of infection, making interpretation difficult. Recently, recommendations for the conduct of comparative studies of antibiotic treatments in UTI have been published in an attempt to address the above issues (132). Despite these shortcomings, a historical perspective of studies, which have influenced current treatment, is presented. Tables 2 and 3 summarize the results of comparative studies of antibiotic treatment of cystitis and pyelonephritis respectively (140-160). Antibiotics commonly employed in North America for the treatment of UTI over the last several decades include aminopenicillins (e.g., amoxicillin,

ampicillin), nitrofurantoin, TMP-SMX, and the fluoroquinolones. All the above agents have been, or continue to be, used in both upper and lower tract disease, with the exception of nitrofurantoin which does not attain sufficient tissue concentrations to be useful in the treatment of upper tract disease (161). Reviewed studies are restricted to those which differentiate between upper and lower tract disease, either by restriction or by separate analysis, and which compare antibiotics commonly employed in North America. Due to the small number of studies of pyelonephritis, studies of pyelonephritis treatment which included male subjects were included provided males accounted for less than 25% of study subjects.

Table 2. **Studies of antibiotic efficacy in the treatment of cystitis**

Author	N	Drug	Duration (days)	Resistant Pathogens*	Bacteriologic Cure Early (%)	Bacteriologic Cure Late	Clinical Cure Early (%)	Clinical Cure Late	Adverse Effects (%)
Studies Comparing efficacy between different antibiotics with the same treatment duration									
Sigurdsson *et al.* (137)	215	Amoxicillin	3	-	77.6	70.3	-	-	15
		Co-Trimazine	3		100	82.7	-	-	8
Hooton *et al.* (135)**	180	Amoxicillin	3	+	86	67	-	-	25
		TMP-SMX	3		97.5	82	-	-	35
		Nitrofurantoin	3		84	61	-	-	43
		Cefadroxil	3		100	66	-	-	30
Block *et al.* (141)	250	TMP-SMX	3	-	-	88	-	90	22
		Ofloxacin	3		-	92	-	95	19
Hooton *et al.* (140)	45	Amoxicillin	1	+	50	42	-	-	46
		TMP-SMX	1		85	54	-	-	31
		Cyclacillin	1		30	13	-	-	8
McCarty *et al.* (142)	866	TMP-SMX	3	+	93	84	95	91	41
		Ciprofloxacin	3		94	89	93	91	31
		Ofloxacin	3		97	87	96	89	39
Studies comparing efficacy between different durations of the same antibiotic									
Fang *et al.* (138)	82	Amoxicillin	1	-	96	91	-	-	18
		Amoxicillin	10		100	91	-	-	44

Table 2. Continued

Author	N	Drug	Duration (days)	Resistant Pathogens*	Bacteriologic Cure Early (%)	Bacteriologic Cure Late	Clinical Cure Early (%)	Clinical Cure Late	Adverse Effects (%)
Osterberg *et al.* (151)	613	TMP-SMX	1	+	82	71	-	-	14
		TMP-SMX	7		94	87	-	-	20
Counts *et al.* (149)	113	TMP-SMX	1	-	82	76	-	-	13
		TMP-SMX	10		95	87	-	-	31
Fihn *et al.* (147)	255	TMP-SMX	1	+	-	-	68	56	12
		TMP-SMX	10		-	-	79	64	25
Tolkoff-Rubin *et al.* (150)	109	TMP-SMX	1	-	-	83	-	-	4
		TMP-SMX	10		-	90	-	-	24
Saginur *et al.* (154)	219	Norfloxacin	1	-	81	78	-	-	-
		Norfloxacin	3		94	88	-	-	-
Gossius and Vorland (148)	464	TMP-SMX	1	-	96	96	-	93	5
		TMP-SMX	3		96	94	-	90	9
		TMP-SMX	10		98	98	-	94	28
Studies Comparing efficacy between different antibiotics with the different treatment durations									
Rubin *et al.* (139)	218	Amoxicillin	1	-	-	90	-	-	4
		Ampicillin	10		-	96	-	-	38
		TMP-SMX	10		-	100	-	-	33
Hooton *et al.* (153)	208	TMP-SMX	7	+	93	88	-	-	19
		Ofloxacin 200	3		96	88	-	-	23
		Ofloxacin 200	7		91	86	-	-	27
		Ofloxacin 300	7		96	100	-	-	19

Table 2. Continued

Author	N	Drug	Duration (days)	Resistant Pathogens*	Bacteriologic Cure Early (%)	Bacteriologic Cure Late	Clinical Cure Early (%)	Clinical Cure Late	Adverse Effects (%)
Iravani *et al.* (144)	713	TMP-SMX	7	-	93	79	95	90	38
		Nitrofurantoin	7		86	82	93	89	34
		Ciprofloxacin	3		88	91	95	90	28
Stein *et al.* (155)**	209	TMP-SMX	10	+	100	95	-	-	15
		Norfloxacin	3		96	91	-	-	14
Hooton *et al.* (152)	150	TMP-SMX	7	+	95	98	-	-	40
		Ofloxacin	3		92	89	-	-	32
		Ofloxacin	1		93	81	-	-	30

*Resistant Pathogens; + indicates inclusion of organisms resistant to study drug, - indicates exclusion of resistant organisms
**Cure based on a combination of clinical and bacteriological outcomes

Table 3. **Studies of antibiotic efficacy in the treatment of pyelonephritis**

Author	N	Drug	Duration	Resistant Pathogens*	Bacteriologic Cure		Clinical Cure		Adverse Effects (%)
					Early (%)	Late	Early (%)	Late	
Stamm *et al.* (136)**	98	Ampicillin	14	-	-	65	-	-	22
		Ampicillin	42		-	40	-	-	27
		TMP-SMX	14		-	90	-	-	17
		TMP-SMX	42		-	83	-	-	23
Harding *et al.* (143)	39	TMP-SMX	10	-	-	71	-	-	-
		Norfloxacin	10		-	83	-	-	-
Mouton *et al.* (145)	63	TMP-SMX	14	+	89	67	68	56	17
		Lomefloxacin	14		100	80	65	50	12
Talan *et al.* (146)	378	TMP-SMX	14	+	89	74	83	77	33
		Ciprofloxacin	7		99	85	96	91	24

*Resistant Pathogens; + indicates inclusion of organisms resistant to study drug, - indicates exclusion of resistant organisms
**Cure based on a combination of clinical and bacteriologic outcomes

2.4.4.1.1 Cystitis

In the 1970s aminopenicillins (e.g., ampicillin, amoxicillin) and TMP-SMX were considered first-line treatment of UTI, and a number of RCT to compare the efficacy of these treatments were undertaken (140, 142-145). Fang *et al.* reported cure in 91% of women treated with a single dose or 10 days of amoxicillin who tested negative for antibiotic-coated bacteria (ACB) (143). Rubin *et al.* reported cure in 90% and 96% of women with negative ACB tests, treated with a single dose or 10 days of amoxicillin respectively (144). Exclusion of women with positive tests for ACB, and those with resistant pathogens, may have contributed to the high proportion of cure in these studies. Rubin *et al.* demonstrated that women presenting with symptoms indicative of cystitis and positive ACB tests experienced worse outcome; with cure achieved in 33% and 85% of subjects treated with a single dose or 10 days respectively (144). While it is accepted that a proportion of patients presenting with symptoms indicative of lower tract infection may have involvement of the upper tract (as evidenced by a positive test for ACB), laboratory techniques to localize the site of infection are impractical in office practice, and treatment decisions are based on clinical presentation. Studies which relied on clinical presentation to determine the site of infection, and included amoxicillin-resistant pathogens, reported lower cure rates with amoxicillin (145).

In a study of women with clinically identified cystitis, which excluded subjects with resistant pathogens, Sigurdsson *et al.* reported early cure in 100% and 88.1%, and late cure in 90.7% and 81.3% of subjects after 3-day treatments of cotrimazine or amoxicillin respectively (142). In the above study, the authors considered re-infections among the

cures. However, patients treated with amoxicillin had more re-infections than those treated with co-trimazine, especially at the early follow-up. The investigators concluded this was likely due to poor eradication of bacteria from the vaginal and/or fecal reservoirs. When re-infections were no longer classified as cures, a greater difference between the performance of amoxicillin and co-trimazine was evident. The proportion of subjects achieving cure became 100% and 77.6% at early follow-up, and 82.7% and 70.3% at late follow-up, for co-trimazine and amoxicillin respectively. Comparable results were reported by Hooton *et al.* following a study of women with clinically identified cystitis, (including those with antibiotic-resistant pathogens), treated with TMP-SMX or amoxicillin for 3 days (140). In the above study cure was achieved in 82% and 67% of women treated with TMP-SMX and amoxicillin respectively. In addition, Hooton *et al.* reported the efficacy of each antibiotic in eradicating *E. coli* from the vaginal reservoir (140). Vaginal *E-coli* colonization was evident in 69% and 78% of subjects treated with TMP-SMX and amoxicillin respectively before treatment. At late follow-up, vaginal colonization was evident in only 21% of TMP-SMX versus 45% of subjects treated with amoxicillin. Concerns of increased potential for re-infection and increasing resistance among uropathogens to aminopenicillins (140, 162-164) led to abandonment of this treatment in favour of TMP-SMX

With the introduction and promotion of the fluoroquinolones for use in UTI, in North America in the late 1980s, more studies were needed. Fluoroquinolones demonstrated excellent efficacy in the treatment of UTI, however, cost of treatment was approximately twenty times that of equivalent treatment with TMP-SMX. A significant difference in safety or efficacy would need to be demonstrated before fluoroquinolones could be

considered first-line therapy. Fluoroquinolones demonstrated excellent efficacy in the treatment of cystitis, however, did not demonstrate superiority over TMP-SMX and this was true irrespective of whether subjects with TMP-SMX resistant organisms were retained in the analysis. Block *et al.* reported no significant difference in bacteriologic or clinical cure following treatment of cystitis with TMP-SMX or ofloxacin for 3 days (146). Bacteriologic/clinical cure was evident in 92/95%, and 88/90%, of ofloxacin and TMP-SMX treated women respectively. The time at which cure was determined was not apparent, and subjects with resistant organisms were excluded from the analysis. More recently the results of a large study by McCarty *et al.* indicated no significant differences in the proportion of cure between ciprofloxacin, ofloxacin and TMP-SMX when administered for 3 days (147). In the above study subjects with resistant strains were included in the analysis. The results of similar studies utilizing different treatment durations have failed to show significant differences in cure between TMP-SMX and fluoroquinolones (149, 157, 158). Currently, TMP-SMX is recommended as first-line empiric treatment of cystitis (11, 12, 139).

2.4.4.1.2 Pyelonephritis

Although studies of pyelonephritis are fewer in number and contain fewer subjects, changes in the treatment of pyelonephritis have mirrored those seen with cystitis. However, both bacteriologic and clinical cure rates tended to be lower than those seen in cystitis studies (Tables 2 and 3). The superiority of TMP-SMX over ampicillin in the treatment of pyelonephritis was demonstrated by Stamm *et al.*, who reported cure in 90% and 65% of subjects treated with TMP-SMX and ampicillin for two weeks respectively

(141). With the introduction of the fluoroquinolones additional studies were performed. Harding *et al.* compared the use of norfloxacin and TMP-SMX for 10 days in the treatment of pyelonephritis (148). Subjects with resistant strains were excluded from analysis, and cure (based on clinical and bacteriologic outcome) was reported in 83% and 71% of subjects taking norfloxacin and TMP-SMX, respectively. It was unclear whether this referred to cure at early or late follow-up. This difference did not achieve significance due to the low numbers of evaluable subjects (norfloxacin:18 and TMP-SMX:21). Similar results were reported by Mouton *et al.* following a study of predominantly female patients (approximately 75%) in which subjects with resistant strains were included (150). Treatment with either lomefloxacin or TMP-SMX for 14 days resulted in bacteriologic/clinical cure rates at late follow-up of 80%/50% and 66.7%/56.2% for lomefloxacin and TMP-SMX respectively. Once again low numbers of study subjects may have contributed to the lack of a significant finding. Most recently, Talan *et al.* reported the results of a large multicentre study which compared treatment with ciprofloxacin and TMP-SMX for 7 and 14 days respectively in women with pyelonephritis presenting to physicians' offices or emergency departments (151). Subjects with resistant pathogens were retained in the analysis. In this study *E. coli* was responsible for greater than 90% of all infections, and 18% of these isolates were resistant to TMP-SMX. Bacteriologic/clinical cure rates at late follow-up were 85%/91% and 74%/77% for ciprofloxacin and TMP-SMX respectively.

To date there is little evidence with which to assess the comparative efficacy of TMP-SMX and fluoroquinolones. Early studies were underpowered to identify all but the largest treatment differences and there is evidence that resistance to TMP-SMX among

uropathogens has increased significantly. The significance of antibiotic-resistant pathogens in the treatment of UTI is explored later in this chapter. Currently, both TMP-SMX and fluoroquinolones are recommended as first-line empiric treatment of pyelonephritis (11, 12, 139).

2.4.4.1.3 Adverse Effects

The reported frequencies of adverse effects varied considerably between studies. The frequency of adverse effects varied between 4 and 46% for amoxicillin, 4 and 41% for TMP-SMX, and 14 and 39% for fluoroquinolones (Tables 2 and 3). The variability may be due to the method used to solicit this information; spontaneous reporting versus direct questioning. The proportion of subjects with adverse effects which resulted in discontinuation of treatment was relatively low. McCarty *et al.* (147) indicated adverse effects resulting in treatment discontinuation was significantly more likely to occur with TMP-SMX than a fluoroquinolone, however Iravani *et al.* (149) reported no significant difference between TMP-SMX and fluoroquinolone regarding treatment discontinuation related to adverse effects.

2.4.4.2 Duration of Treatment

Controversy regarding optimal duration of treatment for UTI has existed for many years. Shorter durations of treatment may be expected to result in increased patient convenience and compliance, in addition to decreased adverse effects, cost, and potential for the emergence of resistant organisms. However, inappropriately short durations of treatment increase the risk of relapse due to inadequately treated infections and a

resultant increase in morbidity and healthcare costs. Optimal duration is conditional on the site of infection, with cystitis requiring a shorter duration of treatment than pyelonephritis (11, 12, 139). Comparative studies of treatment duration are discussed below.

2.4.4.2.1 Cystitis

Many studies comparing duration of treatment for cystitis, between and within drug classes, have been undertaken (143, 144, 149, 152-160). Traditionally, treatment durations of a single dose to 3 days have been considered "short", while durations of 7 to 10 days have been considered "conventional". There is ample evidence to support short courses of treatment of cystitis. Gossius and Vorland, Counts *et al.*, Fihn *et al.*, and Tolkoff-Rubin *et al.*, reported no significant difference in cure rates between a single dose or 10 day treatments of cystitis with TMP-SMX (152-155). However, the largest study, performed by Osterberg *et al.*, indicated conventional treatment resulted in a significantly higher proportion of subjects achieving cure than short course treatment (156). Hooton *et al.* reported no significant difference in the proportion of cure between short course (3-day) and conventional treatment (7-day) with a fluoroquinolone (158). Subsequent studies by Hooton *et al.* and Saginur *et al.* identified no significant difference in the proportion of cure between a single dose or 3-day fluoroquinolone treatment (157, 159). Further, Stein *et al.* and Hooton *et al.* reported no significant difference in the proportion of subjects achieving cure between short course fluoroquinolone and conventional TMP-SMX treatment (157, 160). McCarty *et al.* further reported no difference in the proportion of cure between short course fluoroquinolone, and short

course TMP-SMX treatment (147). Thus, cystitis may be adequately treated with a short course of either a fluoroquinolone or TMP-SMX. However, short courses of amoxicillin and nitrofurantoin were found to be inferior to short course TMP-SMX (140).

Although evidence suggests that single dose treatment with TMP-SMX or a fluoroquinolone are equivalent to longer durations of treatment, guidelines suggest a short course treatment of three days (11, 12, 139). Even with successful treatment, symptoms of cystitis may persist for two to three days, prompting unwarranted return physician visits and increased healthcare costs. Thus, the recommended duration of therapy is three days for trimethoprim or TMP-SMX with recommendations for nitrofurantoin varying from 3 to 7 days (11, 12, 139). When second-line therapy with a fluoroquinolone is required, 3-day treatment is recommended (11, 12, 139).

2.4.4.2.2 Pyelonephritis

Optimum duration of out-patient treatment of pyelonephritis has received little study. Stamm *et al.* reported no significant difference between two and six weeks of treatment for pyelonephritis with ampicillin or TMP-SMX (141). Although being underpowered, this study is commonly cited as the rationale for the current recommendation of a two-week treatment for pyelonephritis. Recently, Talan *et al.* demonstrated a significant difference in the proportion of subjects achieving clinical cure subsequent to treatment with ciprofloxacin for 7 days or TMP-SMX for 14 days (151). Current guidelines suggest a 14-day course of treatment with either TMP-SMX or a fluoroquinolone (11, 12, 139).

2.4.5 Resistance

Studies of antibiotic resistance among uropathogens are summarized in Table 4. Since *E. coli* is the most commonly isolated pathogen in community-acquired UTI, several of these studies report antibiotic resistance separately for this pathogen, in addition to all urinary pathogens isolated. Gruneberg reported relatively low resistance among urinary pathogens to ampicillin/amoxicillin in London in the early 1970s, however, by 1978 over 20% of urinary isolates were resistant to these agents (162). The proportion of ampicillin/amoxicillin resistant isolates had risen to over 38% by 1989 (163). This increase in resistance contributed to the abandonment of amoxicillin and/or ampicillin as first-line treatment for UTI. Amoxicillin was largely replaced as first-line treatment by such agents as TMP-SMX, trimethoprim, and amoxicillin-clavulanic acid. Amoxicillin-clavulanic acid was little used in North America for UTI; rather TMP-SMX was commonly prescribed (2). However during the 1980s and 1990s uropathogens evidenced increasing resistance to TMP-SMX, and trimethoprim alone (7, 163). The proportion of uropathogens exhibiting resistance to TMP-SMX rose from 4.3% to 16.3% in London from 1981 to 1989 (163) and from 8.0% to 16.0% in the USA from 1992 to 1996 (7). However, more moderate increases were reported by Dyer *et al.* (165). In 1998, in Canada, 41.0% of community isolated uropathogens were resistant to ampicillin while 19.2% were resistant to TMP-SMX (10). This level of resistance has resulted in concern regarding the suitability of TMP-SMX for empiric treatment of UTI (7). Use of fluoroquinolones in Canada exhibited a steady increase from 1995 to 1999. Whether increasing use is warranted due to increasing resistance to older agents is unknown.

Currently antibiotic resistance to fluoroquinolones among community-acquired uropathogens is below 2% (10).

When interpreting results of antibiotic resistance studies, especially those of a retrospective nature, it is important to note the conditions under which the isolates were collected. Subjects providing a urine culture may not be reflective of the general population, or the population of interest. Physicians may preferentially request urine cultures for patients they consider more likely to harbour resistant organisms, such as males, the elderly and patients with diabetes. In addition, physician practice patterns may change in this regard over time due to external influences (e.g., policy changes, publication of practice guidelines) leading to spurious results in longitudinal studies. For example, Gupta *et al.* noted that a practice guideline adopted by physicians in a Health Maintenance Organization in 1995/6 may have affected physician decisions regarding the ordering of urine cultures (7). Specifically, it was thought that physicians may have increasingly reserved urine cultures for those who had failed initial empiric treatment. However, a chart review of a random sample of subjects' charts revealed that 95% of urine cultures continued to be for patients who had not recently failed therapy for UTI. Thus, the investigators considered changes in antibiotic resistance over the study period to be reflective of actual changes in susceptibilities, and not due to a difference in the patient population being cultured. However, it remains that cultures may still be ordered specifically for populations deemed more likely to harbour resistant organisms.

Wright *et al.* performed a retrospective review of antibiotic susceptibilities of uropathogens among adult outpatients diagnosed with UTI to identify risk factors for multi-drug resistant pathogens (166). Possible risk factors examined included: older age,

male gender, history of greater than two previous UTI, use of antibiotics or hospitalization within the previous three months, presence of diabetes, and presence of urological or neurological disorders (excluding seizure). Exclusion of patients with catheter usage revealed, age greater than 65 years, presence of diabetes, and previous use of antibiotics were independently associated with UTI caused by multi-drug resistant uropathogens. History of UTI, male gender, recent hospitalization or urologic or neurological disorder were not independently associated with infection due to multi-drug resistant organisms. Eiband *et al.* confirmed the association between diabetes and multi-drug resistant uropathogens (167), however, Lye *et al.* failed to find a significant association between the presence of diabetes and UTI caused by an antibiotic-resistant pathogen (168). Goldstein *et al.* refuted the association between age and antibiotic resistance; these researchers maintained that possessing one or both of the risk factors, antibiotic use within the previous three months or hospitalization within the previous six months, was significantly associated with UTI caused by multi-drug resistant *E. coli* (169).

The relationship between antibiotic resistance and treatment outcome is poorly described. Therefore, little is known about the clinical importance of *in vitro* resistance in treating UTI. Indeed many studies designed to compare treatment efficacy exclude subjects with pathogens resistant to one or more of the study drugs (141-144, 146, 148, 149, 153, 154, 159). The clinical importance of *in vitro* resistance may depend on the site of infection; upper versus lower urinary tract. Cystitis is a superficial infection of the bladder epithelium and inadequately treated infections are unlikely to progress to more invasive infections. Mabeck indicated that 80% of women with cystitis treated with

placebo were spontaneously cured within 5 months (170). Thus, while symptoms associated with cystitis are worthy of treatment, the potential for serious sequelae in situations of antibiotic resistance are small.

Achievement of cure of cystitis in the situation of antibiotic resistance is likely multi-factorial; dependent upon factors such as infecting organism, antibiotic treatment, duration of treatment, and patient related variables. Stein *et al.* reported bacterial eradication in three out of three subjects infected with TMP-SMX resistant *E. coli* after a 10-day treatment with TMP-SMX (160). Hooton *et al.* reported two of three subjects infected with TMP-SMX resistant bacteria achieved bacteriologic cure following treatment with TMP-SMX for seven days (157). In a comparison of amoxicillin and TMP-SMX for three days, Hooton *et al.* reported only one of five subjects with pathogens resistant to amoxicillin were cured (140). In contrast, both subjects with pathogens resistant to TMP-SMX obtained bacteriologic cure with TMP-SMX. In a comparison of a single dose and 7-day treatments of TMP-SMX, Osterberg *et al.* reported failure in both subjects infected with TMP-SMX resistant pathogens who received a single dose, and five of eleven subjects treated with 7-day treatments (156).

Pyelonephritis is an invasive infection, with the potential for serious sequelae in the situation of inadequate treatment. The lack of studies which include subjects with resistant pathogens, results in little information regarding the clinical implications of resistant pathogens in pyelonephritis. However, Talon *et al.* reported bacteriologic failure in seven of fourteen (50%) subjects infected with TMP-SMX resistant *E. coli* treated with a 14-day course of TMP-SMX (151).

Table 4. **Studies reporting the proportion of uropathogens exhibiting resistance to commonly used antibiotics**

Author	Study Country	Study Type	Study Year	All uropathogens (%)				E-coli (%)			
				AM*	TS#	TMP†	NF‡	AM*	TS#	TMP†	NF‡
Gruneberg (157)	UK	Retrospective	1971	11.8	3.4	6.0	14.4	8.6	0.8	1.5	2.4
			1978	20.6	3.0	9.1	9.4	13.7	1.8	3.5	1.8
Gruneberg (158)	UK	Retrospective	1981	33.8	4.3	8.9	15.9	24.4	1.6	4.3	4.7
			1989	38.1	16.3	17.5	12.2	34.2	17.3	17.6	3.0
Dyer *et al.* (160)	USA	Retrospective	1991	-	-	-	-	30.3	14.6	-	0.0
			1997	-	-	-	-	38.9	15.4	-	0.0
Gupta *et al.* (7)	USA	Retrospective	1992	29.0	8.0	9.0	7.0	26.0	9.0	9.0	1.0
			1996	38.0	16.0	16.0	6.0	34.0	18.0	18.0	0.2
Goldstein *et al.* (164)	France	Prospective	1996/7	45.6	22.1	-	-	41.3	21.8	-	-
Zhanel *et al.* (9)	Canada	Prospective	1998	41.0	19.2	-	5.0	41.0	18.9	-	0.1

*Ampicillin; #Trimethoprim-sulfamethoxazole; †Trimethoprim; ‡Nitrofurantoin

2.4.6 Patient Variables and Response to Treatment

In addition to the influence of site of infection, choice of antibiotic, duration of treatment, and resistant organisms, a few studies have examined the effect of patient variables on the response to treatment. In a comparison of 1 and 3-day regimens of norfloxacin for treatment of cystitis, Saginur *et al.* indicated, women greater than 40 years of age were significantly less likely to be cured with either regimen than women less than 40 years of age (159). This difference was irrespective of the tendency for older subjects to harbour resistant pathogens, as subjects with resistant pathogens were excluded from the study. Contrasting results were reported by Iravani *et al.*, indicating no significant difference in cure between women less than 30 years of age and those greater than 30 years of age. (149). A history of UTI within the previous six weeks was reported by Fihn *et al.* to be significantly associated with treatment failure, however, a history of UTI within the previous six to twelve months was not (152). Osterberg *et al.* reported no significant difference in the proportion of cure between women who had experienced two or more UTI within the previous two years and those who had not (156).

2.4.7 Need for additional comparative studies

Fluoroquinolones are a class of broad-spectrum oral antibiotics, which have been shown to be highly efficacious in the treatment of UTI. However, a course of treatment with fluoroquinolones is approximately 20 times the price of an equivalent course of TMP-SMX. In addition, overuse of fluoroquinolones presents a concern due to the potential for the development of antibiotic resistance to this valuable class of agents.

Thus, if both fluoroquinolones and TMP-SMX provide comparable treatment outcomes, there seems little justification for the use of fluoroquinolones for this condition.

Many RCT have reported equal efficacy of TMP-SMX and fluoroquinolone in the treatment of cystitis, although subjects with antibiotic-resistant organisms were often excluded. Current treatment guidelines suggest initial treatment with TMP-SMX, reserving fluoroquinolones as second-line agents. Since cystitis is a superficial infection this approach seems reasonable.

There are few comparative studies of TMP-SMX and fluoroquinolones in pyelonephritis. However, Talan *et al.* reported that fluoroquinolones provide superior treatment outcome compared to TMP-SMX, especially in the situation of antibiotic resistance (151). Currently, both TMP-SMX and fluoroquinolones, in combination with a urine culture, are recommended for initial treatment of pyelonephritis. Although urine cultures are recommended in the treatment of pyelonephritis, physicians must treat empirically pending the results of urine culture (12, 139). Thus, recent increases in resistance to TMP-SMX among uropathogens and the invasive nature of the infection, has resulted in concern regarding the suitability of TMP-SMX for empiric treatment of pyelonephritis. However, given the considerably higher cost of fluoroquinolone treatment and the potential for the selection of resistant strains, it is desirable to reserve these agents for the patient population most likely to fail treatment with TMP-SMX. Thus, studies which include both large numbers and a heterogeneous mixture of subjects are needed to establish the comparative effectiveness of TMP-SMX and fluoroquinolones for treatment of pyelonephritis. In addition, analysis of treatment modifying effects may assist in determining the patient population for whom fluoroquinolones should be reserved.

Chapter 3.

Methods

This chapter describes the objectives of the current study, the relevant hypotheses, in addition to the data sources and methodology selected to address the stated hypotheses. As administrative healthcare claims from Manitoba Health were used as a data source, a detailed description of the database is provided, in addition to an explanation of the development of operational definitions of subject variables. Finally, the approach to data analysis is described.

3.1 Objectives

The current study has three major objectives as outlined below.

(i) To determine the patient-specific variables which influence physicians' decisions to prescribe fluoroquinolones over TMP-SMX for out-patient treatment of community-acquired pyelonephritis.

(ii) To determine the comparative effectiveness of these two treatments (fluoroquinolones and TMP-SMX) for community-acquired pyelonephritis, and how patient-specific variables affect the comparative effectiveness.

(iii) To examine the utility and limitations of using administrative healthcare claims to address questions of comparative effectiveness of pharmaceuticals.

3.2 Justification of Study Hypotheses

For the current study the following hypotheses are proposed regarding the effect of subject specific variables on the probability of receipt of a fluoroquinolone for the treatment of pyelonephritis, and treatment outcomes arising from the two recommended treatments; TMP-SMX and fluoroquinolones. Hypotheses 1 to 8 relate to the probability of receipt of a fluoroquinolone, rather than TMP-SMX, for initial treatment of a new episode of pyelonephritis. Hypotheses 9 to 13 relate to the comparative effectiveness of fluoroquinolones and TMP-SMX for initial treatment of a new episode of pyelonephritis.

Hypothesis #1

Age is positively associated with receipt of a fluoroquinolone, compared with TMP-SMX, for initial treatment of an acute episode of pyelonephritis.

Older subjects are hypothesized to be more likely to receive a fluoroquinolone than younger subjects for two reasons; the effect of increasing age on the propensity to harbour antibiotic-resistant pathogens, and the greater likelihood of comorbidities.

Several studies have identified increasing age as a risk factor for UTI caused by resistant uropathogens (166, 171, 172). A study of subjects presenting to the emergency room (ER), indicated that age greater than 64 years was an independent risk factor for UTI caused by multi-drug resistant pathogens (166). Similarly, Ena *et al.* reported age greater than 65 years was an independent risk factor for UTI caused by fluoroquinolone resistant *E. coli* among hospital inpatients (172). Conversely, Eiband *et al.* indicated age

was not significantly associated with the risk of UTI caused by multi-drug resistant pathogens (167). However, this study was restricted to a geriatric hospital population.

Arstila *et al.* examined the antibiotic sensitivity of urinary isolates of *E. coli* among non-catheterized hospital inpatients. Increasing age (measured in decades) was found to be significantly associated with resistant pathogens (171). However, uropathogens resistant to fluoroquinolones are relatively rare in Canada, compared to resistance to TMP-SMX (10). Thus, older subjects with UTI are more likely to harbour uropathogens resistant to TMP-SMX than to fluoroquinolones.

Increasing age may result in physicians prescribing broad spectrum antibiotics for reasons unrelated to the increasing likelihood of antibiotic-resistant pathogens in this patient population. Older subjects are more likely to have comorbidities, which would confer a higher risk of complication from inadequately treated infections. As initial treatment of infectious disease in community practice is largely empirical, physicians may be expected to reserve broad-spectrum antibiotic treatments for older patients. The relationship between increasing age and likelihood of receipt of broad spectrum antibiotics has been previously demonstrated (173, 174). Strand *et al.* examined initial treatment (penicillin V versus other broader spectrum antibiotics) for respiratory infections, for which penicillin V was considered the first antibiotic of choice (173). Subjects aged 13 to 64 years of age were significantly more likely to receive treatment with the narrow spectrum agent (penicillin V) than subjects less than 13 years or greater than 65 years. Similarly, McCombs and Nichol reported increasing age among adults to be an independent risk factor for the receipt of broad spectrum second-line antibiotics in

general (174). Thus, the likelihood of receipt of a fluoroquinolone for the treatment of an acute episode of pyelonephritis is expected to increase with age.

Hypothesis #2

Recent antibiotic use is positively associated with receipt of a fluoroquinolone, compared with TMP-SMX, for initial treatment of an acute episode of pyelonephritis.

Recent antibiotic use (within the previous three months) has been reported to increase fecal carriage of antibiotic-resistant enteric bacteria (175). Similarly, recent antibiotic use has been identified as an independent risk factor for UTI caused by resistant organisms in both community and hospital acquired infections (166, 169, 172, 176, 177). Several studies have focused on the development of resistance to individual antibiotics subsequent to recent consumption of those antibiotics (172, 176, 177). However, the ability of bacteria to carry genes conferring resistance to multiple antibiotics is well known (178-180). Thus, any recent antibiotic treatment may select for bacteria resistant to antibiotics unrelated to the recently used agent. For example, Wright *et al.* reported recent antibiotic use to increase the likelihood of urinary tract infections caused by multi-drug resistant bacteria (166). Therefore, recent use of any antibiotic or class of antibiotics may select for bacteria which possess genes conferring resistance to either of our study drugs, and in turn, increase the likelihood of treatment failure. However, uropathogens resistant to fluoroquinolones are relatively rare in Canada compared to resistance to TMP-SMX. (10). For this reason, subjects with recent antibiotic use would be expected to have a higher likelihood of infection with a TMP-SMX resistant uropathogen than a

fluoroquinolone resistant uropathogen. Thus, physicians are expected to preferentially prescribe fluoroquinolones for subjects reporting recent antibiotic use.

Hypothesis #3

Recent hospitalization is positively associated with receipt of a fluoroquinolone, compared with TMP-SMX, for initial treatment of an acute episode of pyelonephritis.

The proportion of bacterial isolates exhibiting antibiotic resistance is higher in the hospital environment compared to the community (162, 163, 181, 182). Many factors which contribute to the higher prevalence of resistance among hospitalized patients have been suggested (183), including excessive and inappropriate prescribing of broad-spectrum antibiotics. In addition, environmental contamination and the breakdown of basic infection control techniques, which may result from overcrowding and understaffing in hospitals, contributes to the dissemination of antibiotic resistance (183).

Leistevuo *et al.* reported an increased risk of fecal colonization with antibiotic-resistant gram-negative bacilli in hospitalized elderly, compared to the community-dwelling elderly; moreover, increasing duration of hospitalization resulted in increased risk (184). Much of the emergence of antibiotic resistance in hospitals may go undetected, since only a minority of patients, thus colonized, may develop immediate clinical infection. However, the hospital may serve as a reservoir for the dissemination of antibiotic resistance into the community. Recently hospitalized subjects, who develop subsequent infections, may be more likely to be infected with antibiotic-resistant organisms, than those not previously hospitalized. Studies examining the prevalence of resistance among community-acquired UTI confirmed that recent hospitalization (defined

as anywhere from two to six months previous) increased the risk of infection caused by antibiotic-resistant pathogens (167, 169, 175, 177). However, Steinke *et al.* reported that recent hospitalization (within the last six months) was protective for UTI caused by antibiotic-resistant organisms (176). As with other suggested risk factors for infections due to antibiotic-resistant pathogens, recent hospitalization is expected to increase the likelihood of receipt of a fluoroquinolone due to the greater prevalence of TMP-SMX resistance compared to fluoroquinolone resistance among uropathogens.

Hypothesis #4

Recent UTI is positively associated with receipt of a fluoroquinolone, compared with TMP-SMX, for treatment of an acute episode of pyelonephritis.

Wright *et al.* identified a history of recurrent UTI as a significant univariate risk factor for UTI caused by both multi-drug and TMP-SMX resistant organisms (166). However, the effect of recurrent UTI did not maintain significance in multivariate analysis. Ena *et al.* reported no significant association between recurrent UTI, and UTI caused by ciprofloxacin resistant organisms (172). Since there is some evidence to suggest that recent UTI may be a risk factor for UTI caused by resistant pathogens (166), it is reasonable to hypothesize that physicians may preferentially prescribe fluoroquinolones to subjects with a history of recent UTI, due to the greater prevalence of TMP-SMX resistance, compared to fluoroquinolone resistance, among uropathogens.

Hypothesis #5

The presence of diabetes is positively associated with receipt of a fluoroquinolone, compared with TMP-SMX, for initial treatment of an acute episode of pyelonephritis.

As with previous subject characteristics, the effect of diabetes on choice of initial treatment is likely related to the effect of diabetes on the antibiotic susceptibility of uropathogens. Whilst Lye *et al.* reported no significant difference in the antibiotic susceptibility of uropathogens isolated from non-diabetic versus diabetic subjects (168), several researchers have identified diabetes as an independent risk factor for UTI caused by antibiotic-resistant organisms (166, 167, 177). Again, the relative rarity of uropathogens resistant to fluoroquinolones, compared to TMP-SMX, is expected to result in physicians preferentially prescribing fluoroquinolones, in the diabetic population, for treatment of pyelonephritis.

Hypothesis #6

Income is positively associated with receipt of a fluoroquinolone, compared with TMP-SMX, for initial treatment of an acute episode of pyelonephritis.

The relationship between income and health services utilization has been well documented (185-188). In Manitoba, residents with lower household income are higher users of medical services. Metge *et al.* reported differences in pharmaceutical usage in Manitoba by income quintile[b] (189); overall use of pharmaceuticals was highest in those with the lowest income. However, this trend was less clear for the use of antibiotics, specifically. While subjects in the lowest income quintile exhibited the highest antibiotic consumption, no differences were identified between those subjects in the second to fifth

[b] Income quintiles are calculated yearly by the Manitoba Centre for Health Policy, using recent census data from Statistics Canada to assign subjects to an income quintile based on average household income by neighbourhood. The top 20% of the population by mean neighbourhood income is identified as quintile 5 while the lowest 20% of the population is identified as quintile 1.

quintiles. No data were reported regarding differences in the use of broad spectrum versus narrow spectrum agents by income quintile.

Henricson *et al.* examined the effect of various measures of socio-economic status on the likelihood of receipt of penicillin V by children, compared with more broad spectrum antibiotics (190). Neighbourhood income was identified as an independent risk factor for receipt of broad spectrum agents. As income increased the likelihood of receipt of penicillin V decreased and the likelihood of receipt of a broad spectrum antibiotic increased.

The cost of treatment for pyelonephritis with a fluoroquinolone is approximately 20 times higher than that of TMP-SMX. Since the majority of Manitobans are responsible for at least a portion of the cost of their prescription pharmaceuticals, the economically privileged may be expected to absorb the cost of treatment more readily. In addition, the receipt of a fluoroquinolone may be related to income regardless of responsibility or ability to pay for the prescription. Roos and Mustard observed that while use of physician services was highest among subjects in the lowest income group, specialists provided more care to the healthiest, most affluent subjects (186). Stranc reported pregnant women over 35 years of age in the highest income quintile were more likely to use obstetricians (versus general practitioners) for prenatal care than pregnant women in the lowest income quintile (188). Furthermore, higher income quintile was associated with an increased likelihood of being referred for genetic testing. Thus, utilization of higher cost and/or more specialized health services exhibit differences across income quintiles, despite a lack of direct patient responsibility for payment for such services. Broad spectrum/high cost antibiotics may be likened to specialist services, where differences in use by income

quintile exist, regardless of the responsibility for payment. Therefore, the proportion of subjects receiving initial treatment with a fluoroquinolone is expected to increase with increasing income.

Hypothesis #7

Rural residence is associated with an increased likelihood of receipt of a fluoroquinolone, compared with TMP-SMX, for initial treatment of an acute episode of pyelonephritis.

Differences in the use of health care services, by urban/rural status, have been examined from the perspective of the location of health service or location of subject residence. McCombs and Nichol reported rural residence of subject to be associated with an increased likelihood of receipt of second-line broad spectrum antibiotics (174). Straand *et al.* reported similar results utilizing location of physician practice (173); that is, broad spectrum antibiotics were more likely to be received by subjects who presented to physicians in rural practice locations. Molstad *et al.* used pharmacy location to examine differences in antibiotic use by urban/rural status (191). Penicillin V (a narrow spectrum antibiotic) accounted for a greater proportion of antibiotic prescriptions dispensed by rural pharmacies, than urban pharmacies. However, this difference was thought to be explained by differences in the type of physician servicing these areas. Care by district physicians was more common in rural areas while care by private practitioners was more common in urban areas, and private practitioners prescribed more broad spectrum agents than district physicians. In Manitoba, private practitioner/non-private practitioner distinctions are not a factor, thus, a larger proportion of subjects residing in

rural areas are expected to receive a fluoroquinolone, due to the possibility of reduced access to care in rural areas.

Hypothesis #8

Presentation to an emergency room (ER) is associated with an increased likelihood of receipt of a fluoroquinolone, compared with TMP-SMX, for initial treatment of an acute episode of pyelonephritis.

No data supporting a hypothesis of differences in antibiotic prescribing practices, between ER physicians and those engaged in office practice, could be found. However, differences in patient characteristics between those subjects presenting to ER versus those presenting to physicians' offices may impact prescribing decisions. Patients with greater severity of symptoms may be more likely to present to an ER than those subjects with less severe symptoms, and those with more severe symptoms may be more likely to receive a fluoroquinolone, due to physicians' assumptions of greater efficacy.

In addition to severity of illness, other patient factors may determine the likelihood of presentation to an ER, and consequently receipt of a fluoroquinolone. Mustard *et al.* reported treaty Indian status, and lower neighbourhood income were positively associated with use of an ER (187). Treaty status and low income status may identify those persons who, for cultural and/or social reasons, choose the ER for primary care. Such people may be more mobile, and/or have family/work situations which make it difficult to keep appointments and are less accessible for follow-up, resulting in poor continuity of care. Mustard *et al.* reported treaty status and low neighbourhood income among children to be associated with a lower continuity of care (192).

In the treatment of pyelonephritis urine culture is recommended. Initial treatment, especially with TMP-SMX, may need to be amended based on the results of urine culture and susceptibility testing due to the prevalence of antibiotic-resistant organisms. Subjects who choose the ER for primary care may be presumed to be less accessible for such follow-up, thus resulting in a decision to treat initially with a fluoroquinolone.

Hypothesis #9

Increasing age is positively associated with treatment failure, acting as an effect modifier[c] in the relationship between initial antibiotic treatment (TMP-SMX versus fluoroquinolones) and treatment failure. Specifically, increasing age will exert a greater effect on treatment failure for subjects treated with TMP-SMX than those treated with a fluoroquinolone.

As previously indicated, several studies have identified increasing age as a risk factor for UTI caused by resistant uropathogens (166, 171, 172). The impact of age on treatment outcome in UTI has been infrequently examined using RCT. In a comparison of single dose and 3-day norfloxacin treatments of cystitis, age greater than 40 years was reported to result in significantly reduced cure for both treatment durations (159). However, this was independent of the tendency for older subjects to harbour resistant pathogens as subjects with resistant pathogens were excluded from the analysis. Conversely, Irvani *et al.* reported no association between age greater than 30 years and treatment failure in cystitis (149). However, once again subjects with resistant pathogens were excluded from the analysis.

Increasing age is expected to impact treatment outcome due to the increasing tendency of older subjects to harbour resistant pathogens. Due to the relatively rarity of

[c] Effect modification exists when the strength of association between two variables differs according to the level of a third variable. The third variable is considered an effect modifier.

uropathogens resistant to fluoroquinolones in Canada (10), increasing age is expected to negatively impact cure subsequent to initial treatment with TMP-SMX, to a greater degree than treatment with a fluoroquinolone. In addition, age may also be an risk factor for treatment failure apart from its relationship to antibiotic resistance.

Hypothesis #10

Recent antibiotic use is positively associated with treatment failure, acting as an effect modifier in the relationship between initial antibiotic (TMP-SMX versus a fluoroquinolone) and treatment failure.

As subjects with recent antibiotic use are commonly excluded from RCT of treatment of UTI, little data are available regarding the effect of recent antibiotic use on treatment outcome. However, recent antibiotic use has been identified as a risk factor for UTI caused by antibiotic-resistant uropathogens (166, 172, 176, 177). Since resistance among uropathogens to fluoroquinolones is relatively rare, compared to TMP-SMX (10), recent antibiotic use is expected to negatively impact cure in subjects treated with TMP-SMX to a greater degree than those subjects treated with a fluoroquinolone.

Hypothesis #11

Recent hospitalization is positively associated with treatment failure, acting as an effect modifier in the relationship between initial antibiotic treatment (TMP-SMX versus fluoroquinolones) and treatment failure.

No data regarding the impact of previous hospitalization on outcome of treatment with TMP-SMX or a fluoroquinolone for UTI are available. However, as previously indicated, recent hospitalization has been identified as a risk factor for UTI caused by antibiotic-resistant uropathogens (167, 169, 175, 177). Again, due to the relatively rarity of

uropathogens resistant to fluoroquinolones in Canada (10), recent hospitalization is expected to negatively impact cure subsequent to initial treatment with TMP-SMX to a greater degree than treatment with a fluoroquinolone.

Hypothesis #12

Recent UTI is positively associated with treatment failure, acting as an effect modifier in the relationship between initial antibiotic treatment (TMP-SMX versus fluoroquinolones) and treatment failure.

Several studies have reported the effect of previous UTI on outcome of treatment of UTI (140, 142, 152, 156). Fihn *et al.* reported, history of UTI in the previous 6 weeks to be an independent risk factor for treatment failure, while a history of UTI in the previous 6-12 months was not (152). Sigurdson reported recurrent UTI was not associated with treatment failure, however subjects with resistant strains were excluded from the study (142). Several other investigators who included subjects with antibiotic-resistant organisms reported no significant association between treatment failure and history of UTI (140, 156).

The effect of previous UTI on the prevalence of resistant organisms in subjects with UTI and subsequent treatment outcome appears controversial. However, there is some evidence to suggest that previous UTI increases the likelihood of UTI caused by antibiotic-resistant pathogens and subsequent treatment failure. Therefore recent UTI is expected to negatively impact cure subsequent to initial treatment with TMP-SMX to a greater degree than treatment with a fluoroquinolone.

Hypothesis #13

The presence of diabetes is positively associated with treatment failure, acting as an effect modifier in the relationship between initial antibiotic treatment (TMP-SMX versus fluoroquinolones) and treatment failure.

The relationship between diabetic status and treatment failure of UTI has not been explored using RCT. Several trials have excluded subjects with diabetes (144, 146, 151, 153, 155), while others have excluded subjects with neurogenic bladder or functional abnormalities of the urinary tract (140, 141, 149, 150, 156-160). Given that neurogenic bladder and functional abnormalities of the urinary tract are complications of long-term diabetes, exclusion of such subjects may be, in effect, an exclusion of subjects with long-term diabetes. As previously indicated, diabetes has been identified as an independent risk factor for UTI caused by antibiotic-resistant organisms (166, 167, 177), and resistance to fluoroquinolones among uropathogens is less common than resistance to TMP-SMX (10). Thus, diabetes is expected to negatively impact cure subsequent to initial treatment with TMP-SMX to a greater degree than that with a fluoroquinolone.

3.3 Selection of Methodology

If drug effectiveness is that which results from a drug's use in everyday practice, it follows that to determine treatment effectiveness everyday practice must be observed. In keeping with this perspective, the present study is of a retrospective observational cohort design. Being able to Observe treatment outcomes in a sufficiently large and comprehensive a patient pool in order to provide the necessary power for an examination of effects of patient variables on treatment outcome, provides a formidable challenge. Administrative healthcare claims of the province of Manitoba were used as the data source, as their use conferred many advantages for the current study. As Manitoba residents enjoy universal healthcare coverage, records of healthcare utilization are available for all services (with some exceptions) for all Manitobans, thus enhancing the external validity of results. In addition, administrative data have the benefit of being objective, non-obtrusive and less labour intensive than medical chart review. Furthermore, loss to follow-up is minimized since only subjects' claims need be followed up, rather than the subjects themselves, and finally, large numbers of subjects may be studied at minimal cost.

The study of treatment outcomes of infectious disease may be particularly suited to the use of administrative data, providing that data regarding both access to medical care and pharmaceuticals are available. Since symptoms of acute bacterial infection are by their nature of sudden onset, the prompt seeking of healthcare services is to be expected. Thus, the identification of the initial presentation of infection is facilitated, and subjects should be fairly comparable in terms of disease stage at presentation to the healthcare system.

As cure is the desirable and expected outcome of treatment for pyelonephritis, lack of resolution of symptoms should result in the seeking of further healthcare services, and the generation of additional healthcare claims. The existence of additional healthcare claims may be used as a proxy measure of treatment failure. To address the stated hypotheses, healthcare claims from the Manitoba Health database (accessed through the Manitoba Centre for Health Policy), were evaluated using a retrospective observational cohort design. Following is a description of the contents and organization of this administrative healthcare database.

3.4 Data Sources

Manitoba Health has provided computerized healthcare claims data to the Manitoba Centre for Health Policy (MCHP) since the 1970s. Using these data, the MCHP has undertaken research in the area of healthcare utilization for the purpose of informing decisions regarding healthcare policy. The MCHP acts as a steward of the data, maintaining patient anonymity while ensuring the ability to construct detailed patient histories by linking data across multiple datasets, through the use of scrambled patient identifiers. Linkage of healthcare utilization data with other data sources (e.g., Public Access Census Data) has facilitated research examining patient factors affecting the health of Manitobans (186, 193).

The province of Manitoba has a universal healthcare system. Costs of medical and hospital care (with a few exceptions), for approximately 1.1 million residents are borne by the government of Manitoba's Ministry of Health. Funding of healthcare costs is financed from general revenues of the province of Manitoba with additional funds

provided by the federal government of Canada. All persons are eligible for healthcare benefits who make Manitoba their principle residence and are physically present in Manitoba for at least six months of a calendar year. Persons moving from Manitoba, either within or outside Canada, maintain healthcare benefits for the month in which they move plus an additional two months.

Insured health benefits include medically required physician services, provided at home, in office, or in institutions (e.g., hospitals and/or personal care homes). Diagnostic services, including X-ray and laboratory services upon a physician's order, are covered, as are services provided in hospitals (accommodation, nursing, pharmaceuticals and diagnostic services). Individual healthcare claims are maintained in a computerized database by Manitoba Health and are subsequently made available to the MCHP on an annual basis. Although the cost of pharmaceuticals by out-patients is not wholly borne by the Ministry of Health, data describing the majority of non-hospital prescription pharmaceutical use are captured by Manitoba Health (99).

The existence of unique patient identifiers allows for computer linkage across the various components of the data repository and ensures that complete histories of medical care received by each resident may be constructed. Four components of the Manitoba Health database were linked for this study. These include the Medical Claims, Hospital Separation Abstracts, Drug Programs Information Network claims, and the Registry File, as described below.

3.4.1 Medical Claims

The Medical Claims (MC) contain records for reimbursement of services rendered by physicians, in addition to diagnostic services (e.g., laboratory, radiology) provided by private laboratories upon a physician's order. Claims may include those provided in a variety of settings (e.g., home, office, hospital, or personal care home) and include such services as physician visits, surgical procedures, and special tests. An explanation of the MC data-fields examined for the current study may be found in Table 5.

Since remuneration for the majority of Manitoba physicians is based on a fee-for-service model, under-reporting is unlikely. However, physician services in certain instances are provided by salaried physicians. For example, although the cost of providing emergency room (ER) treatment is included in a hospital's global budget, salaried ER physicians in certain areas of Manitoba are required to submit "shadow billings". These include ER physicians at the Health Sciences Centre and St. Boniface General Hospital in Winnipeg, as well as ER physicians in non-Winnipeg hospitals. ER physicians at Winnipeg hospitals (other than the Health Sciences Centre and St. Boniface General Hospital) are not required to shadow bill, thus underreporting of ER claims is expected. Office based physicians in rural areas may also be salaried, as are physicians providing care in a few Winnipeg clinics; these physicians are also required to shadow bill.

Diagnostic services required by ER patients are provided by in-hospital laboratories which are funded by the hospital's global budget. Claims for diagnostic services provided in hospital are not submitted to, or recorded by, Manitoba Health. In addition, few private laboratories providing diagnostic services to out-patients exist in rural areas. Diagnostic

services to rural residents are provided by Laboratory and Imaging Services of Manitoba Health. patient-specific claims for these services are not included in the MC. Thus, under-reporting of diagnostic services for rural residents and those accessing care in the ER is expected.

3.4.2 Drug Programs Information Network (DPIN)

The DPIN contains records of pharmaceuticals dispensed by Manitoba pharmacies. The DPIN has been previously described (see section 2.3.1). Instituted in 1994, the DPIN has been determined to be a valid and reliable source of information regarding out-patient prescription pharmaceutical use by Manitoba residents (99). An explanation of the DPIN data-fields examined for the current study may be found in Table 6.

3.4.3 Hospital Separation Abstracts

The Hospital Separation Abstracts (HSA) contain data regarding hospital stays for all Manitoba residents admitted to Manitoba hospitals. Upon patient death or discharge, medical records personnel abstract and submit data relevant to the hospital stay to Manitoba Health. In certain circumstances, HSA are generated for patients who were not technically admitted to hospital. These include patients receiving same-day surgery or diagnostic procedures. In addition, claims for hospital care provided outside the province, are contained in the HSA. An explanation of the HSA data-fields examined for the current study may be found in Table 7.

3.4.4 Registry File

The Registry File (RF) contains a listing of persons currently covered by Manitoba Health benefits. As Manitoba has universal healthcare coverage, this listing is essentially a listing of all Manitoba residents. Exceptions include members of the armed forces and Royal Canadian Mounted Police (RCMP), and residents of federal correctional institutions. Changes in the RF resulting from births/deaths and immigration/emigration are recorded by Manitoba Health and semiannual updates to the RF are provided to the MCHP. In addition, the MCHP creates additional data linkages with other datasets (vital statistics, HSA and Nursing Home claims) to capture any additional deaths not reported by Manitoba Health. An explanation of the RF data-fields examined for the current study may be found in Table 8.

Table 5. **A description/explanation of data-fields in the Medical Claims dataset of Manitoba Health used in the current study**

Data-field	Description/Explanation
Personal Health Identification Number (PHIN)	– used to identify individual subjects and is the basis for linkage across datasets to construct medical histories. To maintain subject anonymity, PHINs are scrambled by Manitoba Health prior to release of data to MCHP.
Gender	– only those subjects identified as female were included in the study.
Date of service	– the date on which the service (physician visit, diagnostic test) was provided.
Diagnosis code	– one diagnosis code may be submitted for each physician visit which describes the primary reason for the visit. Currently, and since 1979, the International Classification of Disease Version 9, with clinical modifications (ICD-9-CM), has been utilized by Manitoba Health. ICD-9-CM codes in the MC are truncated at three digits.
Tariff prefix	- a one digit code that describes the general category of service provided (e.g., physician visit or special test, laboratory, surgical services).
Tariff	- a four digit code which describes the particular service provided (e.g., office visit for complete history and examination, hospital care for regional history and examination, complete urinalysis).
Hospital number	- assigned to all Manitoba hospitals, nursing stations, and personal care homes. In the case of hospital care provided to Manitoba residents in non-Manitoba hospitals, the hospital number indicates the province or country in which the care was provided.
Outpatient indicator	- care provided within a hospital to non-hospitalized patients are designated as either occurring in the emergency room (ER) (indicator = "E") or provided on an outpatient basis (indicator = "O").
Quintile	- an income quintile defined at the MCHP. Data from the public access census files reporting average household income for enumeration areas, and postal or municipal code data from the registry file are used to construct income quintiles. Income quintiles are calculated separately for urban and rural areas.

Table 6. **A description/explanation of data-fields in the Drug Programs Information Network dataset of Manitoba Health used in the current study**

Data-field	Description/Explanation
Personal Health Identification Number (PHIN)	- used to identify individual subjects and the basis for linkage across datasets to construct medical histories. To maintain subject anonymity, PHINs are scrambled by Manitoba Health personnel prior to release of data to MCHP.
Date provided	- the date on which medication is dispensed by the pharmacy.
Drug identification number (DIN)	- an eight digit number assigned by Health Canada to identify drugs which have received a notice of compliance for use in Canada. A single drug entity may have many DINs as different forms (e.g., tablet, capsule, suspension), strengths, and manufacturers will require unique DIN. For the current study DIN were used to identify agents of interest in the situation of missing ATC codes.
Anatomic Therapeutic Chemical (ATC) code	- a system developed by the World Health Organization which uses a five level classification system as a means to identify individual drugs or drug classes (78). ATC codes are assigned to each drug claim by matching DINs on original claims to the Master Formulary maintained by MCHP.
Generic Name	- generic name of drug; used to identify antibiotics when ATC code is absent.
Metric quantity	- number of units supplied by the pharmacy; tablets/capsules for solid dosage forms or, most commonly, milliliters in the case of liquid dosage forms.
Days supply	- number of days supply of drug dispensed when used according to physician order.

Table 7. **A description/explanation of data-fields in the Hospital Separation Abstracts dataset of Manitoba Health used in the current study**

Data-field	Description/Explanation
Personal Health Identification Number (PHIN)	-used to identify individual subjects and the basis for linkage across datasets to construct medical histories. To maintain subject anonymity, PHINs are scrambled by Manitoba Health personnel prior to release of data to MCHP.
Admission date	- date on which patient was admitted to hospital.
Separation date	- date upon which patient was discharged or died in hospital.
Diagnosis codes	- the ICD-9-CM system is used to code up to 16 diagnosis codes for each HSA. Diagnoses may be coded to the fifth digit of the ICD-9-CM codes. The first diagnosis code listed is the usually the "most responsible diagnosis", as described below.
Diagnosis type	- associated with each of 16 possible diagnosis codes, the diagnosis type specifies the relationship of the diagnosis with other listed diagnoses. Possible diagnosis types include: most responsible, primary, or secondary. The most responsible diagnosis is the diagnosis considered to be responsible for the greatest length of a hospital stay. More than one most responsible diagnosis may be submitted.
Length of stay	- the number of days elapsed between admission date and separation date. Hospitalizations which last less than 24 hours, even if admission and separation dates are the same are assigned a length of stay of one day. A length of stay of zero days indicates the HSA was generated for a subject receiving same-day surgical or diagnostic procedures.
Gestation period	- the number of weeks of gestation at admission based on maternal self-report of date of last known menstrual period. This field is required only for obstetric admissions.

Table 8. **A description/explanation of data-fields in the Registry File of Manitoba Health used in the current study**

Data-field	Description/Explanation
Personal Health Identification Number (PHIN)	- used to identify individual subjects and is the basis for linkage across datasets to construct medical histories. To maintain subject anonymity, PHINs are scrambled by Manitoba Health personnel prior to release of data to MCHP.
Date of birth	- used to restrict cohort to those subjects who were between 18-65 years of age on index date.
Date of coverage	- date on which a subject was registered for coverage with Manitoba Health.
Date of cancellation	- date on which a subject's coverage with Manitoba Health was cancelled.

3.5 Development of operational definitions of independent variables

While use of administrative data offers advantages in terms of availability and low cost, lack of clinical data provides challenges in terms of defining study variables. Following are the operational definitions used in the current study for (i) a new episode of pyelonephritis, (ii) explanatory variables (e.g., diabetes, recent antibiotic use), and (iii) outcome variables (initial antibiotic treatment and treatment failure). While it was necessary to construct many of the definitions from existing variables, wherever possible, definitions previously developed by researchers at the MCHP were utilized. If no suitable definitions were available, literature reports of related studies were used to construct suitable operational definitions.

3.5.1 New Episode of Pyelonephritis

Identification of new episodes of pyelonephritis is accomplished by the examination of diagnosis codes submitted for both medical and hospital claims. For Medical Claims (MC), ICD-9-CM codes are truncated at three digits, whereas the Hospital Separation Abstracts (HSA) allow for the recording of diagnoses to five digits. For consistency, and since the number of medical claims was expected to far exceed the number of hospital claims, only the first three digits of ICD-9-CM codes were used, regardless of source.

Three different ICD-9-CM codes are relevant to the diagnosis of urinary tract infection (UTI); specifically, 590 (infection of the kidney), 595 (cystitis) and 599 (other disorders of the urethra and urinary tract). Use of truncated diagnosis codes may result in some uncertainty regarding diagnosis or etiology. For example, the three digit ICD-9-CM code 599, includes such relatively diverse disorders as: urinary obstruction (599.6),

hematuria (599.7), and urinary tract infection of unspecified site (599.0). Thus, claims containing an ICD-9-CM code of 599 may include episodes of upper urinary tract infection (pyelonephritis). As it is not possible to differentiate these episodes from episodes of lower tract infection or other non-infectious conditions included in the three digit truncated code, only those claims for females containing the ICD-9-CM code 590, were eligible for identification as a new episode of pyelonephritis.

It was further necessary to ensure that the physician visit for which the appropriate diagnosis code (ICD-9-CM=590) was submitted identified the first contact for the recorded diagnosis, rather than a repeat visit for standard follow-up care or a repeat visit due to inadequate treatment of an earlier diagnosed UTI. A relapse of an inadequately treated infection is considered to occur within two weeks of cessation of treatment. Guidelines for the evaluation of antibiotic treatments for UTI suggest final treatment evaluation be made four to six weeks after cessation of initial treatment (132). Recommended duration of initial treatment for acute pyelonephritis is fourteen days (11, 12, 139). Thus, a subject with a MC for a physician visit (tariff=7) with an ICD-9-CM code of 590, whose claim history contains no evidence of healthcare claims (either MC or HSA) consistent with a UTI (ICD-9-CM codes 590, 595, 599) in the previous 42 days was defined as having a new episode of pyelonephritis.

The current study concerns the treatment of community-acquired pyelonephritis. Urinary tract infections among the hospitalized and institutionalized have a wider etiology and are more likely to be caused by antibiotic-resistant pathogens (108). Thus, only MC for physician visits for non-institutionalized subjects were defined as new

episodes of pyelonephritis. The procedure used to exclude institutionalized subjects from the cohort is described further in Section 3.6.

UTI are infrequent in childhood, in both males and females, unless complicated by structural abnormalities (109, 115). The incidence of UTI rises sharply for females in young adulthood with the onset of sexual activity (108, 120). The incidence of UTI in young males remains low and is often associated with structural abnormalities (113, 114). Increasing incidence of UTI in the geriatric population is consistent with increasing functional abnormalities, institutionalization, and instrumentation (112, 122). UTI which occur in situations of functional or structural abnormalities and/or institutionalization are considered complicated infections, and are not the subject of this study. In addition, patient age and pregnancy status dictate the suitability of pharmaceutical agents for treatment. Fluoroquinolones are contraindicated during pregnancy and childhood due to the potential for arthropathies (128). Thus, to limit our study population to subjects least likely to have complicated infections, and to be eligible to receive both study drugs, study subjects are restricted to non-pregnant females between the ages of 18 and 65 years.

To summarize, for a MC to be identified as a new episode of pyelonephritis, the following criteria were required:

(i) MC for a physician visit (tariff prefix=7) containing the ICD-9-CM code 590.

(ii) Claimant a non-institutionalized, non-pregnant female aged 18-65 years of age having continuous coverage with Manitoba Health for the study period.

(iii) Claimant with no MC or HSA containing ICD-9-CM codes, 590, 595, or 599 within the previous 42 days.

The MC which met the above criteria identified a new episode of pyelonephritis and is hereafter referred to as the "initial physician visit". The service date of the initial physician visit is labeled the "index date".

3.5.2 Presentation to Emergency Room (ER)

As previously indicated, the MC contain records of physician services provided in hospital ERs. Salary agreements for ER physicians obviates the need for the submission of detailed billings to Manitoba Health for financial remuneration. However, agreements exist (dependent upon the hospital) which require the submission of "shadow billings" by ER physicians. In Winnipeg, ER physicians in St. Boniface General Hospital and the Health Sciences Centre are required to submit shadow billings, as are ER physicians in non-Winnipeg hospitals. However, ER physicians in other Winnipeg hospitals are not required to submit shadow billings, thus, no ER claims from these hospitals are expected.

Claims for physician visits originating from the ER may be differentiated from other physician visits by the out-patient indicator field (see Table 5). Therefore, an ER visit was defined as a MC, meeting the definition of a new episode of pyelonephritis, which contained an "E" in the out-patient indicator field.

3.5.3 Diabetic Status

Identification of subjects with diabetes mellitus may be accomplished by the examination of diagnostic codes present on both medical and hospital claims data. Several researchers have examined the use of diagnostic codes in the MC and HSA of the Manitoba Health database to identify persons with diabetes in Manitoba (24, 194). While

medical and hospital claims were deemed to be valid measures of disease status, differences existed in the number of health care claims required to accurately define diabetic status.

Robinson *et al.* examined agreement between self-reported diabetes and healthcare claims containing diagnoses of diabetes (24). Agreement between self-report and medical and/or hospital claims data was determined for varying time periods (one to three years), and for varying requirements of numbers of claims bearing the appropriate diagnosis (one to three claims). Agreement between self-report and healthcare claims was highest when the greatest number of years of data was used and the fewest number of separate claims were required. In addition, it was noted that medical claims (versus hospital) accounted for the majority of cases ascertained. Among those identified as diabetics from three years of healthcare claims, 68% had medical claims, 27.4% had both medical and hospital claims, and 4.6% of subjects had a hospital claim only.

Blanchard *et al.* examined the healthcare claim histories of persons referred to the Manitoba Diabetes Education Resource (DER) program to develop a method for the identification of persons with diabetes using medical and hospital claims (194). An examination of nine years of healthcare claims (1984 to 1993) revealed that every DER client had at least two medical claims and one hospitalization. In addition the probability of having a subsequent medical contact within two years of a previous contact was 0.96. Based on these findings, Blanchard *et al.* developed a case definition of diabetes for further research. Specifically, individuals with a least 2 separate physician claims (on separate dates) within 2 years, or 1 hospitalization, bearing the ICD-9-CM code 250 were identified as diabetic. It must be noted that Blanchard *et al.* examined a greater number of

years of data than did Robinson *et al.* and this may have offset the impact of the requirement for a greater number of claims.

It is likely that referral to the DER program is reserved for those patients with the most severe disease and/or who make the greatest number of physician contacts. Indeed the probability of being referred to the DER would be expected to be highest for those with the greatest number of healthcare contacts. Thus, the claim history of subjects utilizing the services of the DER may not be reflective of the diabetic population as a whole. Given this, the case definition developed by Blanchard *et al.* may underestimate the number of diagnosed diabetics in Manitoba. Conversely, a case definition requiring only one healthcare claim, as suggested by Robinson *et al.*, may overestimate the number of diagnosed diabetics by including those subjects whose claims may include erroneous diagnosis codes or the recording of a differential diagnosis which was subsequently ruled out.

Decisions regarding the number of claims required and number of years of data examined for case ascertainment will inevitably result in a trade-off between sensitivity and specificity. A requirement for only one healthcare claim with the appropriate diagnosis code may result in false positives (or lowered specificity) due to errors in coding. Requiring the presence of several health care claims may result in false negatives (or lowered sensitivity) by eliminating those subjects who rarely seek medical care.

Since these studies were conducted, pharmaceutical claims have been added to the Manitoba Health database. Pharmaceutical usage may be useful for case ascertainment, particularly in disease states where drug treatments are specific to the disease in question. This is the case with diabetes, where agents to control hyperglycemia do not find use in

other disease states. The addition of pharmaceutical claims to the Manitoba Health database may result in the use of such data to refine case definitions.

While insulin and oral hypoglycemics are specific to diabetes treatment, they may not be used as the sole requirement for case definition since their use is not absolute. Indeed for type 2 diabetes, which accounts for the majority of prevalent diabetes cases, the Canadian Diabetes Association recommends initiating treatment with diet modification and exercise (195), and a lack of treatment has been reported (196). In a 10-year follow-up study of newly diagnosed type 2 diabetics, Brown *et al.* reported 12% of subjects failed to have prescriptions for antidiabetic agents dispensed in the year of diagnosis. In the year subsequent to diagnosis, the proportion of subjects failing to have a prescription for an antidiabetic agent dispensed had risen to 37%.

Due to the uncertainties in using healthcare claims for case ascertainment in diabetes, two definitions of diabetic status were utilized. The difference in case ascertainment was examined and a decision was made regarding the optimum definition for the current study. In summary, diabetic status was assigned based on the following criteria:

Definition I

(i) One or more physician visits (tariff prefix=7) containing a diagnosis of diabetes mellitus (ICD-9-CM = 250).

or

(ii) One or more HSA containing a diagnosis of diabetes mellitus (ICD-9-CM = 250).

or

(iii) One or more DPIN claims for insulin (ATC code = A10A) or an oral hypoglycemic (ATC code = A10B).

Definition II

(i) Two or more separate physician visits (tariff prefix=7) on separate dates within two years containing a diagnosis of diabetes mellitus (ICD-9-CM = 250).

or

(ii) One or more HSA containing a diagnosis of diabetes mellitus (ICD-9-CM = 250).

3.5.4 Recent Antibiotic Use

Studies reporting antibiotic use as a risk factor for UTI caused by antibiotic-resistant pathogens have used varying time periods to define recent use (166, 169, 172, 176, 177). Time periods examined ranged from four weeks to six months prior to the development of UTI, with three months the most commonly employed time period. Justification for these different time periods is unclear and none of the studies differentiated between use of short courses of antibiotics for treatment of infection, versus long-term treatment, versus intermittent low-dose prophylaxis. There are few data in the literature regarding UTI or fecal colonization, that describes dosage or length of time of antibiotic use required to promote colonization with antibiotic-resistant organisms. Further, little is known regarding duration of persistence of resistant organisms upon discontinuation of antibiotic treatment.

Available data are derived from studies of oropharyngeal or nasopharyngeal colonization with antibiotic-resistant organisms, subsequent to treatment or prophylaxis of respiratory tract infections in children. Dagan *et al.* reported the emergence of antibiotic-resistant pneumococci colonizing the nasopharynx within three to four days of treatment for acute otitis media with azithromycin (197). Similarly, Morita examined the emergence and persistence of erythromycin-resistant pneumococcal colonization of the nasopharynx after five days of treatment with azithromycin (198). The prevalence of erythromycin resistant isolates increased from 2% on day zero, to 4% and 8% on days 17 and 32 (12 and 27 days after treatment cessation) respectively.

The effect of low-dose once daily amoxicillin on colonization of the oropharynx with antibiotic-resistant bacteria was examined by Brook and Gober (199). Children were treated with four to six months of amoxicillin for prophylaxis of acute otitis media. The proportion of subjects colonized with β-lactamase producing bacteria increased from 20% at initiation of prophylaxis to 85% and 100%, after two and five months of prophylaxis respectively. However, upon withdrawal of prophylaxis, colonization of the oropharynx with β-lactamase producing bacteria fell abruptly, reaching baseline at three to five months after withdrawal. Whether these data are applicable to the selection and persistence of antibiotic-resistant organisms within the gastrointestinal tract is unclear. Although, these data support the definition of previous antibiotic use (commonly within the past three months) which was used by researchers to examine the impact of previous antibiotic use on the incidence UTI caused by antibiotic-resistant pathogens.

For purposes of the current study, receipt of systemic antibiotics by subjects up to ninety days prior to the index date will be considered evidence of recent antibiotic use.

Receipt of an antibiotic may be determined from the date provided on the submission of a claim to the DPIN. As previously discussed, use of the DPIN records may not capture all subjects exposed to antibiotics, as they may be acquired in various ways and not captured by the DPIN. For example, antibiotics provided through physicians' offices in the form of samples, northern nursing units, and the sexually transmitted disease and meningitis prophylaxis programs, are not captured by the DPIN. In addition, subjects on chronic prophylaxis may receive antibiotic prescriptions of a quantity exceeding a ninety-day supply. Thus, a subject who received a prescription for a 100-day supply of antibiotic 100 days prior to a new episode of pyelonephritis would not be classified, by our definition, as a recent user of antibiotics. Additionally, patients receiving chronic prophylaxis may use antibiotics intermittently; seasonally in the case of prevention of respiratory tract infections, or post-coital in the case of prevention of UTI. For these patients it is difficult to make assumptions regarding the timing of antibiotic use. However, the number of subjects on chronic prophylaxis receiving in excess of a 90-day supply of medication, was expected to be few. Therefore, our operational definition of recent antibiotic use for the current study included subjects with one or more DPIN claims for any systemic antibiotic (ATC codes[See Appendix B] = J01A, J01B, J01C, J01D, J01E, J01F, J01G, J01M, J01R, J01X, G04A) up to ninety days prior to the index date.

3.5.5 Recent Hospitalization

Hospitals are thought to act as a reservoir for the dissemination of antibiotic-resistant organisms into the community. Studies confirming a higher prevalence of antibiotic-resistant organisms among previously hospitalized subjects have used time periods

ranging from two to six months to characterize recent hospitalization (167, 169, 175, 177, 184). As the higher prevalence of antibiotic resistance in hospitals may be contributed to by the frequent use of antibiotics in this setting, the same time period was selected for recent hospitalization as was selected for recent antibiotic use; that is, ninety days.

Therefore, the operational definition of recent hospitalization for the current study includes subjects with at least one HSA with a separation date within ninety days prior to the index date of the initial physician visit.

3.5.6 Recent Urinary Tract Infection

Challenges in defining recent UTI result from the lack of specificity inherent in ICD-9-CM codes. Due to the use of truncated ICD-9-CM codes within the Medical Claims (MC) it is difficult to make assumptions regarding diagnosis when the ICD-9-CM code 599 is used. The 599 code encompasses non-site specific UTI in addition to other non-infectious urinary tract disorders. Elimination of this commonly used code from the definition of previous UTI would likely result in underestimation of subjects with previous UTI. Therefore, the decision was made to include all UTI related codes in the definition of recent UTI. Thus, the resulting definition might more properly be considered to specify a previous urinary tract disorder. For this reason no requirement for an associated claim for antibiotic or hospital treatment was made. Indeed, such a requirement would lead to duplication and co-linearity with other previously defined risk factors, such as recent antibiotic use and recent hospitalization, since out-patient antibiotic use or hospitalization is expected to be associated with a diagnosis of UTI.

Studies examining the relationship between previous UTI and infection with antibiotic-resistant organisms commonly did not specify a time interval between the current and previous, UTI (166, 172). For reasons of consistency between measures a ninety-day time-period was selected. Thus, our definition of a recent urinary tract infection (or disorder) includes a subject with one or more MC and/or HSA, containing a service date or discharge date up to ninety days prior to the index date, and which contains one of the ICD-9-CM codes 590, 595, or 599.

3.5.7 Pregnancy

Stranc reported that 69% of 12,116 pregnancies among Manitoba women greater than 34 years, resulted in live births (188). For those failing to reach term, termination due to miscarriage or social termination was reported. Claims for physician services related to pregnancy and childbirth are contained in the MC; in addition, hospital in-patient births result in the generation of a HSA. Only a small proportion of deliveries in Manitoba were expected to occur in non-hospital settings. Midwifery services were not funded by Manitoba Health until June 2000, and thus midwifery claims cannot be used as a source of pregnancy data.

For the current study, pregnancy status at index date was of interest. Hospitalizations resulting in birth may be identified by the ICD-9-CM code V27 (outcome of pregnancy), and these claims may be used to identify a period of pregnancy. HSA for hospitalizations resulting in birth contain the mother's gestation period on admission, in weeks. Delivery was assumed to occur on date of admission, and the period of pregnancy was calculated

by subtracting the number of weeks of gestation from the admission date. Subjects whose index date fell within a period of pregnancy were assigned a positive pregnancy status.

However, as noted not all pregnancies end in delivery. Until recently, physicians were paid a flat fee for standard prenatal care for which they submitted one global claim. Since April 1, 1999 physicians have the option of billing for each prenatal visit. MC for physician visits for prenatal care, and non-obstetrical HSA provide no information regarding the timing of pregnancy. Thus, for pregnancies which did not result in a hospital delivery, there was no way to determine the period of pregnancy with any accuracy.

To minimize the possibility of misclassification of pregnancy status, a conservative method of assignment was undertaken. MC or HSA, containing ICD-9-CM codes indicative of pregnancy, but not delivery, (ICD-9-CM codes 632-676, V22, V23, V24, V28), or MC containing obstetrical tariff codes (4800-4899), with service dates or admission dates not included in a period of pregnancy as determined above, were assigned a gestational age of 280 days and a possible pregnancy period calculated. Subjects whose index date fell within a possible period of pregnancy, and who were not assigned a positive pregnancy status as above, were assigned a pregnancy status of "indeterminate". Subjects who were not assigned a pregnancy status of positive or indeterminate as above, were assigned a pregnancy status of negative.

In summary, pregnancy status was assigned based on the following criteria:

Positive

(i) HSA contained the ICD-9-CM code V27

(ii) Index date contained in the period of pregnancy, which was determined by subtracting the gestational age at hospital admission from the hospital admission date.

Indeterminate

(i) Not assigned positive pregnancy status as above.

(ii) Index date was within 280 days prior to a HSA or MC containing relevant ICD-9-CM codes (632-676, V22, V23, V24, V28) or tariff codes (4800-4899) which did not fall within a previously defined period of pregnancy calculated above.

Negative

(i) Not assigned a positive or indeterminate pregnancy status as above.

3.5.8 Income

Income quintiles are calculated yearly by the Manitoba Centre for Health Policy (MCHP) using census data from Statistics Canada; these have been used extensively to examine the effect of income on healthcare utilization and health status (186, 188, 189, 192). Income quintiles for the current study were based on data derived from the 1996 census. Statistics Canada reports the average household income by enumeration area, designated as urban or rural based on population density.

Enumeration areas with greater than 400 persons per square kilometer were designated as urban. Urban and rural enumeration areas are ranked separately, from poorest to wealthiest, based on mean household income. On a yearly basis, MCHP assigns residents to an income quintile based on postal or municipal code from the registry file of

Manitoba Health. In urban areas, assignment to enumeration area is accomplished by postal code. In rural areas, assignment to enumeration area is based on municipal code. In 1996, there were 1,749 enumeration areas in Manitoba; 781 in Winnipeg, and 968 non-Winnipeg.

Persons with treaty Indian status may have postal and municipal codes which denote conflicting areas of residence. For those with treaty Indian status, municipal code will reflect the municipal code for their home reserve regardless of place of residence. Persons with treaty status and urban postal codes will be assigned an enumeration area, and subsequently an income quintile, based on their postal code. Persons with treaty status and rural postal codes will be assigned to an enumeration area and income quintile based on their municipal code.

A small proportion of subjects may not be assigned an income quintile. This may occur when a resident has an out of province postal code, a postal code which is designated as an institution (e.g., Selkirk Mental Health Centre), or a newly assigned postal code which did not exist at the time of last census. Although income quintile is based on mean neighbourhood (not individual) household income, Mustard *et al.* demonstrated that this accurately reflects household income (200). Income quintiles are calculated separately for urban and rural areas, resulting in separate income rankings for urban and rural residents. As urban/rural residence was to be a separate variable within the current study, quintile ranks were merged for urban and rural areas to create a single ordinal ranking of income for all Manitobans.

3.5.9 Residence

Subject residence was defined as urban or rural, based on the enumeration area in which the subject resided according to the current Manitoba Health Registry File for the fiscal year examined. As previously indicated, enumeration areas are designated as urban/rural by Statistics Canada based on population density. Enumeration areas, with greater than 400 persons per square kilometer were designated as urban. Those subjects with treaty Indian status were assigned to an enumeration area by postal or municipal code as previously described in Section 3.5.8.

3.5.10 Initial Treatment

Observational studies using healthcare claims data to examine treatments for specific indications commonly use temporal association and subject knowledge to make assumptions regarding diagnosis and treatment provided (39, 61, 80, 84, 201). In the case of chronic conditions where treatments are specific to a disease state (e.g., diabetes or asthma) the timing of physician and pharmaceutical claims are unlikely to be critical. However, for acute conditions such as infectious diseases, physician visit claims indicating an diagnosis of bacterial infectious disease would be expected to be immediately followed by a healthcare claim for an appropriate treatment. In this study, a DPIN claim for out-patient antibiotic treatment, or a HSA indicating hospitalization for antibiotic treatment and supportive therapy were expected. Assumptions of a relationship between diagnosis and subsequent pharmaceutical claims are necessary since pharmaceutical claims typically do not include a field indicating the indication for treatment. Time periods of up to seven days subsequent to a physician visit have been

used by some researchers to make assumptions regarding initial antibiotic treatment for infectious diseases (80, 84, 201).

As the time-period between initial physician visit and a claim indicative of treatment increases, associations may become more dubious. Conversely, selection of a very short time-period for identification of treatment claims may increase the risk of missing cases for which there was a delay in treatment, or submission of claims. For the current study a period of two days was utilized as prescriptions for acute infections were expected to be filled promptly. A HSA for which one of the ICD-9-CM codes, 590, 595, or 599 was submitted as the most responsible diagnosis, was assumed to reflect initial treatment if the admission date matched or was up to two days subsequent to the index date. Similarly, a DPIN claim for an antibiotic was assumed to reflect initial treatment if the date provided matched or was up to two days subsequent to the index date.

To strengthen the cause and effect assumption between a physician visit and a DPIN claim for an antibiotic, the antibiotic was required to be an appropriate choice for treatment of UTI. Antibiotics considered appropriate choices for treatment of UTI included: penicillins, cephalosporins, sulfonamides, aminoglycosides, fluoroquinolones and urinary antiseptics. Third level ATC codes were used to identify such agents (see Appendix B). An exception was the use of the third level ATC code J01X, which includes miscellaneous agents with dissimilar spectrums of activity. Only one agent in this class (fosfomycin) was considered appropriate initial antibiotic treatment of UTI. Thus, the fifth level of ATC classification was used to identify claims for this agent. DPIN claims containing the following third and fifth level ATC codes were considered

appropriate choices for treatment of UTI: G04A, J01C, J01D J01E, J01G, J01M, J01R, J01XX01.

In summary, initial treatment of pyelonephritis included one of hospitalization or out-patient antibiotic treatment, if the following criteria were met.

Hospitalization

(i) A HSA for which the admission date matched, or was up to two days subsequent to, the index date, and for which the most responsible diagnosis submitted was one of ICD-9-CM codes 590, 595, or 599.

Out-patient antibiotic

(i) A DPIN claim for which the date provided matched, or was up to two days subsequent to, the index date, and which contained one of the ATC codes: G04A, J01C, J01D, J01E, J01G, J01M, J01R, or J01XX01.

3.5.11 Treatment Failure

Current guidelines for evaluation of antibiotics in the treatment of UTI in RCT recommend that final evaluation of treatment outcomes be performed four to six weeks after completion of initial treatment (132). At this time, resolution of bacteriuria and clinical symptoms (dysuria, fever, flank pain) are assessed. Although in RCT cure is commonly assessed based on bacteriological cure, with or without clinical cure, symptom resolution is likely of greater relevance to patients. In everyday practice, clinical cure is likely assessed by the patient, with those having continuing or recurring symptoms presenting for further treatment, and those that are symptom free assuming resolution.

Thus, treatment failure relevant to patients may be determined by the presence or absence of further healthcare claims consistent with further treatment of the initial infection.

In the current study, healthcare claims for 42 days subsequent to the index date were examined to assign a treatment outcome of "cure" or "failure". Healthcare claims examined included MC (which include in-office and ER physician visits, and laboratory services) in addition to HSA and DPIN claims. MC alone, are not sufficient to indicate treatment failure since these may reflect follow-up care and assessment. Thus, treatment failure is defined as either the need for hospitalization, or additional out-patient antibiotic treatment related to the UTI, subsequent to initial antibiotic treatment. Subjects having a claim for a hospitalization, subsequent to initial antibiotic treatment, with an admission date within 42 days of the index date, and a length of stay of one day or greater for which an ICD-9-CM code of, 590, 595, or 599 was submitted as the most responsible diagnosis, were considered to have failed initial treatment.

In the absence of hospital claims as described above, claims which indicate the receipt of further antibiotic treatment within 42 days of the index date, may or may not be indicative of treatment failure, depending upon associated medical and hospital claims. To be considered a possible treatment failure, the antibiotic was required to be an appropriate treatment of UTI, that is, one of the previously indicated antibiotic classes; penicillins, cephalosporins, sulfonamides, aminoglycosides, fluoroquinolones, urinary antiseptics, or fosfomycin (ATC codes: G04A, J01C, J01D J01E, J01G, J01M, J01R, J01XX01).

Whether an antibiotic was prescribed for treatment or prophylaxis/suppression was also considered. Prophylaxis or suppressive treatment to prevent future UTI is warranted

for subjects who experience frequent UTI. Commonly recommended regimens include TMP-SMX, and nitrofurantoin, once daily or post-coital (11, 12). To minimize the possibility of prophylactic/suppressive treatment being considered evidence of treatment failure, the quantity and days supply indicated on the claim were used to calculate the number of units per day dispensed for solid dosage forms. Antibiotics with less than two units per day were not considered possible evidence of treatment failure (with the exception of antibiotics for which once daily dosing is recommended –See Appendix B). Antibiotic claims considered possible evidence of treatment failure were assigned status (yes/no) in 6 categories, to assess possible indications for use (Table 9).

Table 9. **Categorization of additional antibiotic treatments to assess indication for use and assignment of treatment outcome**

CATEGORY	DEFINITION
I	Antibiotic dispensed within two days of a MC for a physician visit for which a diagnosis code indicative of an infectious disease unrelated to the urinary tract was submitted.
II	Antibiotic dispensed within two days of a MC for a physician visit for which a diagnosis code indicative of UTI was submitted (ICD-9-CM codes 590, 595, 599).
III	Antibiotic dispensed within two days of a MC for laboratory services, for which a tariff code indicative of performance of urinalysis, urine culture and/or sensitivity was submitted (tariff codes 9641, 9644, 9702, 9711, 9663).
IV	Antibiotic dispensed within two days of a HSA (discharge date) for which any of the possible 16 listed diagnoses contain a diagnosis code indicative of an infectious disease unrelated to the urinary tract was submitted.
V	Antibiotic dispensed within two days a HSA (discharge date) for which any of the possible 16 listed diagnoses contain a diagnosis code indicative of UTI (ICD-9-CM codes 590, 595, 599).
VI	Antibiotic dispensed, for which none of the above hold true.

Any DPIN claim for an antibiotic may fall into one or more of the above categories. Decisions regarding determination of likely indication for treatment follow:

1. Antibiotics assigned to categories I or IV alone were not indicative of treatment failure since the evidence suggested the dispensed antibiotic was employed for the treatment of an infection unrelated to the urinary tract.
2. Antibiotics assigned to categories II and/or III provided sufficient evidence that the dispensed antibiotic was used for the treatment of UTI, and were considered evidence of treatment failure.
3. Antibiotics assigned to category V alone were not indicative of treatment failure. Although the evidence suggested that the antibiotic was employed for the treatment of UTI, it was unclear whether treatment was related to the original infection since UTI are a common complication of hospitalization. It is important to keep in mind, that hospital claims for which the most responsible diagnosis submitted was UTI, were previously identified as treatment failures, regardless of any further antibiotic treatment.
4. Antibiotics assigned to category VI (where no recent medical or hospital claims provided evidence of the indication for use), required further elucidation. For these antibiotics, the decision regarding treatment failure was based on type of antibiotic. Antibiotics were separated into two classes, "urinary" or "non-urinary". Urinary antibiotics included TMP-SMX, fluoroquinolones and nitrofurantoin. Thus, antibiotic claims for TMP-SMX, fluoroquinolones, or nitrofurantoin assigned to category VI were considered evidence of treatment failure.

5. Antibiotics assigned to category V in combination with categories II and/or III were considered evidence of treatment failure since the MC, in addition to the hospital claim, provided evidence of treatment related to the original infection.

Where an antibiotic was assigned to two or more categories (other than described above) which resulted in opposing decisions regarding evidence of treatment failure, elucidation of treatment failure was based on service dates, service type, and antibiotic type, in that order. Decisions based on service dates required that the date of each medical and/or hospital claim be compared. The service provided closest to the date upon which the antibiotic was dispensed was considered the indication for treatment. For example, two services (in this case physician visits) on June 15th and 16th for which diagnoses indicative of UTI and sinusitis were submitted respectively, coupled with a prescription for TMP-SMX on June 16th would not result in a "treatment failure" classification. Since the claim for the physician visit which occurred closest to the dispensed date of the antibiotic carried a diagnosis of sinusitis, the antibiotic would be deemed to be treatment of sinusitis, and thus not indicative of treatment failure for a UTI.

When service or discharge dates for two or more medical and/or hospital services fell on the same date, the type of claim (MC or HSA) was considered. Diagnoses submitted on a HSA took precedence over those on MC as they were expected to indicate more severe conditions. Finally, if two or more claims were for the same service type the decision about treatment failure was based on antibiotic type. For example, if both of the previously described MC occurred on the same date as the dispensing date of the TMP-SMX the following decision would be reached. Since TMP-SMX is designated as a

urinary antibiotic, the treatment would be considered additional treatment for pyelonephritis, and as such would have been indicative of treatment failure.

3.6 Identification of Study Subjects

Data files for HSA, MC, and the DPIN are archived by MCHP based on the year in which the service was provided. As the fiscal year-end for Manitoba Health is March 31st of any calendar year, claims are organized based on this date. The period for identification of new episodes of pyelonephritis was February 15, 1996 to March 31, 1999. However, data for the 90 days preceding all identified new episodes of pyelonephritis were required to enable assignment of subject variables such as recent antibiotic use, recent hospitalization, and recent UTI. In addition, data were required for a period of approximately nine months subsequent to the identification of new episodes of pyelonephritis to enable the assignment of pregnancy status at the time of the new episode. Therefore, the study period was determined to encompass November 15, 1995 to December 31, 1999. Thus data files for five fiscal years for the period April 1, 1995 to March 31, 2000 were utilized for the current study.

Medical claims for females which contained the ICD-9-CM codes, 590 (infection of the kidney), 595 (cystitis), or 599 (other disorders of the urethra and urinary tract) were abstracted from the MC files for the period April 1, 1995 to March 31, 2000. Similarly, claims for hospitalizations for females containing the above ICD-9-CM codes in any of the 16 possible diagnosis fields were abstracted from the HSA for the same period.

The following procedure was used to identify new episodes of pyelonephritis which met the previously described operational definition.

(i) MC for a physician visit associated with a diagnosis code of 590 during the period February 15, 1996 to March 31, 1999 were identified as possible new episodes.

(ii) Possible new episodes which occurred within 42 days subsequent to any MC for which a diagnosis of 590, 595, or 599 was submitted were excluded from further consideration.

(iii) Possible new episodes which occurred within 42 days subsequent to the discharge date of a hospital claim, for which the diagnosis codes, 590, 595, or 599 were submitted as any of a possible 16 diagnoses, were excluded.

For the remaining possible new episodes, further examination of related claims was necessary to identify those claims which met the definition of a new episode of pyelonephritis. As the current study addresses the treatment of community-acquired pyelonephritis, it was necessary to determine the site of care for the initial physician visit to exclude episodes which occurred in hospitalized patients or those residing in personal care homes. Data fields within the MC provide information regarding the site of care; specifically, the hospital number and outpatient indicator.

Each hospital, personal care home, or nursing station has a unique identification number and thus, claims originating from these facilities may be identified in the MC. Outpatient physician services provided in a hospital, may be identified by the existence of an out-patient indicator. The out-patient indicator further differentiates care provided in an emergency room (outpatient indicator = "E") from that provided in an out-patient setting (outpatient indicator = "O") Out-patient care can include such services as day

surgery, dialysis care, or physician services which occur in specialized out-patient clinics located within a hospital.

To restrict our study to episodes of community-acquired pyelonephritis, the following claims were eligible for inclusion.

(i) MC containing no hospital number

(ii) MC containing a hospital number accompanied by an out-patient indicator consistent with emergency room or out-patient care.

As submission of the out-patient indicator is not a mandatory component of MC, it is possible that some MC containing a hospital number but no out-patient indicator may still reflect out-patient care. Thus, MC containing a hospital number and having blank out-patient indicator fields were compared with admission/discharge dates from the HSA to determine hospitalization status at index date. The following procedure was used.

(i) MC for subjects who were identified as not being in hospital on the index date were eligible for inclusion.

(ii) MC for subjects whose index date was observed to match the admission date of a HSA were deemed to have community-acquired pyelonephritis, which resulted in hospitalization on that date, and were eligible for inclusion.

(iii) MC for subjects whose index date occurred within the dates of a hospitalization (but did not coincide with the admission date) were determined to have hospital acquired pyelonephritis, and were excluded.

(iv) MC for initial physician visits which contained a hospital number consistent with care in a personal care home were excluded.

To be eligible for selection to the study cohort, the new episode of pyelonephritis must be for a female between the ages of 18 to 65 years who maintained continuous coverage with Manitoba Health for the duration of the study. Personal Health Identification Numbers (PHINs) for subjects with possible new episodes of pyelonephritis were compared to the Registry File, to obtain information on birth-date and eligibility for healthcare coverage. Those subjects who were eligible for healthcare benefits through Manitoba Health on both November 15, 1995 and December 31, 1999 were assumed to be eligible for benefits for the entire study period. Those subjects who were not eligible for healthcare benefits with Manitoba Health on both November15, 1995 and December 31, 1999 were excluded from further consideration.

Age at time of new episode of pyelonephritis was calculated using the service date of the initial physician visit and date of birth recorded on the Registry File; in some instances date of birth was incomplete. Birth year and month were available for all subjects, however, no day was specified in some instances. Subjects with missing birthdays were assigned a birthdate on the first day in the month and year of their birth. Age of subjects was then calculated as age at index date. All subjects who were not between 18 and 65 years at index date were excluded from further study. In addition, to ensure independence of observations within our cohort, all but the most recent episode of pyelonephritis for each subject was excluded.

Remaining episodes were retained for further study. Thus the study cohort consists of non-institutionalized females between the ages of 18 and 65 years of age, with one recent episode of community-acquired pyelonephritis.

3.7 Identification of Independent Variables

Upon identification of our cohort of interest, it is necessary to determine subject status with regard to the independent variables of interest. Several such variables were previously determined in the process of cohort identification; age and presentation to emergency room. HSA, MC and DPIN data for the period November 15, 1995 to December 31, 1999 were utilized to determine diabetic status (as described in Section 3.5.3). MC, HSA, and DPIN claims for the period up to ninety days prior to the index date were examined to assign status related to recent antibiotic use, recent hospitalization, and recent UTI (as described in sections 3.5.4, 3.3.5, and 3.5.6 respectively). MC and HSA for the period February 15, 1995 to March 31, 2000 were examined to assign pregnancy status (as described in section 3.5.7). Finally, area of residence and income quintiles were assigned to subjects based on the Registry File data for the fiscal year containing the new episodes of pyelonephritis (as described in sections 3.5.8 and 3.5.9 respectively).

3.8 Identification of Initial Treatment and Final Cohort for Analysis

Identification of initial treatment was performed, by examining HSA, and DPIN claims within two days of the index date, as described in section 3.5.10. For DPIN claims with missing ATC codes, generic names and DIN were examined to identify pertinent antibiotic claims. Subjects with a claim for only one of the possible treatment options (hospitalization or out-patient treatment) were assigned that status. Further investigation was required for those subjects having claims for both antibiotic treatment and

hospitalization within two days of the initial physician visit. Assignment to outpatient or hospitalized status was based on claim dates; date provided (for drug claims) and admission date (for hospital claims). Thus, a claim for hospitalization which predated a claim for outpatient antibiotic treatment, resulted in assignment to hospitalized status and *vice versa*. Subjects with identical dispensing and admission dates were assigned an initial treatment status of indeterminate. Hospitalized subjects or those with indeterminate status were excluded from further study. The consequence of the choice of a two-day interval for identification of initial treatment was examined by varying the time interval from zero to seven days.

To obtain the final cohort needed to address the hypotheses proposed by the current study, additional exclusion criteria were applied to subjects who received initial antibiotic treatment. Exclusions from the cohort resulted when a single initial antibiotic treatment could not be determined. If more than one antibiotic was provided to a subject within the two days subsequent to the initial visit, the antibiotic with the earliest dispensing date was considered to be the single initial treatment. If more than one antibiotic was dispensed on the same date it was unclear whether both antibiotics were prescribed simultaneously, or if one antibiotic prescription preceded the other, and in which order. Therefore, episodes with more than one antibiotic dispensed on the same date were excluded, as a single initial antibiotic could not be determined.

Further exclusions resulted when an antibiotic identified as initial treatment may have been prescribed for an alternate indication. Any MC or HSA with a service date or separation date up to two days prior to the date provided of the initial antibiotic, and which contained an ICD-9-CM code indicative of an infectious disease unrelated to the

urinary tract, were identified as possible alternate reasons for antibiotic treatment. Subjects with an initial antibiotic treatment for which additional possible reasons for treatment existed were excluded. Finally, the remaining subjects were restricted to those non-pregnant females whose initial antibiotic treatment consisted of TMP-SMX or a fluoroquinolone for a duration of 1 to 15 days.

3.9 Identification of Treatment Failure

To identify treatment failure, MC, HSA, and DPIN claims for 42 days subsequent to the index date were examined. Subjects with a HSA with an admission date up to 42 days subsequent to the index date for which the most responsible diagnosis was one of ICD-9-CM codes 590, 595, or 599 were determined to have failed treatment.

For subjects who did not experience hospitalization as above, DPIN claims containing the ATC codes J01C, J01D, J01E, J01G, J01M, J01R, J01XX01, or G04A (or generic names or DIN of antibiotics included in the above ATC categories) were identified. These antibiotic claims were categorized according to likely indication for use, and treatment outcome assigned as described in Section 3.5.11.

3.10 Statistical Analysis

For the current study, two related analyses were performed. The first tested the relationship between subject variables and the probability of receipt of a fluoroquinolone for initial treatment of pyelonephritis (hypotheses 1 to 8). The second, tested the relationship between initial antibiotic treatment in conjunction with subject specific variables, and the probability of treatment failure (hypotheses 9 to 13).

A description of the study variables used in the analyses are given in Table 10. The majority of explanatory variables are dichotomous, and nominal. These include: diabetes, presentation to an emergency room (ER), subject residence, recent antibiotic use, recent UTI, and recent hospitalization. Age is a continuous, ratio scaled variable which is constrained to take values between 18 and 65 years. The income variable provides ordinal level data since the categories have a rank order. Income quintile 1 represents subjects living in neighbourhoods with the lowest average income, and income quintile 5, the highest. Outcome variables for both analyses are dichotomous and nominal.

A logistic regression model was chosen as the method of analysis to determine the combined effects of explanatory variables on the probability of receipt of a fluoroquinolone for initial treatment of pyelonephritis, and subsequently the probability of treatment failure. Logistic regression is widely used in health services research in which the outcome variable is dichotomous. Explanatory variables in a logistic regression may be nominal, ordinal, interval or ratio scaled. Statistical analysis was performed using Statistical Analysis System software (SAS Institute, Version 8.1).

Table 10. **Study Variables for Logistic Regression Analysis**

Variable	Explanation	Variable Type
Age	Age in years at index date. Constrained between 18-65 years	Ratio/Continuous
Diabetic (Definition II)	1 = Yes 0 = No	Nominal/Dichotomous
Recent Antibiotic Use	1 = Yes 0 = No	Nominal/Dichotomous
Recent UTI	1 = Yes 0 = No	Nominal/Dichotomous
Recent Hospitalization	1 = Yes 0 = No	Nominal/Dichotomous
Rural Residence	1 = Yes 0 = No	Nominal/Dichotomous
Income Quintile	1 to 5 1 = lowest; 5 = highest	Ordinal
Initial Antibiotic Treatment	1 = Fluoroquinolone 0 = TMP/SMX	Nominal/Dichotomous
Treatment Duration	Days supply of antibiotic when used according to instructions	Ratio/Continuous
Treatment Failure	1 = Yes 0 = No	Nominal/Dichotomous

3.10.1 Analysis of patient characteristics and the probability of receipt of a fluoroquinolone

This analysis tested hypotheses one to eight by modeling the effects of age, diabetes, recent antibiotic use, recent UTI, recent hospitalization, presentation to an ER, rural residence and income on the probability of receipt of a fluoroquinolone, for initial treatment of treatment of pyelonephritis. The proposed model takes the form:

$$\text{logit}\,(P) = \beta o + \Sigma \beta i Xi + e$$

Where Xi is the vector of explanatory variables as indicated above, and βi, their respective regression coefficients. P is the probability of receipt of a fluoroquinolone and e represents the unexplained variation from the observed outcome. The techniques used for exploratory data analysis and logistic regression modeling, as described below, are suggested by Hosmer and Lemeshow (202).

Prior to performing the multivariate analysis, exploratory data analysis was performed to examine bivariate relationships between subject variables. Contingency tables of the outcome variable and nominal or ordinal explanatory variables were examined. Pearson chi-squared tests were used to test for the significance of relationships. Crude odds ratios were computed for all binary explanatory outcome combinations. The relationship between the continuous explanatory variable (age) and the outcome variable was assessed by fitting a univariate logistic regression model. The likelihood ratio chi-squared test was used as the measure of significance. A Logit plot of the continuous explanatory variable (age) was examined to detect non-linear effects.

To assess confounding between explanatory variables, stratified analysis was performed for each nominal or ordinal scaled variable. Adjusted odds ratios were computed and the Cochran-Mantel-Haenszel statistic was used to assess significance. Contingency tables, both stratified and not, were used to examine data for problems of quasi-complete, and complete separation. Assessment of possible confounding involving continuous variables was accomplished at the model building stage.

Statistical models with even a moderate number of variables may potentially have large numbers of interaction terms; some of which may not be germane to the purpose of the analysis. Prior to analysis it is prudent to identify possible interactions which are felt to be of interest and/or theoretically important. For consideration of inclusion of possible interactions, explanatory variables were considered to belong to one of the following categories:

1. subject variables which may indicate increased potential for infection with antibiotic-resistant pathogens and thus, possible requirement for treatment with a fluoroquinolone (age, diabetes, recent antibiotic use, recent UTI, recent hospitalization)
2. subject variables which may indicate greater severity of illness and/or reduced likelihood of patient availability for follow-up (presentation to an ER, or rural residence)
3. subject variables which indicate ability of patient to pay for antibiotic treatment, which is considered to be unrelated to the need for a fluoroquinolone (income quintile)

Interactions between variables of different categories were of interest. For example, would the effect of a subject's ability to pay for initial antibiotic treatment (as measured by income quintile) on the likelihood of receipt of a fluoroquinolone differ for subjects with or without risk factors for infection with antibiotic-resistant pathogens (e.g., age, or recent antibiotic use). Using these categories of variables, all two-way interactions between explanatory variables from different categories were considered to be of interest or importance.

Prior to model building, interactions of interest between nominal, or ordinal level variables were examined using the stratified analysis described above. Breslow-Day statistics were used as a measure of significance. Interactions of interest involving the continuous explanatory variable age, were assessed during model building.

Results of exploratory data analysis were used to guide model building. Hosmer and Lemeshow recommend all variables of known biological importance and/or those with univariate test p values <0.25 be considered as candidates for entry into the multivariate model (202). Although not all explanatory variables achieved this level of significance in univariate testing, all were entered into the candidate model based on their theoretical, or biological, significance. Interactions between nominal and ordinal variables which achieved a significance of 0.10 in univariate tests, as measured by the Breslow-Day statistic, were also entered into the model

At this point, problems with entry of interaction terms between income and other explanatory variables became evident. Inclusion of ordinal scaled variables in a logistic regression is commonly accomplished by the creation of a set of design variables; n-1 (in this case four). Further examination of interactions between the income indicators and

other predictors necessitated the production of interaction terms with all of the design variables. The effect of the design variables describing the interaction between income and diabetes on the logistic regression model, were particularly troublesome.

The number of subjects in the highest income quintile was small relative to lower income quintiles. Similarly, the number of subjects with diabetes in the highest income quintile was small relative to the numbers in other income quintiles. Stratification of the data based on income and diabetes status produced small cell numbers, resulting in a compromised ability to effectively model interaction effects, as evidenced by an inflated standard error for the interaction term created for diabetes and income quintile five.

This problem may be addressed by collapsing the upper income quintiles. However, this would result in a loss of explanation regarding the effect of income, at all levels, on the probability of receipt of a fluoroquinolone. It has been previously demonstrated that a gradient in health, and the use of health services, occurs over all income levels (186, 188, 189). Thus, to preserve the ability to examine such differences, collapsing of income categories was not attempted. Instead, consideration was given to the use of income as an interval-scaled variable. Hosmer and Lemeshow recommend the use of ordinal level variables as interval level variables as a modeling strategy, in cases of zero or small cells (202). Thus, for the current study, income was modeled as an interval scaled variable, as it facilitated the examination of interactions within the data. A logit plot of the probability of receipt a fluoroquinolone and income exhibited a linear pattern. Therefore, income, was entered into the logistic model as a continuous variable, as were the relevant income related interactions.

In addition, previously unexplored relevant interactions between age and other explanatory variables (presentation to ER, residence) were entered into the logistic model to test for significance. Interactions which did not attain significance at the 0.05 level in the multivariate model were removed from the model. The remaining variables and interactions thus represent our full model.

To identify the most parsimonious model further refinement was accomplished by removing the least significant contributor to the model in a stepwise fashion. The significance of the contribution of each predictor to the model was assessed by the likelihood ratio chi-squared test. Model hierarchy was maintained. That is, the inclusion of significant interaction terms necessitated that the main effects remain in the model. The effects of removal of non-significant explanatory variables on the regression coefficients of remaining variables was noted. Explanatory variables whose removal were judged to produce large changes in one or more of the regression coefficients of remaining variables were maintained in the model due to the confounding effects exerted, regardless of statistical significance. Variables not involved in significant interactions or which were not judged to be confounders were maintained in the model only if significant at the 0.10 level. An α level of 0.10 was selected rather than the more conventional 0.05 since previous support for the hypothesized associations exist. It is recognized that selection of α levels is somewhat arbitrary, however p-values of <0.10 are considered suggestive evidence against the null hypothesis (203).

The full and final parsimonious model are reported. The effect of explanatory variables on the probability of receipt of a fluoroquinolone are reported as odds ratios, with 95% confidence intervals.

3.10.2 Analysis of initial antibiotic treatment in conjunction with patient characteristics, and the probability of treatment failure.

This analysis tested hypotheses 9 to 13 by modeling the effects of initial antibiotic treatment, treatment duration, age, diabetes, recent antibiotic use, recent UTI and recent hospitalization on the probability of treatment failure. A logistic regression model was used, taking the form as previously described. In contrast to the earlier analysis, interactions between predictors were hypothesized.

As hypothesized, and tested in the earlier analysis, initial antibiotic treatment is not a random event but is expected to be dependent on patient characteristics. Many of the hypothesized explanatory variables for initial antibiotic treatment were in turn expected to influence the probability of treatment failure. Explanatory variables which are related both to the outcome variable (treatment failure) and the exposure (initial antibiotic treatment) are possible confounders in an assessment of the relationship between initial antibiotic treatment and treatment outcome. Several of the explanatory variables used in the earlier analysis were further expected to be effect modifiers (age, diabetes, recent antibiotic use, recent UTI, recent hospitalization); as stated in hypotheses 9 to 13. Additional significant explanatory variables included in the final parsimonious model from the earlier analysis (testing hypotheses 1 to 8), which were not to be tested in this analysis as effect modifiers, may be confounders. Thus, significant predictors from the earlier analysis were entered into the present candidate model. Potentially this included presentation to ER, rural residence, income, and any significant interactions involving these predictors. Any predictors and interactions from the earlier analysis, not already

hypothesized for the present analysis, were then removed from the candidate model if non-significant or not judged to be a confounder.

Although no specific hypotheses were to be tested regarding the effect of the duration of antibiotic treatment on treatment outcome, there is evidence to suggest that the effect of treatment duration on outcome may differ between antibiotics (151). Thus, treatment duration is entered into the candidate logistic regression model to control for its effect on treatment outcome.

Exploratory data analysis included an examination of contingency tables of the outcome variable (treatment failure) and explanatory variables. Income quintile was again regarded as a continuous variable to overcome problems of small cell counts in the highest income quintile. For continuous variables (age, income quintile) the univariate effects on treatment failure were assessed by fitting univariate logistic models. Logit plots were examined to determine the nature of any relationship between continuous explanatory variables and the outcome variable.

An assessment of possible confounding and interactions between nominal variables was accomplished by stratified analysis using Cochran-Mantel-Haenszel and Breslow-Day statistics to test for significance. Interactions of interest and theoretical importance were hypothesized *a priori*. Assessment of confounding and interactions involving continuous predictors was accomplished during the model building stage.

The full model consisted of all hypothesized explanatory variables and interaction terms, in addition to any significant variables from the earlier analysis not already included in the model. Interaction terms which did not attain significance at the 0.05 level were removed from the model. Further refinement of the model was accomplished by

removing the least significant contributors to the model in a step-wise fashion. Model hierarchy was maintained. The significance of the contribution of the removed variable to the model was assessed by the likelihood ratio chi square test. Possible confounding effects of the removed variables was assessed by observing the effects of variable removal on the regression coefficients of the remaining variables. Explanatory variables judged to act as confounders were maintained in the model regardless of statistical significance. Variables not involved in significant interactions or which were not judged to act as confounders were maintained in the model only if significant at the 0.10 level. The full and parsimonious models are reported. The effect of explanatory variables on the probability of treatment failure are reported as odds ratios, with 95% confidence intervals.

Chapter 4.

Results

This chapter describes the selection of the study cohort based upon application of inclusion/exclusion criteria described in the previous chapter. The status of the cohort with regard to independent variables (e.g., diabetes, income quintile) and dependent variables (initial antibiotic, treatment failure) is described. Results of the planned analysis to address study hypotheses are presented. In addition, the ramifications of inclusion/exclusion criteria and decisions related to the development of operational definitions of subject variables are examined through sensitivity analysis.

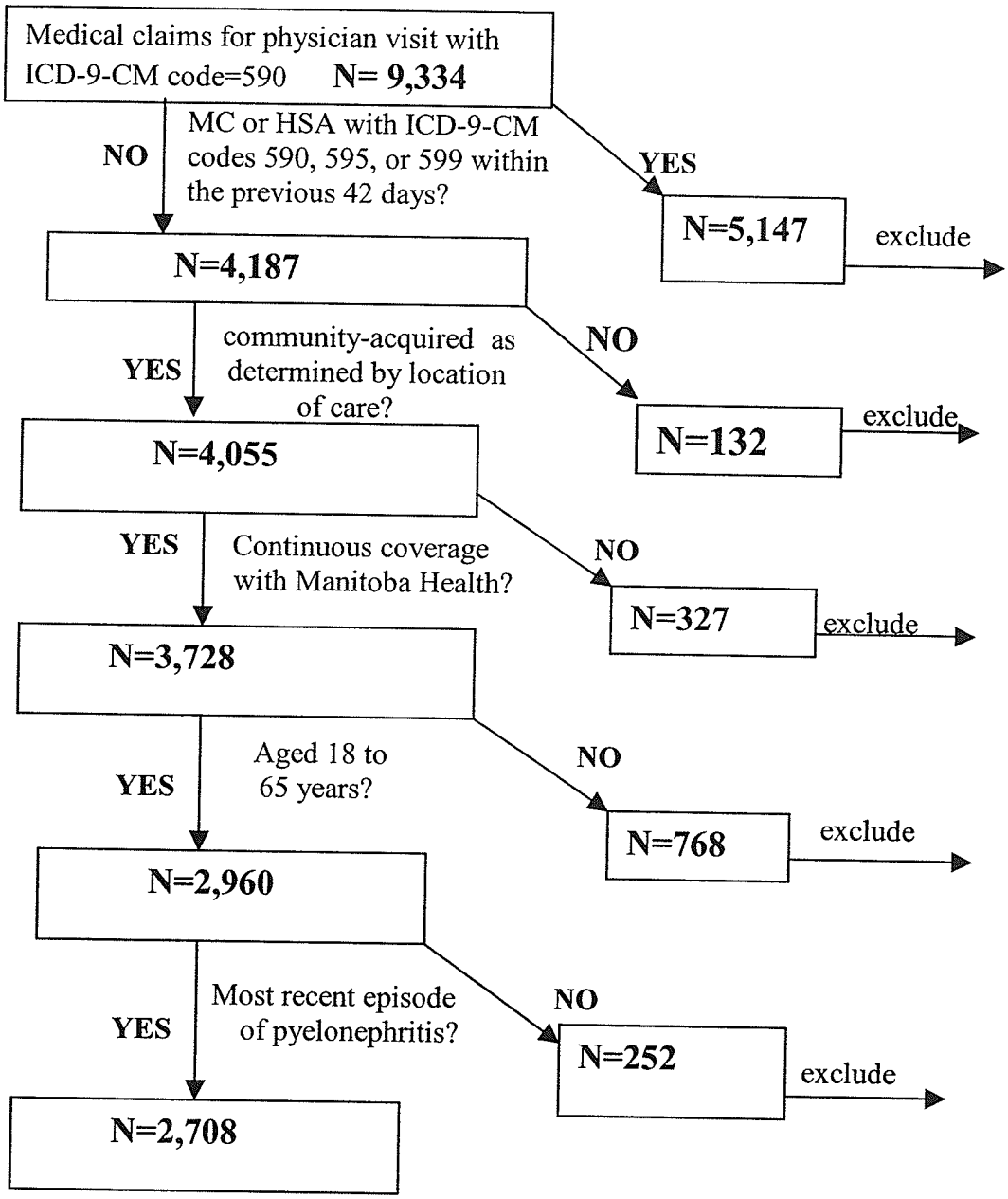
4.1 Study Subjects

Examination of Medical Claims (MC) for the period February 15, 1996 to March 31, 1999 identified 9,334 claims for physician visits (tariff=7) for females bearing the ICD-9-CM code 590. Of these, 4,187 were not preceded by one or more MC or HSA bearing ICD-9-CM codes 590, 595, or 599 in the previous 42 days, and thus were eligible for entry to the study cohort; subject to inclusion criteria (Section 3.5.1). Figure 8 illustrates additional refinement of the study cohort. Restriction of the cohort to subjects experiencing community-acquired pyelonephritis was accomplished by determining the

location of care. Location of care was determined by an examination of hospital numbers and outpatient indicators associated with individual MC, in conjunction with an examination of HSA to identify periods of hospitalization.

Of 4,187 MC claims which identified new episodes of pyelonephritis, 1,602 contained hospital numbers, identifying Manitoba hospitals, nursing stations, or personal care homes as the location of care. Examination of indicators of location of care, resulted in the exclusion of 132 episodes which were not considered to be community-acquired . Thus, 4,055 new episodes remained for further consideration (Figure 8). Reasons for the inclusion or exclusion of episodes are documented below.

Figure 8. **Identification of new episodes of pyelonephritis for the period February 15, 1996 to March 31, 1999**



1. Twenty-eight of the 1,602 claims had a hospital number which indicated the location of care as a personal care home and were excluded from further study.
2. An additional 445 of the 1,602 claims lacked an out-patient indicator. Of these, 104 had an index date which overlapped a period of hospitalization, and thus were excluded from further study. A further 136 claims did not overlap with periods of hospitalization, while the remaining 205 claims had an index date which matched the admission date of a hospitalization. In these later instances, the episodes of pyelonephritis were considered to be community-acquired and were retained for further study.
3. A final 1,129 of the 1,602 claims contained an outpatient indicator. Of these, 914 visits were recorded as taking place in an ER, while 215 were recorded as outpatient visits. These 1,602 episodes were also retained for further study.

The 4,055 new episodes of pyelonephritis were experienced by 3,717 females; 3,449 of these were identified as eligible for coverage with Manitoba Health on both November 15, 1995 and December 31, 1999, and thus were assumed to be eligible for coverage for the entire study period. The 268 females who did not have continuous coverage were experienced 327 episodes of pyelonephritis. These episodes were excluded, leaving 3,728 new episodes, experienced by 3,449 females (Figure 8).

These community-acquired episodes of pyelonephritis were most commonly identified in young women. Children and women over the age of 65 years accounted for only 21% of episodes. Restriction of new episodes of pyelonephritis to those experienced

by females, aged 18 to 65 years of age, resulted in the exclusion of 768 additional episodes (Figure 8).

Finally, to ensure independence of observations, only the most recent episode of pyelonephritis for each subject was retained for further study. The majority of subjects (92.5%) experienced one new episode during the study period (Table 11). Elimination of all but the most recent episode for each member of the cohort resulted in the exclusion of 252 episodes, leaving a total of 2,708 episodes experienced by an equivalent number of subjects (Figure 8).

4.2 Subject Variables

Subject age was constrained to lie between 18 and 65 years; the median age of subjects was 34 years. The following sections detail subject characteristics for all 2,708 subjects using previously developed operational definitions (Section 3.5). A summary of subject characteristics is provided at the end of this section.

4.2.1 Presentation to Emergency Room

Presentation to ER was recorded for 588 (21.7%) of 2,708 new episodes of pyelonephritis (Table 12); Winnipeg hospitals accounted for 64.0% of ER claims, while non-Winnipeg hospitals accounted for 36.0%. The majority of Winnipeg ER claims originated from the two tertiary care hospitals where agreements with Manitoba Health for submission of shadow billings exist (Section 3.5.2); St. Boniface General Hospital, and Health Sciences Centre.

Table 11. **Number of new episodes of pyelonephritis experienced by 2,708 females aged 18 to 65 between February 15, 1996 and March 31, 1999**

Number of episodes	Number of subjects (%)
1	2,506 (92.5)
2	166 (6.8)
3	27 (1.0)
4+	9 (0.3)
Total	2,708 (100)

Table 12. **Initial physician visits for 2,708 new episodes of pyelonephritis occurring in Emergency Rooms by hospital**

Hospital	Initial physician visits N (%)
Winnipeg Hospitals	
Health Sciences Centre	217 (36.9)
St Boniface	112 (19.1)
Misericordia	7 (1.2)
Grace	4 (0.7)
Victoria	14 (2.4)
Seven Oaks	12 (2.1)
Concordia	10 (1.7)
Total Winnipeg	**376 (64.0)**
Non-Winnipeg Hospitals	
Brandon	52 (8.8)
Portage	25 (4.3)
Morden	18 (3.1)
Bethesda	30 (5.1)
Other non-Winnipeg	87 (14.8)
Total non-Winnipeg	**212 (36.0)**
Total	**588 (100)**

4.2.2 Diabetes

During the study period, 366 subjects had a least one claim for a physician visit or hospitalization associated with an ICD-9-CM code of 250, while 259 subjects had at least one DPIN claim for receipt of insulin or an oral hypoglycemic. The more restrictive definition of diabetes (definition II) (Section 3.5.3) resulted in 304 (11.2%) subjects being identified as diabetic, compared with 376 (13.9%) using the more liberal definition (definition I).

The presence of relevant physician, hospital, and/or pharmaceutical claims related to diabetes for subjects assigned a positive diabetic status using the alternate definitions are reported in Table 13. One or more pharmaceutical claims for insulin and/or oral hypoglycemics were evident for 68.9% or 80.9% of diabetic subjects using definitions I and II respectively. One or more hospital claims containing the ICD-9-CM code 250 were evident for 48.2% and 59.6% of diabetic subjects, while claims for physician visits associated with the ICD-9-CM code 250 were evident for 94.5% and 96.5% of diabetic subjects, using definitions I and II respectively. Claims for multiple healthcare services related to diabetes were common. For example 40.2% and 49.7% of subjects assigned positive diabetic status, by definitions I and II respectively, had one or more claims of all types indicative of diabetes (physician, hospital, pharmaceutical) during the study period.

The greatest contribution to the larger numbers of subjects identified as diabetic, using definition I versus definition II, were those subjects whose claim history contained only 1 relevant physician visit, and whose claim history contained no hospital or pharmaceutical claims indicative of diabetes. These 59 subjects may potentially be subjects whose one medical claim represented a differential diagnosis which was

subsequently ruled out, since no additional claims support the diagnosis. A smaller contribution to the additional subjects identified as diabetics using definition I, were those subjects who had at least one pharmaceutical claim for insulin and/or oral hypoglycemic agents, yet for whom no medical or hospital claims were identified. As diabetes is the sole indication for use of these agents, it is most likely that these subjects are indeed diabetic. These subjects are not captured by definition II since the definition does not include DPIN claims. Thus, the choice between definition I and definition II represents a tradeoff between sensitivity and specificity. Use of the most liberal definition (definition I) would likely capture the greatest number of true diabetics but could potentially include a considerable number of non-diabetics. For this reason, the more restrictive definition of diabetes (definition II) was used for future data analysis, and 304 subjects were so identified.

4.2.3 Recent antibiotic use

Recent antibiotic use (Section 3.5.4) was evident in 964 (35.6%) subjects. These 964 subjects received 1,547 (a range of one to nine) antibiotic prescriptions in the 90 days prior to their respective index dates. For the identified subjects, 604 (62.7%) received one antibiotic in the 90 days prior to the index date, while 236 (24.5%) received two, 74 (7.7%) received three, and 50 (5.2%) received four or more. Amoxicillin (23.5%), TMP-SMX (20.0%), and macrolides (13.9%), were the most common recently used antibiotics (Table 14).

Table 13. **Number of subjects with claims for physician visits (PHY), hospitalizations (HSP) and pharmaceuticals (Rx) related to diabetes management among subjects identified as diabetic using alternate definitions of diabetes**

Claim Type	Definition I Number of subjects (%)	Definition II Number of subjects (%)
PHY only	92 (24.5)	33 (10.9)
HSP only	6 (1.6)	6 (2.0)
Rx only	10 (2.7)	0 (0)
PHY and HSP	19 (5.1)	19 (6.3)
PHY and Rx	93 (24.7)	90 (29.6)
HSP and Rx	5 (1.3)	5 (1.6)
PHY and HSP and Rx	151 (40.2)	151 (49.7)
Total	**376 (100.0)**	**304 (100.0)**

Table 14. **Recent antibiotic use by 964 subjects (1,547 antibiotic prescriptions) with a new episode of pyelonephritis**

Antibiotic/Antibiotic class	Number of prescriptions (%)
Aminopenicillins	364 (23.5)
TMP-SMX	310 (20.0)
Macrolides	215 (13.9)
Fluoroquinolones	181 (11.7)
Cephalosporins	133 (8.6)
Penicillin G/V	71 (4.6)
Metronidazole	70 (4.5)
Tetracyclines	63 (4.1)
Nitrofurantoin	60 (3.9)
Cloxacillin	59 (3.8)
Other	21 (1.4)
Total	**1,547 (100)**

Among recent antibiotic users, receipt of an antibiotic was most common in the week preceding a new episode of pyelonephritis. Specifically 225 (23.3%) of recent antibiotic users received their most recent antibiotic prescription within one week prior to the index date. As time preceding the index date increased, the proportion of subjects receiving their most recent antibiotic prescription decreased. For example, while 23.3% of the subjects received their most recent antibiotic in the first week prior to their index date, only 6.3% received their prescription in the fifth week prior to their index date (Figure 9).

4.2.4 Recent hospitalization

Recent hospitalization (Section 3.5.5) was reported for 322 (11.9%) subjects, who experienced a total of 423 recent hospitalizations. The number of hospitalizations for each subject ranged from one to six. Of the 322 subjects, 249 (77.3%) experienced one hospitalization in the 90 days prior to index date, 52 (16.2%) experienced two hospitalizations, and 21 (6.5%) experienced three or more hospitalizations. Among the recently hospitalized, 55 (17.1%) subjects were discharged from their most recent hospitalization within the week preceding the index date (Figure 10).

Figure 9. **Timing of receipt of most recent antibiotic prescription by 964 subjects with recent antibiotic use**

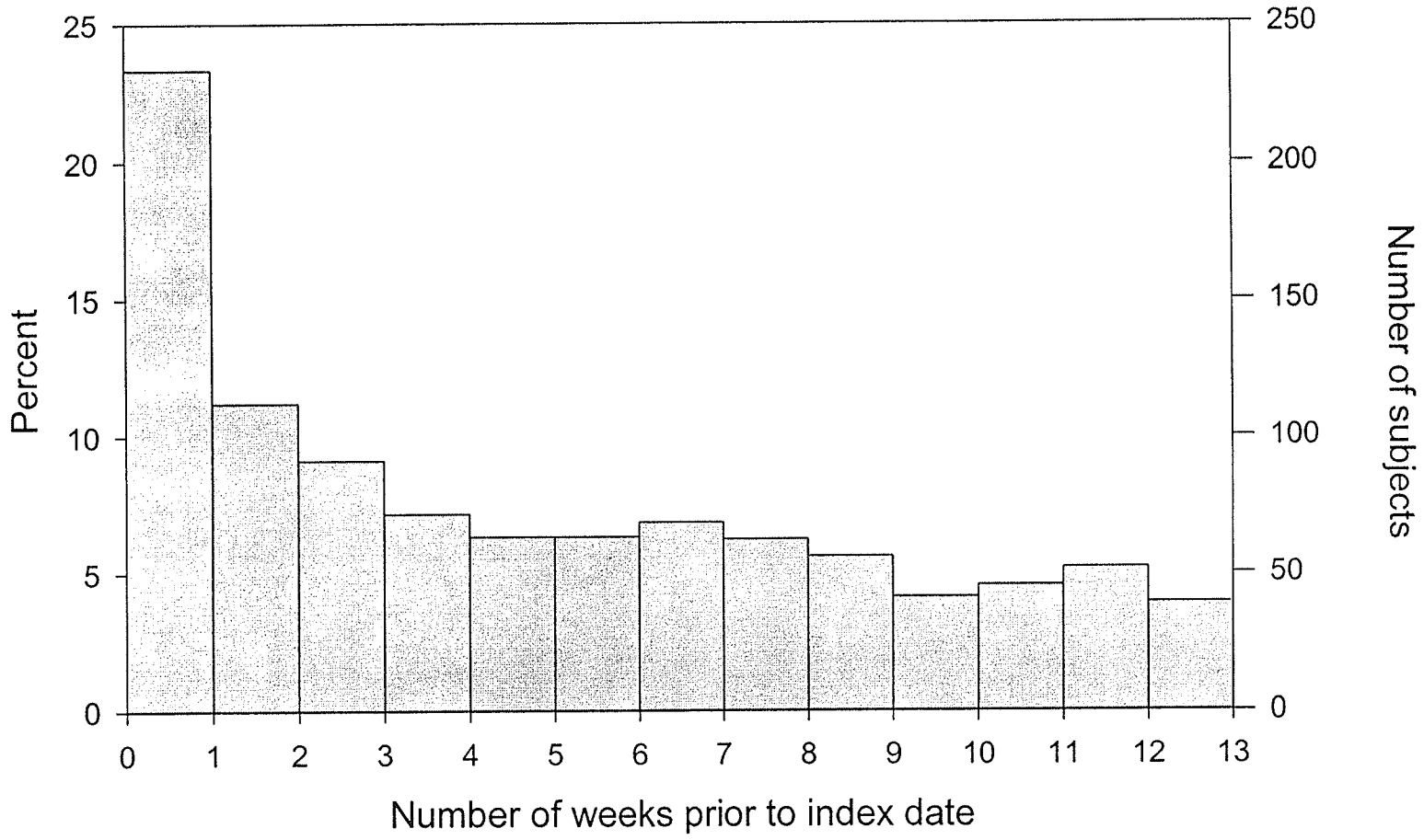
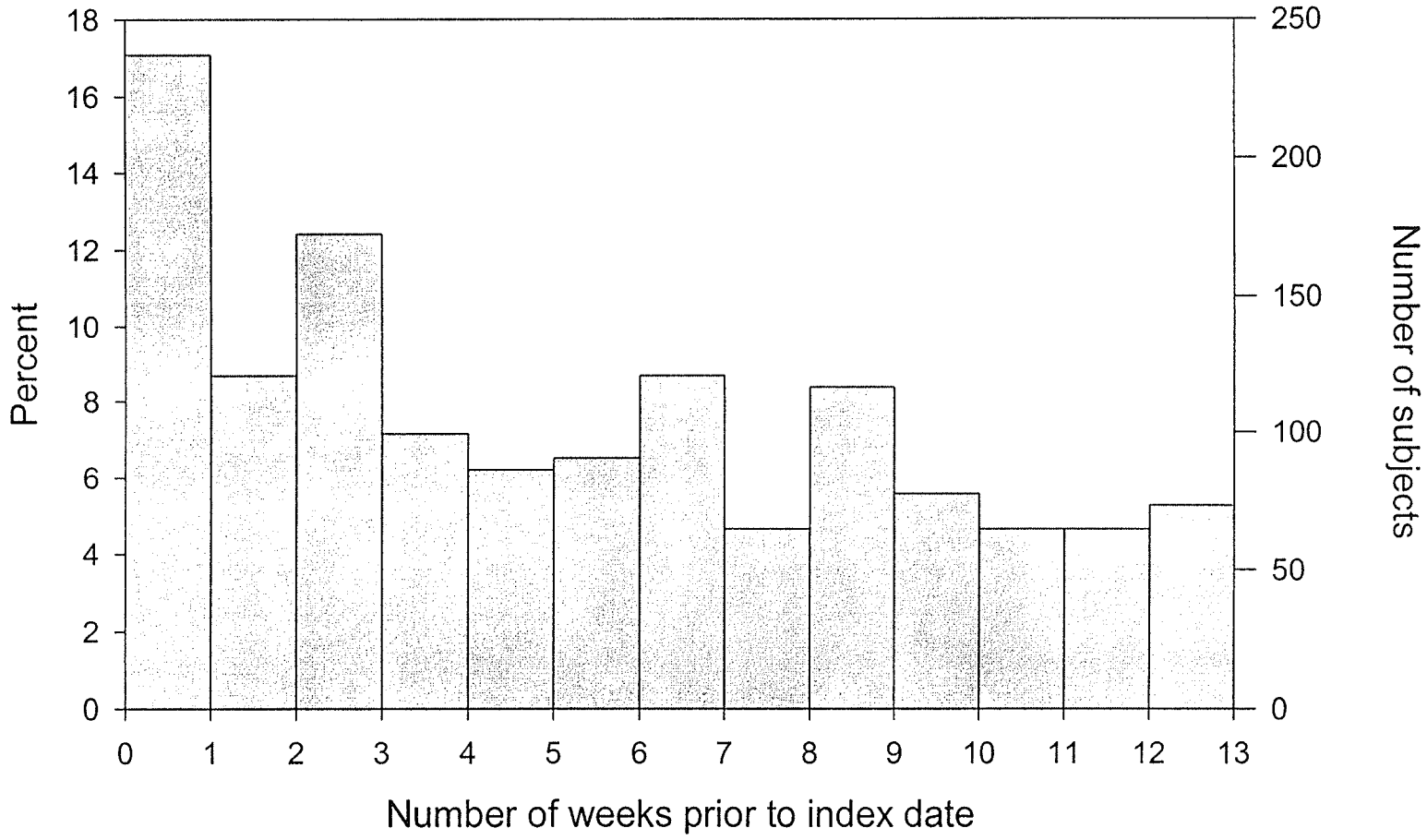


Figure 10. **Timing of most recent hospitalization for 322 subjects with recent hospitalization**



4.2.5 Recent Urinary Tract Infection

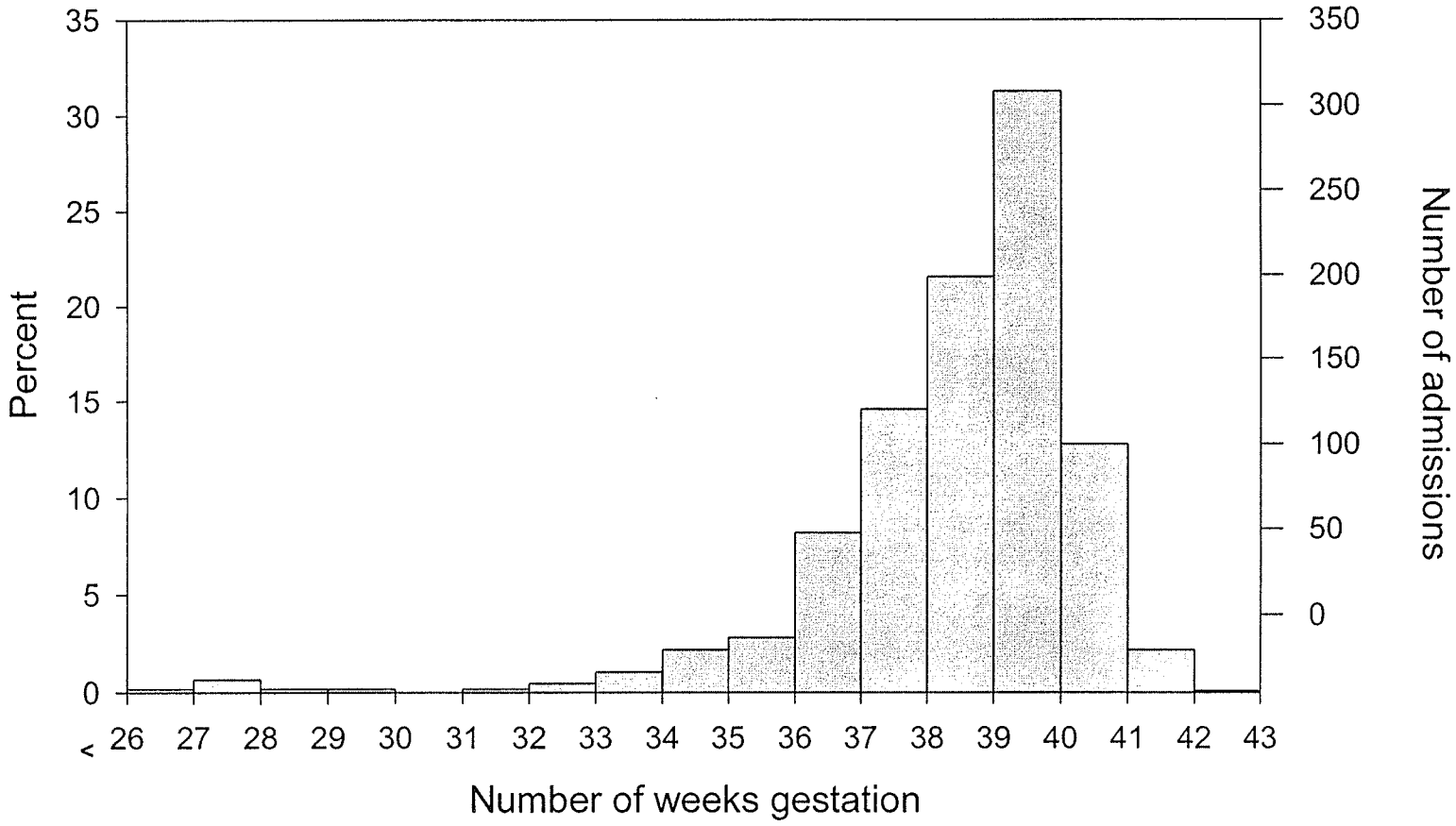
Due to difficulties with use of the truncated ICD-9-CM code 599, (Section 3.5.1) it is difficult to accurately quantify recent UTI. In addition, patients may make one or many physician visits related to a single UTI. Thus, descriptions of the number and timing of previous UTI are difficult. Recent urinary tract infection (Section 3.5.6) was evident in 193 (7.1%) subjects. The number of urinary tract related physician visits ranged from one to eight per subject.

4.2.6 Pregnancy

For the current study, 1061 HSA containing ICD-9-CM codes of V27 (outcome of pregnancy) were identified. These pregnancies were experienced by 738 women. One claim which had a missing gestational age, and eight claims containing a gestational age of zero were assigned a gestational age of 40 weeks. This was consistent with the most commonly observed gestational age (Figure 11). Calculation of period of pregnancy and examination of timing of new episodes of pyelonephritis, resulted in a positive pregnancy status for 183 (6.8%) subjects.

In addition, there were 5,250 MC and HSA containing diagnosis and tariff codes indicative of possible pregnancy for 821 women. These claims fell outside of the previously determined periods of pregnancy and were classified as possible additional pregnancies, which did not result in delivery. These claims were assigned a gestational age of 40 weeks. Calculation of possible period of pregnancy and examination of the timing of episodes of pyelonephritis, resulted in an indeterminate pregnancy status, at index date, for 89 (3.3%) subjects. The remainder of subjects were assigned a pregnancy status of negative.

Figure 11. **Gestational age at hospital admission for 1,061 admissions resulting in delivery**



4.2.7 Rural Residence/Income

Residence and income data could not be obtained for 53 (2.0%) subjects because of missing information regarding area of residence, or suppression of income by Statistics Canada. Among the 2,655 subjects for whom area of residence and income quintile was identified, 31.8% had rural status. The lowest income quintile (quintile 1) accounted for 34.8% of subjects (Figure 12) with the proportion of total subjects in each quintile decreasing as income increased; the highest income quintile (quintile 5) accounted for only 13.2% of subjects.

Figure 12. **Proportion of 2,655 new episode of pyelonephritis by residence and income quintile**

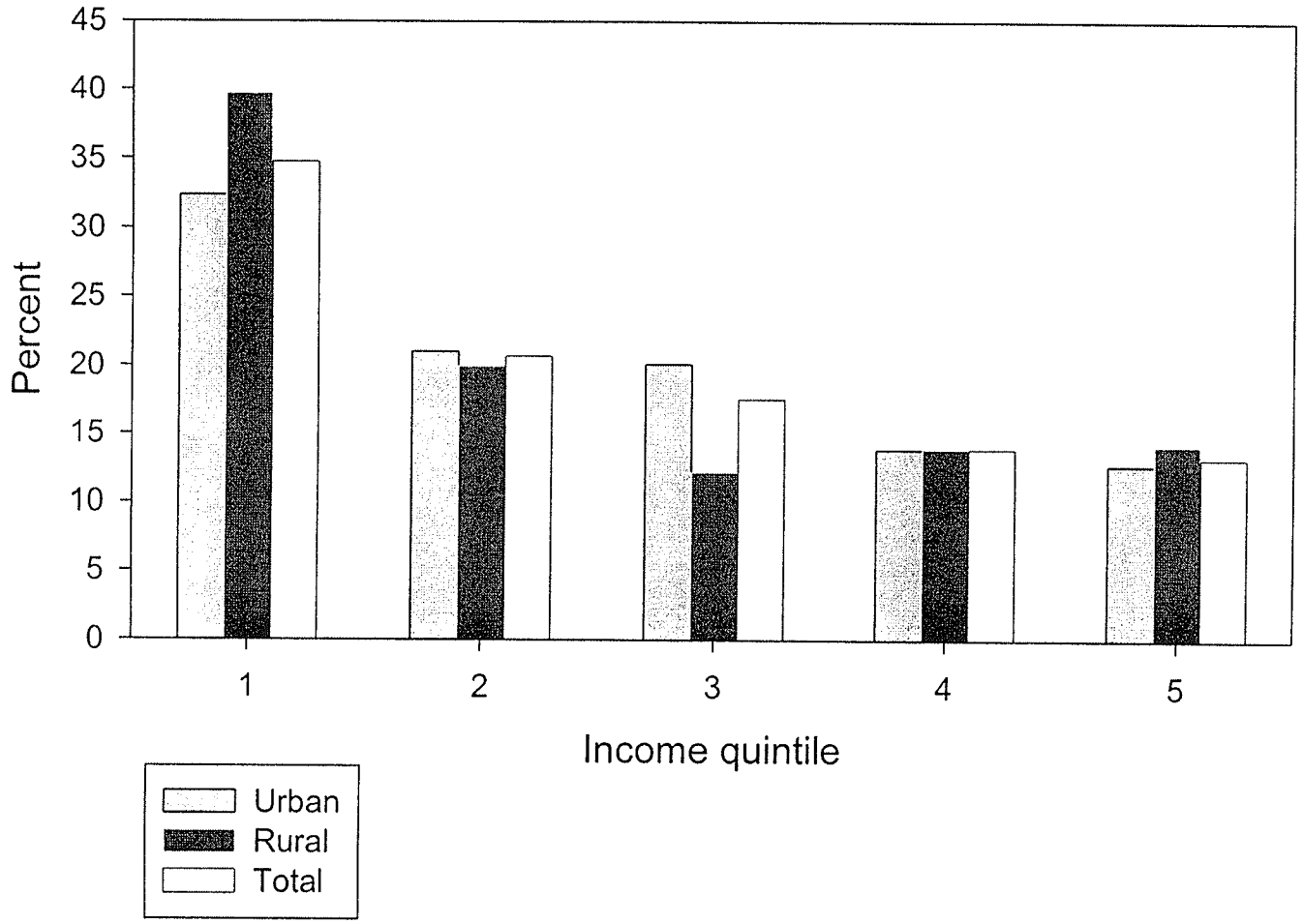


Table 15. **Subject characteristics of 2,708 females experiencing their most recent episode of pyelonephritis**

Variable	Description
Age	Range 18-65 years; median 34 years
Presentation to ER	Yes = 588 (21.7%) No = 2,120 (78.3%)
Diabetic (Definition I)	Yes = 376 (13.9%) No = 2,332 (86.1%)
Diabetic (Definition II)	Yes = 304 (11.2%) No = 2,404 (88.8%)
Recent Antibiotic Use	Yes = 964 (35.6%) No = 1,744 (64.4%)
Recent UTI	Yes = 193 (7.1%) No = 2,515 (92.9%)
Recent hospitalization	Yes = 322 (11.9%) No = 2,386 (88.1%)
Pregnancy Status	Positive = 183 (6.8%) Indeterminate = 89 (3.3%) Negative = 2,436 (90.0%)
Residence	Urban = 1,811 (66.9%) Rural = 844 (31.2%) Missing = 53 (2.0%)
Income Quintile	1 = 923 (34.1%) 2 = 549 (20.3%) 3 = 466 (17.2%) 4 = 368 (13.6%) 5 = 349 (12.9%) Missing = 53 (2.0%)

4.3 Identification of Initial Treatment

Examination of DPIN and HSA claims up to two days subsequent to the index date identified subjects who were admitted to hospital or who received out-patient antibiotic treatment (Figure 13). A DPIN claim for an appropriate antibiotic (Section 3.5.10) within two days of initial physician visit was evident for 1,562 out of 2,708 subjects. A HSA with an admission date within two days of the index date, (for which the most responsible diagnosis submitted was one of ICD-9-CM codes 590, 595 or 599), was evident for 402 of 2,708 subjects. For 834 of 2,708 new subjects, there were no claims for a hospitalization or an appropriate antibiotic within two days of the index date.

For the 1,874 subjects for whom a claim for hospitalization and/or an appropriate antibiotic were evident, 90 had both an antibiotic and a hospitalization claim in the two days subsequent to the index date. Admission date (in the case of hospitalizations) and date provided (in the case of antibiotic claims) were examined to determine if antibiotic treatment preceded hospitalization or vice versa as described below.

1. For 63 of 90 subjects, the hospital admission date preceded the date provided for antibiotic prescriptions, and initial treatment for these subjects was ascribed to hospitalization.
2. For 16 of 90 subjects, the date provided for the antibiotic prescription preceded the admission date of a hospital claim and initial treatment for these subjects was deemed to be outpatient antibiotic treatment.

3. For 11 subjects, the claim date and admission date matched, thus, initial treatment for these subjects could not be classified as either outpatient antibiotic treatment or hospitalization, and initial treatment for these subjects was classified as indeterminate.

Thus, out-patient antibiotic treatment was evident for 1,488 subjects (55.0%), hospitalization for 375 subjects (13.9%), indeterminate treatment for 11 subjects (0.4%), and no treatment evident for 834 subjects (30.8%).

To determine the utility of the "two day window" to identify initial treatment, results obtained with alternate definitions were examined. Definitions which varied the time period for capture of initial treatment from index date (day zero), to seven days subsequent to index date, were utilized (Table 16). A longer period for capture of initial treatment increased the proportion of subjects for whom treatment was identified however, the marginal gain decreased with each additional day of claims examined. For the current study, the original definition related to the time period for capture of initial treatment was retained.

Figure 13. **Subjects with healthcare claims indicative of hospitalization or out-patient antibiotic treatment within two days of the index date.**

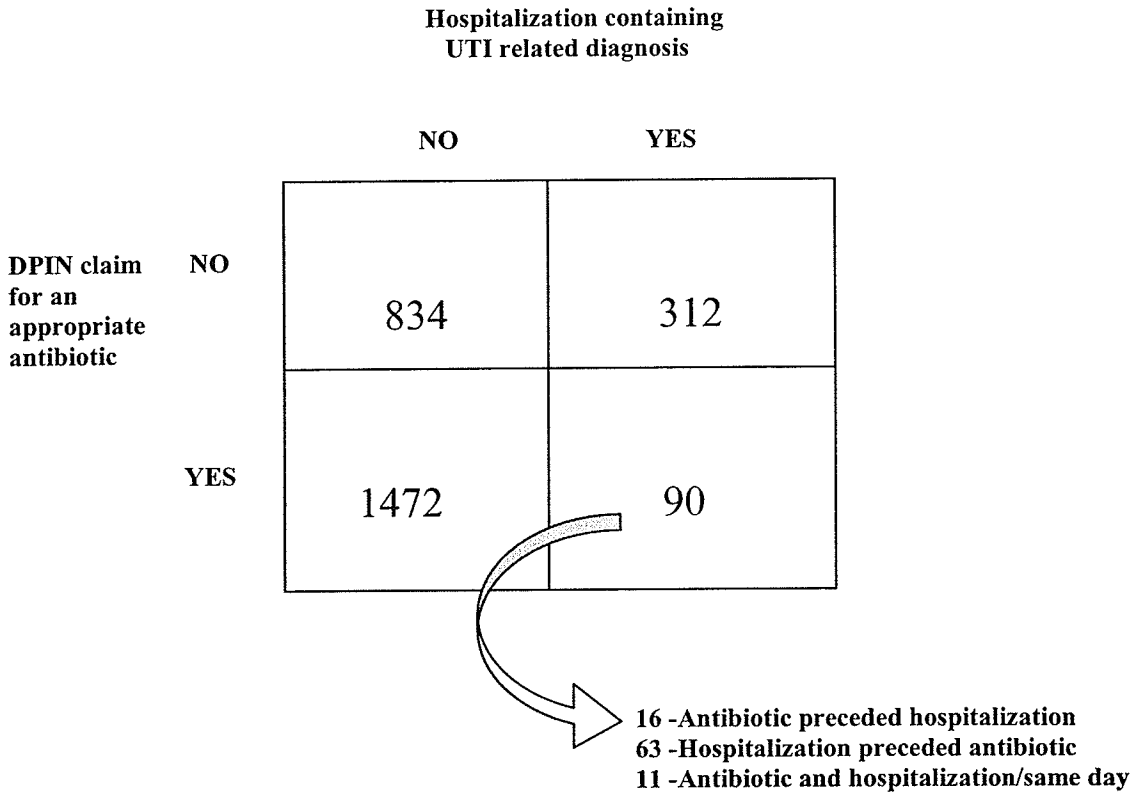


Table 16. **Effect of varying time periods for the identification of initial treatment of new episodes of pyelonephritis.**

	Number of days elapsed since index date							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Treatment	**N** (%)	**N** (%)	**N** (%)	**N** (%)	**N** (%)	**N** (%)	**N** (%)	**N** (%)
Outpatient Antibiotic	1194 (44.1)	1420 (52.4)	1488 (55.0)	1527 (56.4)	1540 (56.9)	1551 (57.3)	1557 (57.5)	1568 (57.9)
Hospitalization	302 (11.2)	359 (13.3)	375 (13.9)	375 (13.9)	377 (13.9)	377 (13.9)	378 (14.0)	380 (14.0)
None evident	1205 (44.5)	920 (34.0)	834 (30.8)	795 (29.4)	780 (28.8)	769 (28.4)	762 (28.1)	749 (27.7)
Indeterminate	7 (0.3)	10 (0.4)	11 (0.4)	11 (0.4)	11 (0.4)	11 (0.4)	11 (0.4)	11 (0.4)
Total episodes	**2,708**	**2,708**	**2,708**	**2,708**	**2,708**	**2,708**	**2,708**	**2,708**

4.3.1 Initial Antibiotic Treatment

Of 1,488 subjects who received outpatient antibiotic treatment of pyelonephritis, 1,471 had a DPIN claim for a single initial antibiotic, 16 had DPIN claims for 2 antibiotics on the same date, and 1 subject had DPIN claims for 3 antibiotics on the same date. For subjects with claims for a single antibiotic, TMP-SMX (48.8%) and fluoroquinolones (31.7%) were the most commonly used agents. Aminopenicillins (8.9%), cephalosporins (5.4%), nitrofurantoin (4.8%) and miscellaneous agents (0.4%) accounted for the remainder of treatments (Table 17).

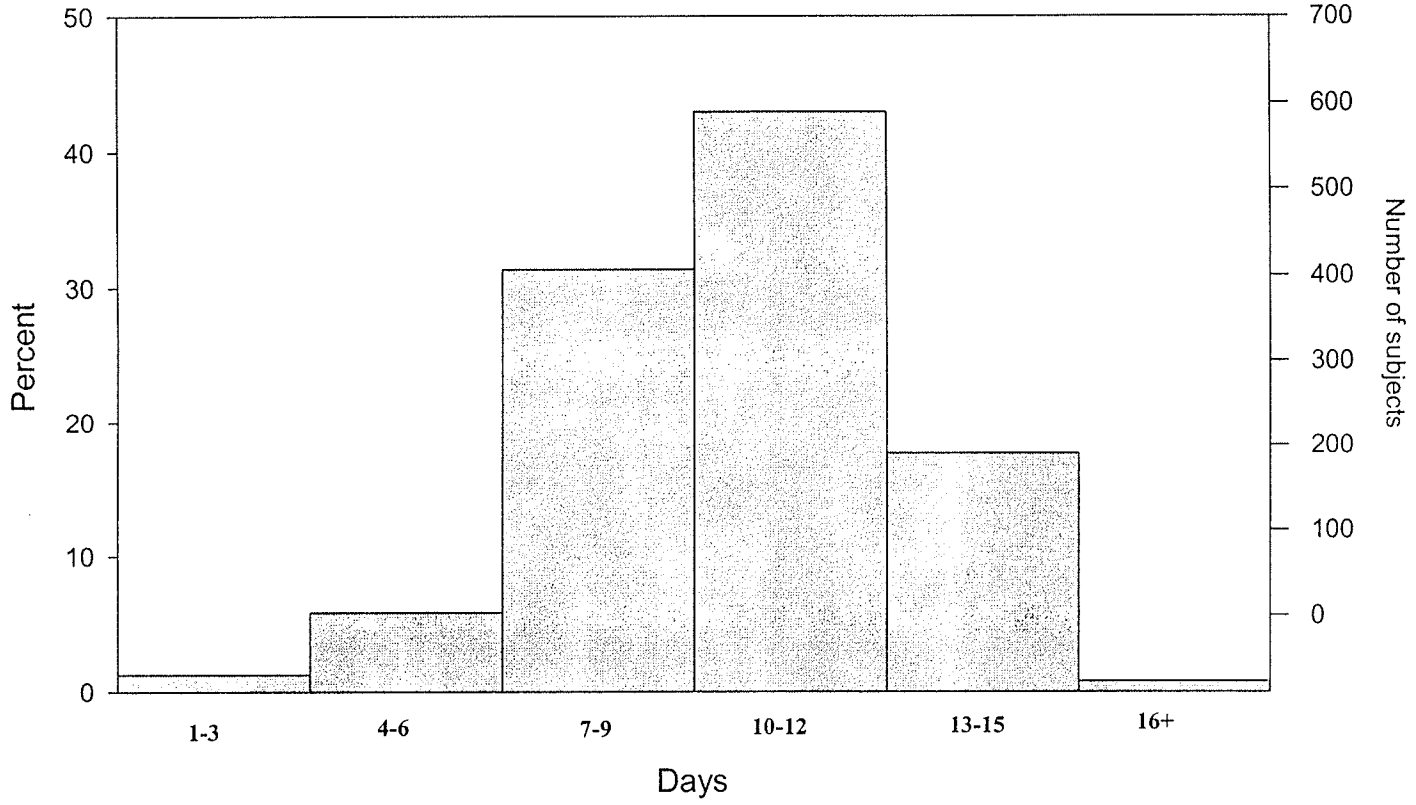
As expected, antibiotic use varied with pregnancy status. Among those subjects with positive pregnancy status, aminopenicillins (33.3%), cephalosporins (27.8%) and nitrofurantoin (16.7%) accounted for the majority of initial antibiotic treatments. Use of TMP-SMX and fluoroquinolones was observed less commonly in those with positive pregnancy status compared to those with negative pregnancy status. Initial antibiotic treatment among subjects with indeterminate pregnancy status was similar, in terms of class of agents used, to that of subjects with negative pregnancy status.

For subjects with a single initial antibiotic, the median treatment duration was 10 days (range 1-150 days), with 92% of subjects receiving between 7 and 15 days of treatment (Figure 14). For the 17 subjects for whom a single initial antibiotic could not be determined (i.e., more than 1 antibiotic was dispensed on the same date) Appendix C provides a description of antibiotics and duration of treatment provided.

Table 17. **Single initial antibiotic treatment, by class of agent and pregnancy status**

Antibiotic class	Non-Pregnant N (%)	Indeterminate N (%)	Pregnant N (%)	Total N (%)
TMP-SMX	682 (50.1)	28 (50.0)	8 (14.8)	718 (48.8)
Fluoroquinolone	446 (32.8)	16 (28.6)	4 (7.4)	466 (31.7)
Aminopenicillins	105 (7.7)	8 (14.3)	18 (33.3)	131 (8.9)
Cephalosporin	63 (4.6)	1 (1.8)	15 (27.8)	79 (5.4)
Nitrofurantoin	59 (4.3)	3 (5.4)	9 (16.7)	71 (4.8)
Other	6 (0.4)	0 (0.0)	0 (0.0)	6 (0.4)
Total	**1,361 (100)**	**56 (100)**	**54 (100)**	**1,471 (100)**

Figure 14. **Duration of initial antibiotic treatment for 1,471 subjects receiving a single antibiotic**



4.4. Missing Data

Subjects (N=141), for whom definitive status on all study variables, as described below, could not be established, were excluded from further study.

1. Definitive pregnancy status could not be determined for 89 subjects.
2. Residence and income quintiles could not be assigned to 53 subjects.
3. One subject had both indefinite pregnancy and income/residence status.

There were no significant differences between those subjects retained for further study and those excluded, with respect to known subject variables, with the exception of age. Excluded subjects were significantly younger than retained subjects; median age 29 years versus 34 years respectively ($p<0.0001$) (Table 18).

4.5 Comparison of subjects with appropriate treatment versus no treatment

For the 2,567 subjects with a new episode of pyelonephritis and no missing data, 1,772 (69.0%) were linked to healthcare claims indicative of appropriate treatment for a diagnosis of pyelonephritis (out-patient antibiotic, in-hospital, or both), while 795 (31%) subjects could not be linked to appropriate health care claims. Subjects linked to claims for appropriate treatment differed from those without claims in terms of:

1. rural residence (29.0% versus 40.0%; $p<0.0001$)
2. pregnancy status (5.9% versus 9.4%; $p<0.001$)
3. presentation to an Emergency Room (25.2% versus 13.1%; $p<0.0001$)

There were no significant differences in age, diabetes status, or the proportion of subjects with recent antibiotic use, recent hospitalization, or recent UTI, between subjects with healthcare claims indicative of treatment and those without (Table 19). Similarly, there was no significant association between income quintile and the presence of healthcare claims for appropriate treatment (χ^2=1.20; df=4, p<0.88).

Table 18. **Comparison of subject variables between retained and excluded episodes**

Subject Variable	Subjects Retained N (%)	Subjects Excluded N (%)	p
Age in years (median)	35.0	29.0	<0.0001
ER visit	551 (26.8)	37 (26.2)	0.18
Diabetic status (Definition II)	287 (11.2)	17 (12.1)	0.75
Recent antibiotic use	913 (34.0)	51 (35.6)	0.88
Recent UTI	182 (6.5)	11 (7.8)	0.75
Recent hospitalization	299 (11.7)	23 (16.3)	0.10
Total	**2567 (100)**	**141 (100)**	

Table 19. **Comparison of subject variables between those with healthcare claims indicative of treatment of pyelonephritis and those without**

Subject Variable	Treatment evident N (%)	No treatment evident N (%)	p
Age in years (median)	34.0	34.0	0.19
ER visit	447 (25.2)	104 (13.1)	<0.0001
Diabetic (Definition II)	184 (10.4)	103 (13.0)	0.06
Recent antibiotic	626 (35.3)	287 (36.1)	0.71
Recent UTI	116 (6.6)	66 (8.3)	0.11
Recent hospitalization	199 (11.2)	100 (12.6)	0.35
Pregnancy	105 (5.9)	75 (9.4)	<0.001
Rural residence	514 (29.0)	325 (40.9)	<0.0001
Total	**1,772 (100)**	**795 (100)**	

4.6 Comparison of subjects receiving initial out-patient antibiotic treatment versus in-hospital treatment

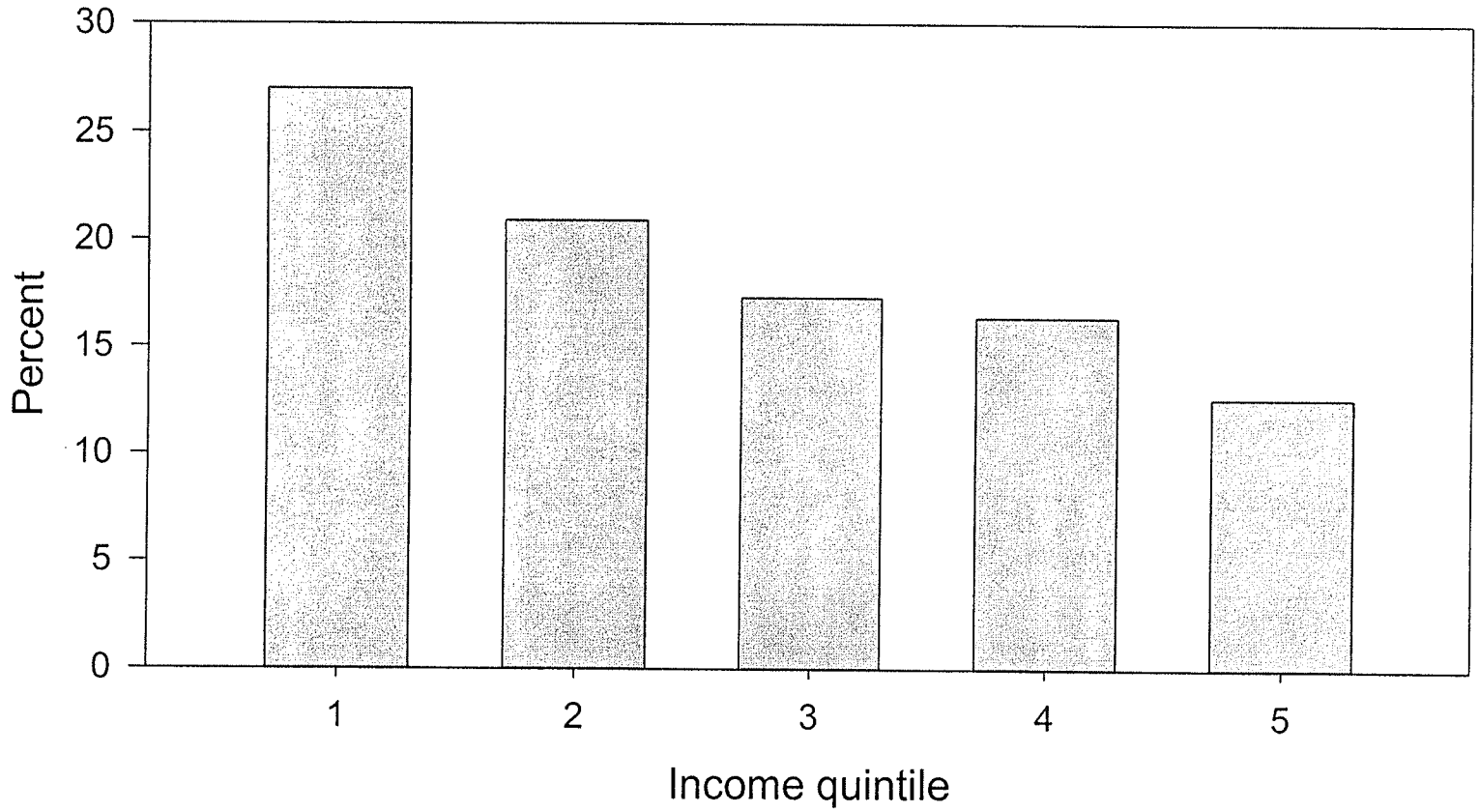
Among the 1,726 subjects (with no missing data who received one of either out-patient antibiotic or in-hospital treatment), 1,370 (79.4%) received out-patient antibiotic treatment, while 356 (20.6%) were hospitalized for initial treatment. Hospitalized subjects were more likely to have presented to an ER for initial physician visit than those subjects treated as out-patients; 41.3% versus 21.0% respectively ($p<0.0001$). In addition, hospitalized subjects were also more likely to be pregnant, diabetic, or have recent antibiotic use, rural residence, or recent hospitalization (Table 20).

There were no significant differences in age, or the proportion of subjects with recent UTI, between those subjects hospitalized and those treated with out-patient antibiotics. Income quintile was significantly associated with the probability of hospitalization for initial treatment ($\chi^2=28.6$, df=4, $p<0.0001$). In the lowest income quintile (quintile 1), 27.0% of subjects were hospitalized for initial treatment. This proportion decreased as income quintile increased from lowest to highest, with 12.6% of subjects in the highest income quintile (quintile 5) being hospitalized for initial treatment (Figure 15).

Table 20. **Comparison of subject characteristics between initial treatment with out-patient antibiotic treatment versus hospitalization**

Subject Variable	Antibiotic treatment N (%)	Hospitalization N (%)	p
Age in years (median)	35.0	34.0	0.25
ER visit	287 (21.0)	147 (41.3)	<0.0001
Diabetic (Definition II)	114 (8.3)	66 (18.5)	<0.0001
Recent antibiotic	459 (33.5)	146 (41.0)	0.008
Recent UTI	87 (6.4)	25 (7.0)	0.65
Recent hospitalization	129 (9.4)	62 (17.4)	<0.0001
Pregnancy	50 (3.7)	49 (13.8)	<0.0001
Rural residence	342 (25.0)	162 (45.5)	<0.0001
Total	**1370 (100)**	**356 (100)**	

Figure 15. **Proportion of 1,726 new episodes of pyelonephritis with a single initial treatment receiving treatment in hospital by income quintile**



4.7 Identification of Final Cohort for Analysis

The purpose of the current study was to examine determinants of receipt of fluoroquinolone versus TMP-SMX for initial treatment of pyelonephritis, and to evaluate comparative treatment outcomes. Figure 16 illustrates the procedure used to identify the final cohort for analysis. Of 1,488 subjects who received initial treatment with outpatient antibiotics, 404 were excluded as described below, resulting in a final cohort of 1,084 subjects for analysis. Exclusions from the cohort were made for the following reasons:

1. Missing data related to subject variables (residence, income quintile, pregnancy) (N=82).
2. Receipt of more than one initial antibiotic on the same day (N=17).
3. Additional MC or HSA (containing an ICD-9-CM code consistent with a non-urinary infectious disease) with service dates and/or discharge dates up to two days prior to the initial antibiotic (Appendix D) (N=19).
4. Initial treatment with other than TMP-SMX or a fluoroquinolone (N=266).
5. Positive pregnancy status (N=12).
6. Duration of treatment greater than 15 days (N=8).

The final cohort for analysis consisted of 1,084 subjects; 653 (60.2%) received TMP-SMX, and 431 (39.8%) received a fluoroquinolone. Of the 431 subjects treated with a fluoroquinolone, 280 (65.0%) received ciprofloxacin, while 151 (35.0%) received norfloxacin. A description of the final cohort is provided in Table 21. The final cohort of subjects was used to test hypotheses 1 to 8 (the effect of subject variables upon the

probability of receipt of a fluoroquinolone), and hypotheses 9 to 13 (the effect of initial antibiotic treatment and subject variables on the probability of treatment failure).

Figure 16. **Identification of initial treatment and final cohort for analysis**

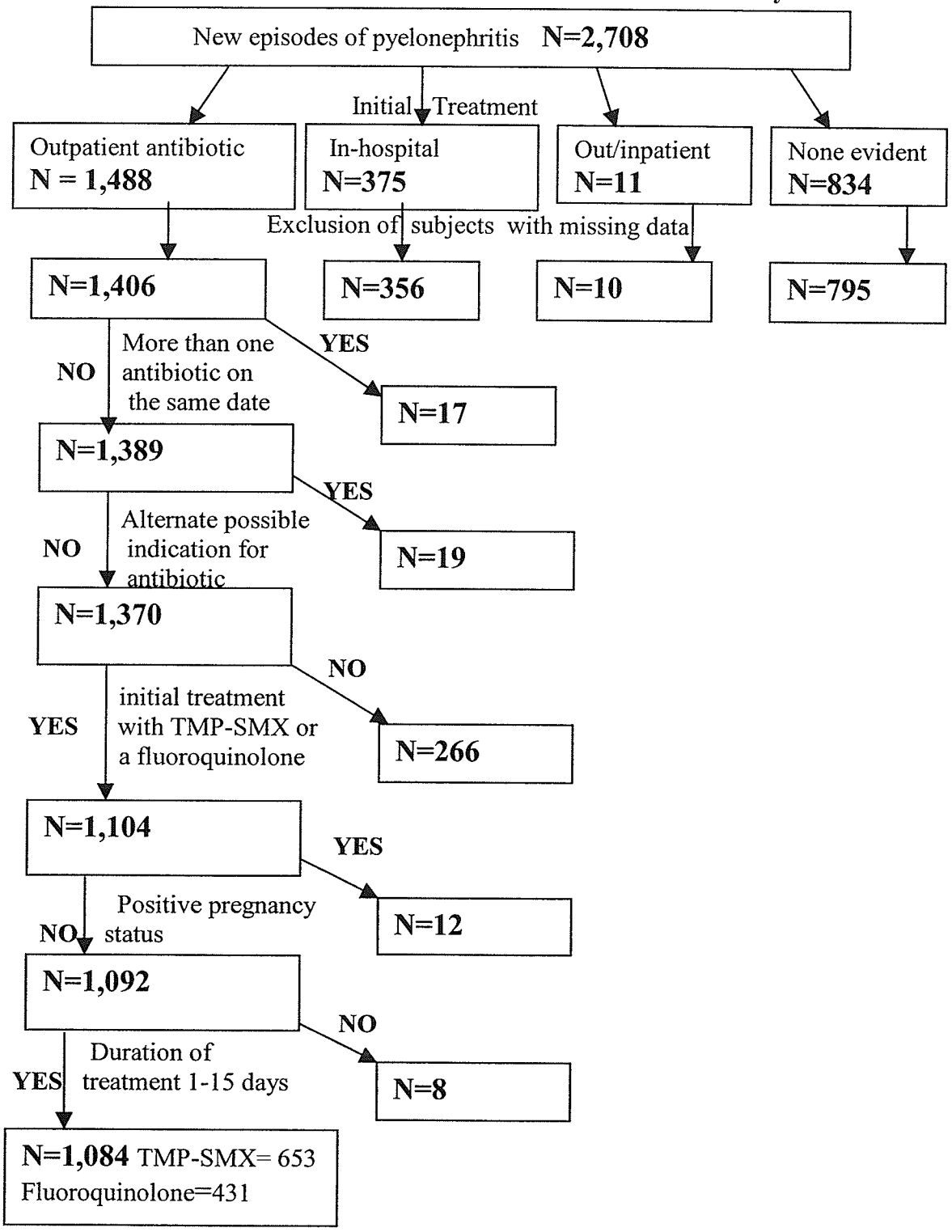


Table 21. **Subject specific variables for the final cohort of 1,084 women, by initial treatment**

Variable	TMP-SMX N (%)	Fluoroquinolone N (%)	Total N (%)
Age in years (median)	33.0	37.0	35.0
ER visit	147 (22.5)	96 (22.3)	243 (22.4)
Diabetic (Definition II)	52 (8.0)	36 (8.4)	88 (8.1)
Recent Antibiotic Use	202 (30.9)	160 (37.1)	362 (33.4)
Recent UTI	40(6.1)	25 (5.8)	65 (6.0)
Recent hospitalization	53 (8.1)	50 (11.6)	103 (9.5)
Rural Residence	148 (22.7)	105 (24.4)	253 (23.3)
Income Quintile	1 = 233 (35.7) 2 = 139 (21.3) 3 = 115 (17.6) 4 = 90 (13.8) 5 = 76 (11.6)	1 = 116 (26.9) 2 = 85 (19.7) 3 = 83 (19.3) 4 = 69 (16.0) 5 = 78 (18.1)	1 = 349 (32.2) 2 = 224 (20.7) 3 = 198 (18.3) 4 = 159 (14.7) 5 = 154 (14.2)
Total	**653 (100)**	**431 (100)**	**1,084 (100)**

4.8 Identification of Treatment Failure

For the final cohort of 1,084 subjects, treatment failure was determined based on the existence of further healthcare claims within 42 days of the index date (Section 3.5.11). This included one or more HSA for which the most responsible diagnosis submitted was one 590, 595, or 599, and/or one or more DPIN claims for an appropriate antibiotic related to the original infection as described in Section 3.5.11.

Of the 1,084 subjects, 17 were admitted to hospital within 42 days of the index date with a diagnosis which met the definition of treatment failure, as described in Section 3.5.11. In addition, there were 353 additional antibiotic prescriptions dispensed within 42 days of the index dates, which were considered appropriate treatment of UTI. Of these, 17 prescriptions were for antibiotics for which single daily dosing is not standard, and had a dispensed quantity which resulted in less than 2 solid dosage units per day. These antibiotics were designated as prophylaxis or suppressive therapy and were not considered indicative of treatment failure. (A description of these 17 antibiotic prescriptions may be seen in Appendix G.) The remaining 336 antibiotics were assigned to one or more of six categories based on the likely indication for use, with treatment failure status assessed as described in Section 3.5.11 (Table 22). Diagnosis codes associated with MC and HSA which resulted in antibiotics being placed in categories I and IV are described in Appendices E and F respectively.

There were 175 antibiotic prescriptions assigned to categories II and III alone, or in combination with category V. These 175 were assigned a status of "treatment failure". There were 48 antibiotic prescriptions assigned to categories I and IV, or a combination

thereof, which were accorded an outcome status of, "non-failure". Five antibiotic prescriptions which were assigned to other combinations of categories I to V, were assigned outcome status based on service dates, service type and antibiotic type. Of these, two antibiotics were assigned an outcome status of "failure" and three were assigned an outcome status of "non-failure".

The remaining 108 antibiotic prescriptions assigned to category VI, represented antibiotics for which the indication for use was unclear. Of these, 46 prescriptions were not for antibiotics considered to be "urinary antibiotics" and were likewise not considered indicative of treatment failure. The remaining 62 antibiotic prescriptions assigned to category VI were assigned an outcome status of "failure".

Overall, 207 (19.1%) of 1,084 subjects were identified as experiencing treatment failure; 190 due to receipt of at least one additional antibiotic prescription, 6 due to admission to hospital for treatment of a UTI, and 11 due to both additional antibiotic treatment and admission to hospital. Treatment failure was experienced by 124 (19.0%) of 653 subjects treated with TMP-SMX, and 83 (19.3%) of 431 subjects treated with a fluoroquinolone. Table 23 describes the first antibiotic, deemed indicative of failure, received by the 190 subjects who received only additional antibiotic treatment.

For the above subjects, the median time to treatment failure was 8 days, with 47% experiencing treatment failure within 1 week subsequent to index date. Median time to treatment failure was significantly shorter for subjects treated with TMP-SMX (7 days), versus 11 days for a fluoroquinolone (11 days) (p=0.02) (Figure 17).

Figure 17. **Time to fail among 207 subjects experiencing treatment failure of initial antibiotic**

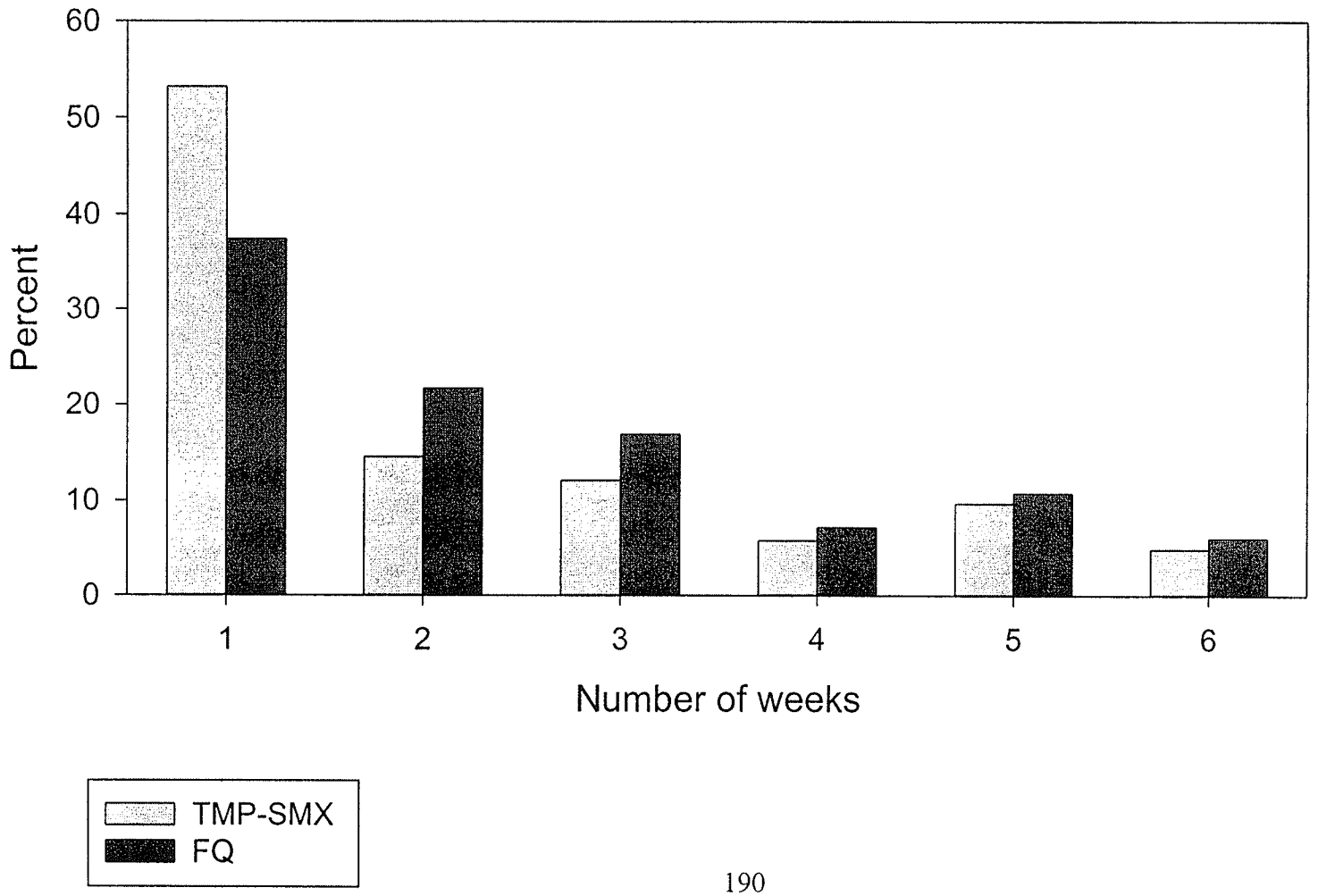


Table 22. **Categorization of additional antibiotic prescriptions and assignment of treatment outcome**

Category	Definition	Number of antibiotic prescriptions	Assignment of Treatment Outcome
I only	Antibiotic dispensed within two days of a MC for a physician visit for which a diagnosis code of an infectious disease unrelated to bacterial infection of the urinary tract was submitted.*	46	No failure
II only	Antibiotic dispensed within two days of a MC for a physician visit for which a diagnosis code indicative of UTI was submitted.	90	Failure
III only	Antibiotic dispensed within two days of a MC for laboratory services for which tariff codes indicative of performance of urinalysis, urine culture and/or sensitivity were submitted.	19	Failure
IV only	Antibiotic dispensed within two days of the discharge date for a hospital claim for which any of the possible 16 diagnoses contain a diagnosis code indicative of an infectious disease unrelated to the urinary tract.**	1	No failure
V only	Antibiotic dispensed within two days of the discharge date for a hospital claim for which any of the possible 16 diagnoses contain a diagnosis code indicative of UTI.	0	No failure
VI only	Antibiotic dispensed for which none of the above definitions apply.	108	Adjudicated based on type of antibiotic - 62 Failure - 46 No failure

Table 22 Cont'd.

Category	Definition	Number of Antibiotics	Assignment of Treatment Outcome
I and III	As described above	3	Adjudicated based on service dates, service type and antibiotic type - 1 Failure - 2 No failure
I and IV	As described above	1	No failure
II and III	As described above	50	Failure
II and V	As described above	14	Failure
IV and V	As described above	1	Adjudicated based on service dates, service type and antibiotic type - 1 Failure
I, II and III	As described above	1	Adjudicated based on service dates, service type and antibiotic type - 1 No failure
II, III, and V	As described above	2	Failure

* Appendix E reports ICD-9-CM codes present on MC, up to two days prior to additional antibiotic prescriptions, considered evidence of infectious disease unrelated to the urinary tract.
**Appendix F reports ICD-9-CM codes present on HSA, up to two days prior to additional antibiotic prescriptions, considered evidence of infectious disease unrelated to the urinary tract.

Table 23. **First additional antibiotic received by 190 subjects assigned treatment failure based on receipt of only additional antibiotic**

First additional antibiotic received	Initial Antibiotic TMP-SMX N (%)	Initial Antibiotic fluoroquinolone N (%)	Total N(%)
TMP-SMX	46 (40.4)	24 (31.6)	20 (36.8)
Fluoroquinolone	42 (36.8)	44 (57.9)	86 (45.3)
Aminopenicillin	6 (5.3)	3 (4.0)	9 (4.7)
Cephalosporin	4 (3.5)	1 (1.3)	5 (2.6)
Nitrofurantoin	16 (14.0)	4 (5.3)	20 (10.5)
Total	**114 (100.0)**	**76 (100.0)**	**190 (100.0)**

4.9 Data Analysis

4.9.1 Analysis of patient characteristics and the probability of receipt of a fluoroquinolone

To test hypotheses 1 to 8 (Section 3.2), regarding the effect of subject variables upon receipt of a fluoroquinolone for initial treatment of pyelonephritis, multivariate logistic regression analysis was undertaken. Prior to multivariate modeling, bivariate relationships between the outcome and explanatory variables were examined. Pearson chi-squared tests of association were utilized for categorical explanatory variables, including: ER visit, diabetic status, recent antibiotic use, recent hospitalization, recent UTI and rural residence. To assess the association between receipt of a fluoroquinolone and the continuous explanatory variables (age and income quintile), univariate logistic models were fitted for each explanatory variable. The likelihood ratio chi-squared test was used as the measure of significance.

Logit plots of probability of receipt of a fluoroquinolone with both age and income quintile revealed a linear relationship with both explanatory variables. Crude odds ratios and 95% confidence intervals are reported in Table 24. Using a 0.10 level of significance, age, income quintile, recent antibiotic use and recent hospitalization were identified as associated with receipt of a fluoroquinolone, whilst diabetic status, ER visit, recent UTI and rural residence were not significantly associated with receipt of a fluoroquinolone. Hypothesized main effects were entered into the candidate model based on their theoretical and/or biological significance.

Table 24. **Association between subject specific variables and receipt of a fluoroquinolone for initial treatment of pyelonephritis**

Subject Variable	χ^2	p	Crude OR (95% CI)
ER visit	0.01	0.93	0.99 (0.74-1.32)
Diabetic (Definition II)	0.05	0.82	1.05 (0.68-1.64)
Recent antibiotic use	4.47	0.04	1.32 (1.02-1.70)
Recent hospitalization	3.67	0.06	1.49 (0.99-2.23)
Recent UTI	0.05	0.83	0.94 (0.56-1.58)
Residence (Rural=1)	0.42	0.52	1.10 (0.83 – 1.46)
Age	10.45	<0.01	0.98 (0.97 – 0.99)
Income quintile	14.84	<0.0001	0.85 (0.78 – 0.92)

Interactions of interest, as described in Section 3.10.1, between categorical variables were entered into the candidate model if significant at the $p<0.10$ level of significance. The Breslow-Day test for homogeneity of odds ratios revealed two interactions eligible for entry to the candidate model. These included, the interaction between ER visit and recent hospitalization ($\chi^2= 4.48$, df=1, p=0.03), and the interaction between rural residence and recent hospitalization ($\chi^2=4.41$, df=1, p=0.04). Interactions of interest involving continuous variables were also entered into the candidate model. All interactions which did not achieve a significance level of $p<0.05$ in the candidate model were removed, resulting in the full logistic model described in Table 25. The Hosmer-Lemeshow goodness-of-fit statistic revealed no significant lack of fit (9.42, df=8, $p<0.31$).

Refinement of the full model was accomplished through sequential removal of the least significant variable. Variables whose removal resulted in large changes in the beta coefficients of the remaining variables were judged to be confounders. Variables not involved in significant interactions, or which were not judged to be confounders were maintained in the model only if significant at the 0.10 level, resulting in a parsimonious model (Table 26) Recent UTI was the only variable excluded from the parsimonious model.

Thus, the multivariate model identified increasing age, ER visit, diabetic status, recent antibiotic use, recent hospitalization, rural residence and higher income quintile as significantly associated with receipt of a fluoroquinolone. However, many of the significant explanatory variables were involved in interactions. To interpret the effect of

significant variables on the likelihood of receipt of a fluoroquinolone, adjusted odds ratios were calculated. The effects of variables which are involved in interactions may not be interpreted individually, but must be interpreted with regard to the status of the other variable involved in the interaction. Table 27 reports the adjusted odds ratios for the full model.

Among subjects who were not diabetic and did not present to an ER, higher income quintile was associated with an increased probability of receipt of a fluoroquinolone. For example, the odds of receipt of a fluoroquinolone among subjects in income quintile 5 were 1.82 times that of subjects in income quintile 1. The effect of income was greater in subjects who presented to an ER, with the odds of receipt of a fluoroquinolone among subjects in income quintile 5 being 9.6 times that of subjects in income quintile 1. The effect of income among diabetics appeared to be reversed with those subjects in the higher income quintiles less likely to receive a fluoroquinolone. However, all odds ratios included 1, indicating there was no difference in the likelihood of receipt of a fluoroquinolone by income among diabetics.

A significant increase in the probability of receipt of a fluoroquinolone with increasing age was observed for rural residents only. For example, for rural residents, the odds of receipt of a fluoroquinolone among subjects aged 60 years were 5.14 times that of subjects aged 20 years. Finally, for subjects presenting to an ER, the odds of receipt of a fluoroquinolone, among recently hospitalized subjects, were 3.9 times that of subjects without recent hospitalization. Recent hospitalization did not significantly affect the probability of receipt of a fluoroquinolone among subjects who did not present to an ER.

Table 25. **Full logistic regression model of the effect of subject specific variables on the probability of receipt of a fluoroquinolone**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.27	0.28	<0.0001
Age	0.01	0.01	0.15
Diabetic (Definition II)	0.74	0.46	0.10
Recent Antibiotic	0.34	0.14	0.02
Recent hospitalization	0.14	0.26	0.59
Recent UTI	-0.22	0.63	0.43
ER visit	-0.99	0.35	0.01
Residence (Rural=1)	-1.15	0.47	0.02
Income quintile	0.15	0.05	<0.01
Recent hospitalization*ER	1.22	0.50	0.01
Diabetic* Income	-0.44	0.22	0.04
ER* Income	0.42	0.12	<0.001
Age*Residence	0.03	0.01	0.01

Table 26. **Parsimonious logistic regression model of the effect of subject specific variables on the probability of receipt of a fluoroquinolone**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.28	0.28	<0.0001
Age	0.01	0.01	0.15
Diabetic (Definition II)	0.72	0.45	0.11
Recent Antibiotic	0.31	0.14	0.02
Recent hospitalization	0.13	0.26	0.61
ER visit	-0.98	0.35	0.01
Residence (Rural=1)	-1.16	0.47	0.01
Income quintile	0.15	0.05	<0.01
Recent hospitalization*ER	1.22	0.50	0.01
Diabetic* Income	-0.44	0.22	0.04
ER* Income	0.41	0.12	<0.001
Age*Residence	0.03	0.01	0.01

Table 27. **Estimated Odds Ratios (main effects and interaction effects) for the probability of receipt of a fluoroquinolone**

Subject Variable	Estimate OR	95% CI
Main effects		
Recent antibiotic use	1.40	1.06 – 1.85
Recent UTI	0.80	0.46 – 1.39
Interaction effects		
non-ER/non-Diabetic*Income Quintile 1	1.00	Reference
non-ER/non-Diabetic*Income Quintile 2	1.16	1.05 – 1.29
non-ER/non-Diabetic*Income Quintile 3	1.35	1.10 – 1.65
non-ER/non-Diabetic*Income Quintile 4	1.57	1.16 – 2.12
non-ER/non-Diabetic*Income Quintile 5	1.82	1.22 – 2.73
ER*Income Quintile 1	1.00	Reference
ER*Income Quintile 2	1.76	1.40 – 2.21
ER*Income Quintile 3	3.10	1.97 – 4.87
ER*Income Quintile 4	5.45	2.77 – 10.75
ER*Income Quintile 5	9.60	3.89 – 23.71
Diabetic*Income Quintile 1	1.00	Reference
Diabetic*Income Quintile 2	0.75	0.49 – 1.13
Diabetic*Income Quintile 3	0.56	0.24 – 1.29
Diabetic*Income Quintile 4	0.42	0.12 – 1.46
Diabetic*Income Quintile 5	0.31	0.06 – 1.65
Urban*20 years	1.00	Reference
Urban*40 years	1.20	0.94 – 1.52
Urban*60 years	1.43	0.88 – 2.31
Rural*20 years	1.00	Reference
Rural*40 years	2.27	1.49 – 3.45
Rural*60 years	5.14	2.23 – 11.87
Non ER*non-Recent hospitalization	1.00	Reference
Non ER*Recent hospitalization	1.15	0.69 – 1.90
ER*non-Recent hospitalization	1.00	Reference
ER*Recent hospitalization	3.90	1.70 – 8.93

4.9.2 Analysis of the effect of initial antibiotic treatment and subject variables, on the probability of treatment failure.

A second logistic model was used to test hypotheses 9 to 13 (See Section 3.2) evaluating the combined effects of initial antibiotic treatment and subject variables on the probability of treatment failure. In addition to the hypothesized main effects and interactions, significant main effects and interactions present in the parsimonious model from the previous analysis (Table 26) were considered for entry into this candidate model. This was undertaken as variables associated with choice of initial antibiotic treatment are possible confounders in the relationship between initial antibiotic treatment and treatment outcome. Thus, the main effects (ER visit, income quintile, rural residence) and interaction terms between recent hospitalization and ER visit, diabetic and income quintile, ER visit and income quintile, and, age and residence were entered into the candidate model.

Prior to multivariate modeling, bivariate Pearson chi-squared tests of association were used to test the association between the outcome (treatment failure), and categorical explanatory variables. These included: ER visit, rural residence, diabetic status, recent antibiotic use, recent hospitalization, and recent UTI. The association between treatment failure and continuous explanatory variables (age, income and treatment duration) were examined using the likelihood ratio chi-squared tests from individually fitted logistic regression models. A logit plot of treatment failure and treatment duration revealed a non-linear pattern, resulting in the transformation of treatment duration to a dichotomous variable. Treatment durations of one to nine days were defined as "short duration"

(treatment duration=1), while treatment durations of ten days or greater were considered "long duration" (treatment duration=0). Subjects initially treated with TMP-SMX were significantly more likely to receive a long duration of treatment than subjects treated with a fluoroquinolone ($\chi 2=28.07$, df=1, $p<0.0001$). Transformation to a dichotomous variable resulted in a larger Pearson chi-squared than that obtained as a continuous variable when the association between treatment duration and failure was examined; ($\chi^2=22.18$, df=1, $p<0.0001$) versus ($\chi^2=14.47$, df=1, $p<0.0001$) respectively.

Crude odds ratios and 95% confidence intervals are reported in Table 28. Based on a selection criteria of a 0.10 level of significance, recent antibiotic use, recent hospitalization, recent UTI and short treatment duration were demonstrated to be associated with treatment failure. Initial antibiotic treatment, increasing age, diabetic status, ER visit, rural residence, and income were not significantly associated with treatment failure.

None of the interactions from the previous model achieved significance at $p<0.05$ and were removed from the candidate model. In addition, main effects from the previous model not already hypothesized for this model (i.e., ER visit, income quintile, and rural residence) did not achieve significance at $p<0.10$, and were removed from the candidate model. Examination of changes in beta coefficients of the remaining variables revealed no confounding effects by the removed variables. All hypothesized interactions which did not achieve significance $p<0.05$ were also removed, resulting in the full logistic model (Table 29). The Hosmer-Lemeshow goodness-of-fit statistic revealed no significant lack of fit (5.06, df=8, $p<0.75$) .

Refinement of the full model was accomplished through sequential removal of the least significant variable. Variables whose removal resulted in large changes in the beta coefficients of the remaining variables were judged to be confounders. Variables not involved in significant interactions, or which were not judged to be confounders were maintained in the model only if significant at the 0.10 level, resulting in the parsimonious model (Table 30). Variables excluded from the parsimonious model included diabetic status and recent hospitalization.

Table 28. **Association between initial antibiotic and subject specific variables, and treatment failure**

Subject Variable	χ^2	p	Crude OR (95% CI)
Initial antibiotic (fluoroquinolone=1)	0.01	0.91	1.02 (0.75-1.39)
Recent antibiotic use	6.76	0.01	1.51 (1.11-2.06)
Recent hospitalization	2.78	0.10	1.49 (0.93-2.40)
Recent UTI	11.88	<0.001	2.49 (1.46-4.23)
Diabetic (Definition II)	0.39	0.54	1.18 (0.70-2.02)
ER visit	0.07	0.80	0.95 (0.66 – 1.37)
Residence (Rural=1)	0.01	0.95	0.99 (0.69 – 1.42)
Income quintile	0.67	0.41	0.96 (0.86 – 1.06)
Age	0.02	0.88	1.00 (0.99 – 1.01)
Treatment duration	22.18	<0.0001	2.09 (1.54 – 2.84)

Table 29. **Full logistic regression model of the effect of subject specific variables on the probability of treatment failure**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.53	0.32	<0.001
Initial antibiotic (fluoroquinolone=1)	-1.10	0.51	0.03
Age	-0.01	0.01	0.19
Diabetic (Definition II)	0.11	0.30	0.71
Recent Antibiotic	0.34	0.17	0.05
Recent hospitalization	0.27	0.25	0.28
Recent UTI	0.70	0.29	0.02
Treatment duration (short=1)	0.78	0.16	<0.0001
Initial antibiotic*Age	0.03	0.01	0.05

Table 30. **Parsimonious logistic regression model of the effect of subject specific variables on the probability of treatment failure**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.53	0.32	<0.001
Initial antibiotic (fluoroquinolone=1)	-1.10	0.51	0.03
Age	-0.01	0.01	0.20
Recent Antibiotic	0.36	0.17	0.04
Recent UTI	0.71	0.29	0.01
Treatment duration (short=1)	0.79	0.16	<0.0001
Initial antibiotic*Age	0.03	0.01	0.05

Thus, the multivariate model identified initial antibiotic, short treatment duration, recent antibiotic use, recent UTI, and age as significantly associated with treatment failure. Table 31 reports adjusted odds ratios for the full model. Among subjects with recent antibiotic use, the odds of treatment failure were 1.4 times that of subjects without recent antibiotic use. The odds of treatment failure among subjects with recent UTI was 2.07 times that of subjects without recent UTI. The odds of treatment failure among subjects with short duration of treatment (1 to 9 days) was 2.18 times that of subjects receiving long durations of treatment (10 days or more).

The effect of initial antibiotic on the probability of treatment failure was dependent upon age. At age 20, subjects receiving fluoroquinolones were less likely to experience treatment failure than subjects receiving TMP-SMX; OR=0.56 (95% CI 0.33 - 0.97). However, by age 40, there was no difference in the probability of treatment failure between the two antibiotics; OR=0.95 (95% CI 0.68 - 1.33). However, by age 60, subjects treated with fluoroquinolones appeared to have a higher probability of treatment failure than subjects treated with TMP-SMX, although this effect did not achieve statistical significance; OR=1.61 (95% CI 0.82 – 3.16).

Table 31. **Estimated odds ratios (main effects and interaction effects) for the probability of treatment failure**

Subject Variable	Estimate OR	95% CI
Main effects		
Diabetic (Definition II)	1.12	0.63 – 2.00
Recent antibiotic use	1.40	1.00 – 1.96
Recent UTI	2.07	1.14 – 3.57
Recent hospitalization	1.31	0.80 – 2.13
Treatment duration (short=1)	2.18	1.59 – 2.99
Interaction effects		
TMP-SMX*20 years	1.00	Reference
Fluoroquinolone*20 years	0.56	0.33 – 0.97
TMP-SMX*40 years	1.00	Reference
Fluoroquinolone*40 years	0.95	0.68 – 1.33
TMP-SMX*60 years	1.00	Reference
Fluoroquinolone*60 years	1.61	0.82 – 3.16

4.9.3 Sensitivity testing selection of final cohort

In generating the final cohort for analysis, the application of exclusion criteria may have resulted in a selection bias, subsequently affecting the results of hypothesis testing. For example, the decision to exclude pregnant subjects from the cohort was based on differences in the extent to which the two drugs are contraindicated in pregnancy. Although fluoroquinolones are contraindicated throughout pregnancy, concerns regarding the use of TMP-SMX in pregnancy are confined to the early and late weeks of gestation (128). Given that this difference would likely result in a larger proportion of pregnant patients treated with TMP-SMX, the decision was made to exclude pregnant subjects from the cohort. However, difficulties in determining period of pregnancy for subjects with claims indicative of pregnancy but without a claim for hospital delivery, resulted in a considerable number of subjects whose pregnancy status at index date was indeterminate. These subjects were subsequently excluded, possibly creating a selection bias.

Decisions to exclude subjects based on uncertainties regarding indication for initial antibiotic treatment may also have added to selections bias. Thus, wherever possible, previous exclusion criteria were omitted to create an expanded cohort. These included, exclusions based on: duration of treatment, pregnancy status, and alternate possible indications for initial antibiotic treatment. In addition, subjects with more than one antibiotic claim on the same date were included if the antibiotic claims contained one of, but not both, TMP-SMX or a fluoroquinolone. The duration of treatment was considered to be the sum of the durations of treatment of all prescriptions for TMP-SMX or a

fluoroquinolone. For example, referring to Appendix C, subject ten was not included in the cohort since the antibiotics on the same day included both TMP-SMX and ciprofloxacin. Subjects six and eight were included since they received only one of TMP-SMX or a fluoroquinolone, and durations of treatment were calculated to be 7 and 114 days, respectively. The resulting expanded cohort, consisted of 1,178 subjects; 709 treated with TMP-SMX and 469 treated with a fluoroquinolone.

Despite the rationale for the development of a broader, more inclusive (and possibly more generalizable) cohort, challenges in identification of initial physician visit may provide the rationale for a more restrictive cohort. Based on a review of the literature, the assumption was made that a physician visit with an ICD-9-CM code of 590, with no MC or HSA bearing the ICD-9-CM codes, 590, 595, or 599 within the previous 42 days represented a new episode of pyelonephritis. Following that, a DPIN claim for an appropriate antibiotic within two days represented the initial antibiotic treatment. However, not all physician visits result in the submission of a claim to Manitoba Health. Although many salaried physicians in rural settings and ER are required to submit shadow billings, it is unclear what proportion of physicians actually do so. In addition, salaried physicians in Winnipeg ER's (with the exception of Health Sciences Centre and St. Boniface General Hospital) are not required to submit shadow billings. Thus, a missing MC for a physician visit may result in a follow-up visit being erroneously identified as the initial physician visit.

Consider a scenario where a subject presents to an ER with a new episode of pyelonephritis and receives a prescription for antibiotic treatment. If no shadow billing is submitted for the physician visit, only the DPIN claim for antibiotic treatment will be

captured on the database. If the prescribed treatment proves ineffective the subject may then present to a physician in the following days or weeks and receive additional treatment. Assuming a claim for this second physician visit is submitted to Manitoba Health, the second visit would erroneously be identified as the initial visit and the additional antibiotic as the initial treatment. The plausibility of this scenario is supported by the pattern of antibiotic use observed in those subjects identified as recent antibiotic users.

If timing of the most recent antibiotic was unrelated to the current episode of pyelonephritis, we would expect the proportion of recent antibiotic users receiving their most recent antibiotic to be evenly distributed over the 13 weeks preceding the index date. However, the proportion of recent antibiotic users who received their most recent antibiotic one week before the identified index date is more than two times the proportion observed in any other of the preceding weeks (Figure 9). Since failure of initial treatment was most common within one week of the index date, with 47% of subjects failing within the first week and 78% failing within three weeks, it is possible that a portion of this recent antibiotic use was earlier treatment of a UTI for which a MC was not evident.

To minimize the number of subjects with initial physician visits erroneously identified, an alternate more restrictive cohort was developed, which excluded those with antibiotic treatment within 3 weeks prior to the index date. The resulting restrictive cohort, consisted of 960 subjects; 599 treated with TMP-SMX and 361 treated with a fluoroquinolone. Subjects thus excluded were older, and significantly more likely to be diabetic, recently hospitalized, and have received a fluoroquinolone as initial treatment (Table 32). The multivariate analysis, testing hypotheses 1 to 8 was repeated using both

the expanded and restrictive cohorts to examine the effects of decisions related to subject selection.

Table 32. **Comparison of subject specific variables between those subjects excluded (N=124) and retained (N=960) in the restrictive cohort**

Subject Variable	Subjects Retained N (%)	Subjects Excluded N (%)	p
Age in years (median)	34.0	40.5	<0.0001
Initial antibiotic (fluoroquinolone=1)	361 (37.8)	70 (56.5)	<0.0001
ER visit	217 (22.6)	26 (21.0)	0.68
Diabetic (Definition II)	64 (6.7)	24 (19.4)	<0.0001
Recent UTI	57 (5.9)	8 (6.5)	0.82
Recent hospitalization	84 (8.8)	19 (15.3)	0.02
Residence (Rural=1)	222 (23.1)	31 (25.0)	0.64
Income - quintile 1	299 (31.2)	50 (40.3)	0.22
- quintile 2	203 (21.2)	21 (16.9)	
- quintile 3	178 (18.5)	20 (16.1)	
- quintile 4	139 (14.5)	20 (16.1)	
- quintile 5	141 (14.7)	13 (10.5)	

Repetition of the previously described modeling strategy using the expanded cohort of 1,178 subjects produced results similar to the original analysis. The full model obtained is reported in Table 33. Age, ER visit, diabetic status, recent antibiotic use, recent hospitalization, rural residence and income quintile were again significantly associated with receipt of a fluoroquinolone. The direction and strength of the relationships between explanatory variables (including those involved in interactions) and outcome were similar to the original analysis (Table 34). However, a significant interaction between recent hospitalization and ER visit observed in the original analysis was not observed using the expanded cohort. Instead an interaction between recent hospitalization and residence was observed, indicating that for urban residence, the odds of receipt of a fluoroquinolone, among those with recent hospitalization, were 1.85 times that of subjects without recent hospitalization.

Repetition of the modeling strategy using the restrictive cohort of 960 subjects also produced results similar to the original analysis. The full model is reported in Table 35. Age, ER visit, recent hospitalization, rural residence, and income quintile were identified as predictors of fluoroquinolone use. The strength and direction of the relationships, including that of the interactions were similar (Table 36). However, for the restricted cohort, recent antibiotic use and diabetes were not associated with receipt of a fluoroquinolone.

Regardless of whether the original, expanded, or restrictive cohort was used, increasing age, ER visit, recent hospitalization, rural residence and higher income were associated with receipt of a fluoroquinolone. The most notable difference between the

cohorts was the lack of association between recent antibiotic use and receipt of a fluoroquinolone when subjects with antibiotic prescriptions in the three weeks prior to the index date were eliminated (restrictive cohort).

Table 33. **Full logistic regression model of effects of subject specific variables on the probability of receipt of a fluoroquinolone (expanded cohort N=1,178)**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.33	0.27	<0.0001
Age	0.01	0.01	0.10
Diabetic (Definition II)	0.88	0.43	0.04
Recent Antibiotic	0.378	0.14	0.01
Recent hospitalization	0.62	0.23	<0.01
Recent UTI	-0.08	0.26	0.75
ER visit	-0.48	0.30	0.11
Residence (Rural=1)	-0.78	0.45	0.08
Income quintile	0.13	0.05	0.01
Recent hospitalization*Residence	-0.90	0.46	0.05
Diabetic* Income quintile	-0.50	0.22	0.02
ER* Income quintile	0.31	0.11	0.01
Age*Residence	0.03	0.01	0.02

Table 34. **Estimated odds ratios (main effects and interaction effects) for the probability of receipt of a fluoroquinolone (expanded cohort N=1,178)**

Subject Variable	Estimate OR	95% CI
Main effects		
Recent antibiotic use	1.45	1.11 – 1.89
Recent UTI	0.92	0.55 – 1.54
Interactions		
non-ER/non-Diabetic*Income Quintile 1	1.00	Reference
non-ER/non-Diabetic*Income Quintile 2	1.14	1.03 – 1.25
non-ER/non-Diabetic*Income Quintile 3	1.29	1.06 – 1.56
non-ER/non-Diabetic*Income Quintile 4	1.46	1.09 – 1.95
non-ER/non-Diabetic*Income Quintile 5	1.65	1.12 – 2.44
ER*Income Quintile 1	1.00	Reference
ER*Income Quintile 2	1.54	1.25 – 1.89
ER*Income Quintile 3	2.37	1.57 – 3.58
ER*Income Quintile 4	3.65	1.97 – 6.76
ER*Income Quintile 5	5.61	2.47 – 12.78
Diabetic*Income Quintile 1	1.00	Reference
Diabetic*Income Quintile 2	0.69	0.45 – 1.04
Diabetic*Income Quintile 3	0.47	0.20 – 1.08
Diabetic*Income Quintile 4	0.32	0.09 – 1.12
Diabetic*Income Quintile 5	0.22	0.04 – 1.16
Urban*20 years	1.00	Reference
Urban*40 years	1.22	0.97 – 1.53
Urban*60 years	1.48	0.93 – 2.35
Rural*20 years	1.00	Reference
Rural*40 years	2.04	1.37 – 3.04
Rural*60 years	4.16	1.88 – 9.22
Urban*No-Recent hospitalization	1.00	Reference
Urban*Recent hospitalization	1.85	1.17 – 2.93
Rural*No-Recent hospitalization	1.00	Reference
Rural*Recent hospitalization	0.75	0.35 – 1.62

Table 35. **Full logistic regression model of effects of subject specific variables on the probability of receipt of a fluoroquinolone (restrictive cohort N=960)**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.23	0.29	<0.001
Age	0.01	0.01	0.25
Diabetic (Definition II)	-0.39	0.30	0.20
Recent Antibiotic	0.08	0.17	0.63
Recent hospitalization	0.25	0.28	0.38
Recent UTI	-0.09	0.31	0.77
ER visit	-1.17	0.39	<0.01
Residence (Rural=1)	-1.34	0.51	0.01
Income quintile	0.15	0.05	0.01
Recent hospitalization*ER	1.31	0.55	0.02
ER* Income quintile	0.45	0.13	<0.001
Age*Residence	0.04	0.01	<0.01

Table 36. **Estimated odds ratios (main effects and interaction effects) for the probability of receipt of a fluoroquinolone (restrictive cohort N=960)**

Subject Variable	Estimate OR	95% CI
Main effects		
Recent antibiotic use	1.09	0.78 – 1.51
Recent UTI	0.91	0.49 – 1.69
Diabetic (Definition II)	0.68	0.38 – 1.23
Interactions		
non-ER/*Income Quintile 1	1.00	Reference
non-ER/*Income Quintile 2	1.17	1.05 – 1.30
non-ER/ *Income Quintile 3	1.36	1.10 – 1.68
non-ER/ *Income Quintile 4	1.58	1.15 – 2.17
non-ER/ *Income Quintile 5	1.84	1.21 – 2.81
ER*Income Quintile 1	1.00	Reference
ER*Income Quintile 2	1.82	1.43 – 2.32
ER*Income Quintile 3	3.31	2.04 – 5.37
ER*Income Quintile 4	6.02	2.91 – 12.46
ER*Income Quintile 5	10.95	4.15 – 23.87
Urban*20 years	1.00	Reference
Urban*40 years	1.16	0.90 – 1.51
Urban*60 years	1.35	0.81 – 2.28
Rural*20 years	1.00	Reference
Rural*40 years	2.59	1.64 – 4.09
Rural*60 years	6.69	2.68 – 16.69
non-ER*no-Recent hospitalization	1.00	Reference
non-ER*Recent hospitalization	1.28	0.74 – 2.24
ER*no-Recent hospitalization	1.00	Reference
ER*Recent hospitalization	4.76	1.88 – 12.02

4.9.4 Sensitivity testing the identification of treatment failure

As with the identification of study subjects, uncertainties in the identification of treatment failure necessitates sensitivity testing using alternate decisions and definitions. Treatment failure was originally defined as either the need for hospitalization, and/or the requirement of additional out-patient antibiotic treatment, subsequent to initial antibiotic treatment. Only a small proportion of treatment failures were identified based on subsequent hospitalization claims. The majority of treatment failures were identified based on additional antibiotic claims. However, determining the indication for additional antibiotic treatment was subject to uncertainty, and was based on:

1. The existence of related MC or HSA.
2. The timing of DPIN claims in relation to MC and HSA,
3. The class of antibiotic.
4. The number of dosing units per day provided.

The large number of antibiotics identified, which fell into category VI (Section 3.5.11) were especially problematic, since there were no associated MC or HSA on which to base decisions regarding indication for use. Thus, a restrictive definition of treatment failure was developed to examine the effects of inclusion of antibiotics for which the indication for use was uncertain.

The restrictive definition of treatment failure was similar to the original definition, with the exception that antibiotics assigned to category VI were not considered indicative of treatment failure. Using the restrictive definition, 164 (15.1%) of 1,084 subjects were identified as having experienced treatment failure; 108 (16.5%) of the 653 subjects

treated with TMP-SMX, and 56 (13.0%) of the 431 subjects treated with a fluoroquinolone. A comparison of subject variables between subjects retained and excluded by the restrictive definition of treatment failure is reported in Table 37. The multivariate analysis testing hypotheses 9 to 13 was repeated, using the restrictive definition of treatment failure. In addition testing of hypotheses 9 to 13 was repeated using the restrictive cohort, as described in Section 4.9.3, to examine the effect of exclusion of subjects whose initial physician visit may have been erroneously assigned

Table 37. **Comparison of subject variables between those subjects excluded (N=43) and retained (N=164) by the restrictive definition of treatment failure**

Subject Variable	Retained N (%)	Excluded N (%)	p
Age in years (median)	32.0	42.0	<0.001
Initial antibiotic (fluoroquinolone=1)	51 (33.8)	32 (57.1)	<0.01
ER visit	35 (23.2)	10 (17.9)	0.41
Diabetic (Definition II)	12 (8.0)	7 (17.9)	0.31
Recent antibiotic	62 (41.1)	23 (41.1)	0.99
Recent UTI	17 (11.3)	6 (10.7)	0.91
Recent hospitalization	19 (12.6)	7 (12.5)	0.99
Residence (Rural=1)	31 (20.5)	17 (30.4)	0.14
Income - quintile 1	46 (30.5)	18 (32.1)	0.96
- quintile 2	42 (27.8)	14 (25.0)	
- quintile 3	26 (17.2)	8 (14.3)	
- quintile 4	17 (11.3)	7 (12.5)	
- quintile 5	20 (13.3)	9 (16.1)	

The restrictive definition of treatment failure produced a model different from that obtained using the original definition (Table 38). The odds of treatment failure among subjects receiving fluoroquinolones were 0.71 times those of subjects receiving TMP-SMX (Table 39). The odds of experiencing treatment failure among subjects with recent UTI or short durations of treatment were 2.09 and 1.86 times that of subjects without these attributes respectively. The effect of age on the probability of treatment failure was opposite to that observed when the original definition was used. The odds of experiencing treatment failure decreased 0.85 times for every ten-year increase in age, and the interaction between diabetic status and income quintile, indicated diabetic status was associated with an increased probability of treatment failure for subjects in income quintiles 4 and 5, but was not associated with treatment failure in income quintiles 1 to 3. Recent antibiotic use and recent hospitalization were not significantly associated with treatment failure.

Table 38. **Full logistic regression model of effects of subject specific variables on the probability of treatment failure (restrictive definition)**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.26	0.33	<0.001
Treatment (FQ=1)	-0.34	0.19	0.07
Age	-0.02	0.01	0.04
Diabetic (Definition II)	-1.37	0.67	0.04
Recent Antibiotic	0.29	0.19	0.12
Recent hospitalization	0.29	0.27	0.29
Recent UTI	0.74	0.31	0.02
Treatment duration (1=short)	0.62	0.18	<0.001
Income quintile	-0.09	0.07	0.18
Diabetic*Income quintile	0.64	0.26	0.01

Table 39. **Estimated odds ratios (main effects and interaction effects) for the probability of treatment failure (restrictive definition)**

Subject Characteristic	Estimate OR	95% CI
Main effects		
Initial treatment (fluoroquinolone=1)	0.71	0.49 – 1.03
Age (10 year increment)	0.85	0.73 –0.99
Recent antibiotic use	1.34	0.93 – 1.94
Recent UTI	2.09	1.13 – 3.85
Recent hospitalization	1.33	0.79 – 2.26
Treatment duration (short=1)	1.86	1.32 – 2.63
Interaction effects		
Income quintile 1*non-Diabetic	1.00	Reference
Income quintile 1*Diabetic	0.48	0.19 – 1.22
Income quintile 2*non-Diabetic	1.00	Reference
Income quintile 2*Diabetic	0.92	0.45 – 1.87
Income quintile 3*non-Diabetic	1.00	Reference
Income quintile 3*Diabetic	1.75	0.78 – 3.93
Income quintile 4*non-Diabetic	1.00	Reference
Income quintile 4*Diabetic	3.32	1.06 – 10.42
Income quintile 5*non-Diabetic	1.00	Reference
Income quintile 5*Diabetic	6.30	1.31 – 30.25

Use of the restrictive cohort produced a model very similar to that obtained using the original model (Table 40). The effect of initial antibiotic on the probability of treatment failure was again dependent upon age. At age 20, subjects receiving fluoroquinolones were less likely to experience treatment failure than subjects receiving TMP-SMX; OR=0.42 (95% CI 0.23-0.77) (Table 41). At age 60, subjects treated with a fluoroquinolone were significantly more likely to experience treatment failure than subjects treated with TMP-SMX; OR=2.36 (95% CI 1.08-5.17). The odds of experiencing treatment failure among subjects with recent UTI, or short duration of treatment were 1.34 and 2.25, respectively, times that of subjects without these attributes. Exclusion of subjects with antibiotic treatment in the three weeks prior to the index date revealed no significant association between recent antibiotic use and treatment failure.

Table 40. **Full logistic regression model of effects of subject variables on the probability of treatment failure (restrictive cohort N=960)**

Subject Variable	β Coefficient	Standard Error	p value
Intercept	-1.14	0.35	<0.01
Initial antibiotic (fluoroquinolone=1)	-1.73	0.57	<0.01
Age	-0.02	0.01	0.02
Diabetic (Definition II)	0.32	0.35	0.36
Recent Antibiotic	0.05	0.21	0.82
Recent hospitalization	0.29	0.28	0.30
Recent UTI	1.01	0.32	<0.01
Treatment duration	0.81	0.18	0.0001
Initial antibiotic*Age	0.04	0.02	<0.01

Table 41. **Estimated odds ratios (main effects and interaction effects) for the probability of treatment failure (restrictive cohort; N=960).**

Subject Variable	Estimate OR	95% CI
Main effects		
Diabetic (Definition II)	1.38	0.70 – 2.73
Recent antibiotic use	1.05	0.69 – 1.59
Recent UTI	2.76	1.46 – 5.20
Recent hospitalization	1.34	0.77 – 2.33
Treatment duration (short=1)	2.25	1.59 – 3.18
Interaction effects		
TMP-SMX*20 years	1.00	Reference
Fluoroquinolone*20 years	0.42	0.23 – 0.77
TMP-SMX*40 years	0.99	Reference
Fluoroquinolone*40 years	0.99	0.68 – 1.46
TMP-SMX*60 years	1.00	Reference
Fluoroquinolone*60 years	2.36	1.08 – 5.17

Chapter 5.

Discussion

5.1 Implications for the use of healthcare claims in assessing drug effectiveness

In Chapter 1 it was noted that effective drug use has many components that deserve attention. The current study addressed several of these components including: (i) whether a drug or class of drugs is being used for indications for which they are known to be safe and efficacious, (ii) whether a drug is producing desirable outcomes, and (iii) an examination of comparative effectiveness between treatments. To examine "real world" use and effectiveness of pharmaceuticals, researchers have relied upon data sources which included, physician surveys (2, 17-20, 23, 59), medical records (61, 62), and administrative healthcare claims (38, 39, 41, 58, 60). The current study employed administrative healthcare claims to examine the three components of effective drug use mentioned above.

The use of healthcare claims for research purposes may prove to be more appropriate to examination of some of the above components than others. Use of healthcare claims appears to be well suited to addressing the first component above. For example, the

current study revealed that the majority of antibiotic treatments provided to subjects with pyelonephritis were known to be efficacious for this indication. Moreover, antibiotic selection varied appropriately with pregnancy status. A small proportion of possibly inappropriate use was also uncovered, such as the prescribing of nitrofurantoin for the treatment of pyelonephritis, and the prescribing of fluoroquinolones during pregnancy.

To utilize healthcare claims to examine the first component of effectiveness, the ability to link drug treatments to the indication for treatment is fundamental. The current study concerned treatment for an acute illness for which subjects were expected to fill prescriptions promptly. Thus, few difficulties were experienced linking drug therapy to the indication for treatment. However, in chronic conditions, linking drug therapy to indication for use may be problematic, especially where drug treatments have a wide variety of indications. The inclusion of the indication for use on administrative prescription claims-data would facilitate such studies.

The utility of healthcare claims to examine the ability of drug treatments to produce desirable outcomes will depend on the outcome desired. Mortality, as an outcome, is well suited to the use of healthcare claims when linked to registry data. Humanistic outcomes such as functional status or quality of life are largely unsuited to the use of healthcare claims as they are not routinely reported in administrative healthcare claims. The study of an acute condition (as in the current study), with symptoms of sufficient severity to prompt the seeking of additional treatment, enabled an assumption of successful outcome when claims for such treatment were lacking. However, incomplete submission of healthcare claims, both medical and pharmaceutical, may complicate such studies.

Mandated submission of claims for all medical and pharmaceutical services would increase confidence in the use of claims data for such studies.

The current study highlighted what may be one of the largest drawbacks to the exclusive use of healthcare claims for examining comparative treatment outcomes. That is, the inability to control "confounding by indication". Confounding by indication results when a treatment is more or less likely to be employed over an alternative, based on the physician's assessment of the clinical status of the patient. That is, there is always a reason a physician selects a particular agent, and this reason may not be readily apparent or readily controlled for in the analysis. In the current study, the relationship between subject age and the initial antibiotic therapy, and treatment failure was in complete opposition to current theory. That is, older subjects experienced less treatment failure with TMP-SMX compared with a fluoroquinolone, rather than the reverse. It seems probable that the clinical status of older patients may have been given greater consideration in the decisions to treat with fluoroquinolones, producing the spurious result.

The recognition of the degree to which confounding by indication may impact observational studies of comparative treatment outcomes led to the development of methods to quantify and control for differences in patients' health status, to address this limitation of healthcare claims (204-207). Many of these methods use additional data available on administrative databases to construct indices of health status. Commonly, these indices make use of the number and/or severity of diagnoses recorded in healthcare databases for individual study subjects. For example, Roos *et al.* developed several claims-based measures of comorbidity and severity and reported significant correlations

with post-surgical readmission and mortality (206). Similarly, Von Korff *et al.* developed a chronic disease score based on the number and type of drug claims recorded in a pharmaceutical claims database which was positively correlated with the risk of mortality and hospitalization (207).

The degree to which these comorbidity/severity indices based on additional claims data can control confounding by indication, may be related to the disease and outcome under study. In the case of acute infection, physiological measures (unavailable from healthcare databases) related to the acute episode may be more relevant to assignment of treatment and subsequent treatment outcome than past and chronic illnesses. For example, Poses reported an association between empiric aminoglycoside use and mortality when a claims-based comorbidity index was used to control for differences in health status (205). However, when physiologic measurements of health status were used (e.g., dyspnea, vital signs, electrolytes) there was no significant association between aminoglycoside use and mortality. Thus, to adequately control for confounding by indication, clinical data may need to be gathered; either prospectively or retrospectively through medical chart review. Unfortunately, the collection of such data may be time consuming and costly, negating many of the advantages of using healthcare claims. Poses indicated that redesigning administrative data to include more clinical information could enhance the validity of comparative treatment studies using administrative data (205).

Despite the advantages conferred by the availability of data for large numbers of subjects at relatively low cost, the limitations of claims data provide challenges for researchers. Indeed the use of healthcare claims alone may prove unsuitable to address questions of comparative drug outcomes. However, the limitations of healthcare claims

may affect different studies to varying degrees depending on the disease state, treatment in question, or specific hypotheses to be addressed. The following section discusses specific methodological issues related to the use of administrative healthcare claims pertinent to the current study, specifically, limitations in the database related to the identification of the cohort of interest, and the identification of treatment outcome.

5.1.1 Assessment of the limitations of healthcare claims related to cohort identification

Uncertainties related to the identification of the study cohort concerned the use of ICD-9-CM codes, identification of the initial antibiotic treatment, and identification of the first physician contact for an episode of pyelonephritis. As previously indicated, truncated ICD-9-CM codes were used to differentiate between pyelonephritis (ICD-9-CM=590) and cystitis (ICD-9-CM=595). However, the ICD-9-CM code 599, which includes non-site-specific urinary tract infection, in addition to non-infectious disorders of the urinary tract, was commonly recorded on the Medical Claims (MC). The inability to identify subjects who might have been diagnosed with pyelonephritis from among these claims, meant that only subjects with MC containing the ICD-9-CM code 590, were eligible for inclusion. This necessarily led to incomplete capture of subjects with new episodes of pyelonephritis. However, this was considered acceptable since submission of the ICD-9-CM code 599 suggests some uncertainty regarding the site of infection (upper or lower), and the certainty of the diagnosis was more desirable than complete capture of all episodes for the present study.

The validity of the ICD-9-CM code 590 also poses concerns. Validation of diagnostic codes within the Manitoba Health database has been accomplished for a number of disease states, including pyelonephritis (36, 48, 131, 194). Nicolle *et al.* reported 80% agreement between HSA and hospital charts for the diagnosis of pyelonephritis (131). Studies validating diagnoses in the Manitoba Health database have used survey data, disease registries and hospital charts as alternate sources of data (36, 48, 131, 194). Chart review to validate out-patient diagnoses for a large and geographically diverse population is time consuming, and given concerns of confidentiality of patient records may not be feasible. In addition, lack of documentation of disease in medical charts may not reflect lack of disease, so much as lack of documentation. Since medical chart review to validate diagnoses in MC and to restrict entry to the cohort may not yield a more appropriate cohort, one was not conducted for the current study. Instead inclusion/exclusion criteria based on related claims, as suggested by several authors (47, 52), and as described below, was used as a method to increase confidence in the validity of the diagnostic code.

For the current study, the close temporal association of claims for an antibiotic prescription appropriate for the treatment of pyelonephritis met this validation requirement. Earlier studies attempting to link antibiotic claims to medical claims, have used time periods of up to seven days subsequent to physician visit (for respiratory tract infections or cystitis) to identify antibiotic treatment (39, 80, 84, 201). Due to the serious and acute nature of pyelonephritis, it was assumed that non-hospitalized subjects would fill their prescription for antibiotic treatment within two days of diagnosis, and this assumption was reflected in the results. Of subjects filling a prescription for an appropriate antibiotic within one week of the index date, 76.2% filled the prescription on

the index date, while 90.6% and 94.9% of subjects had filled a prescription within one or two days after the index date respectively.

The close association of an antibiotic prescription with the MC provided evidence of diagnosis of an infectious disease. Further, that 83% of antibiotic prescriptions filled by non-pregnant women were consistent with recommended treatment for pyelonephritis provided further assurance of the accuracy of the diagnostic code. However, this was somewhat artificially constructed, since prescriptions for macrolides, tetracyclines, and several miscellaneous agents were not included in the definition of "initial antibiotic". Finally, the duration of treatment prescribed, provided further assurance of diagnostic validity. Pyelonephritis is an invasive infection compared to cystitis, which is a superficial infection, and this is reflected in different recommended durations of treatment for the two infections (11, 12, 139). Current recommendations for treatment of acute uncomplicated pyelonephritis are for 14 days of treatment (11, 12, 139), although there is support for durations as short as 7 days (139, 151). The recommended duration of treatment for acute uncomplicated cystitis in young healthy women is three days (11, 12, 139). As the median treatment duration identified in the current study was 10 days, with 92% of subjects receiving 7 to 15 days of treatment, confidence in the diagnosis of pyelonephritis was strengthened.

The large number of subjects identified with new episodes of pyelonephritis who did not have prescriptions for antibiotic treatment dispensed or identified was surprising. Lack of an associated DPIN claim may be due to: (i) receipt of antibiotic treatment not captured in the DPIN, (ii) use of the ICD-9-CM code 590 as a rule-out diagnosis, (iii) non compliance with prescribed treatment by failure to fill a prescription, and (iv) erroneous

coding. Receipt of antibiotic treatment not recorded in the DPIN may occur due to the use of previously obtained antibiotics, use of physician samples, provision of antibiotics through northern nursing units, or non-submission of claims by a pharmacy. Kozyrskyj reported a lower proportion of prescriptions filled by rural pharmacies were submitted to the DPIN than in urban pharmacies (99). In the current study, subjects without evidence of appropriate treatment were significantly more likely to have rural residence. Thus, a number of subjects may have lacked evidence of appropriate treatment due to receipt of antibiotics from a nursing unit, or use of a rural pharmacy which submits a low proportion of prescription claims to DPIN.

Alternatively, some subjects identified with new episodes of pyelonephritis may not have required treatment, due to the use of the ICD-9-CM code as a rule-out diagnosis. For example, screening for bacteriuria is recommended in pregnancy due to the increased risk of pyelonephritis, and the resultant possibility of premature labour (127). Thus, ICD-9-CM codes of 590 for pregnant subjects may reflect diagnostic testing ordered at time of physician visit, rather than an actual diagnosis. This possibility was considered, since subjects without evidence of appropriate treatment were significantly more likely to be pregnant than those subjects with claims for appropriate treatment. The possibility of non-compliance with prescribed treatment, by not having a prescription filled, was considered to be low given the severity of symptoms associated with pyelonephritis. Despite the lack of DPIN claims, and exclusion of a number of subjects who may possibly have received antibiotic treatment, the requirement for a DPIN claim within two days of the index date served as a method to validate the diagnosis for the cohort.

Finally, there were uncertainties surrounding the identification of the initial physician-patient contact for a new episode of pyelonephritis. Based on suggested follow-up times (132), a period of 42 days without evidence of contact with the healthcare system related to UTI was considered evidence that a physician visit represented the initial physician contact for a new infection. However, the possibility of contact with a healthcare provider for which no claim was submitted, must be recognized. Since it is unclear what proportion of salaried physicians actually submit shadow billings, an initial visit to a salaried ER or clinic physician may go undetected, and a subsequent visit for follow-up or additional treatment may have been identified as the initial contact. If the visit was for follow-up and no further treatment was provided this would be identified as a new episode of pyelonephritis without an associated claim for appropriate treatment. If further treatment was provided, the visit would again be identified as a new episode of pyelonephritis, and the additional treatment identified as the initial antibiotic. The possibility of this occurrence was suggested by the relatively high proportion of recent antibiotic users who filled their most recent antibiotic prescription in the three weeks immediately preceding the index date. Thus, a sensitivity analysis was performed for both proposed analyses, which excluded subjects with antibiotic use in the three weeks preceding the index date (i.e., the restrictive cohort). The implications of this sensitivity analysis are discussed further in a later section.

5.1.2 Assessment of the limitations of healthcare claims related to identification of treatment outcome

Uncertainties related to the identification of treatment outcome concern the selection of relevant claims, linking of antibiotic claims to indication for use, and identification of prophylactic or suppressive regimens. As physician visits subsequent to the index date may reflect follow-up care unrelated to treatment outcome, additional MC alone were not considered indicative of treatment outcome (failure). Rather, claims indicating receipt of additional treatment (out-patient antibiotic or hospitalization) were considered evidence of treatment failure. However, unlike identification of initial treatment, where only a "two-day window" was examined, identification of additional treatment necessitated examination of claims over a period of 42 days.

Establishing a link between an episode of pyelonephritis and the need for additional hospital treatment was uncomplicated given that HSA provide an indication of the relative importance of a listed diagnosis to the hospital stay (e.g., most responsible, primary, secondary). Only those HSA for which a diagnosis of UTI was listed as the "most responsible" for the hospital stay were considered indicative of treatment failure. In addition, hospitalization is a relatively rare event (compared to receipt of an antibiotic), as evidenced by the fact that only 17 (8.2%) of 207 identified treatment failures were due to admission to hospital.

Establishing a link between subsequent additional antibiotic treatment to identify treatment failure was more complicated than was the case for identifying a hospital admission, given the lack of indication for use on the DPIN database. In addition, the relatively common use of antibiotics generally provided a greater opportunity to

complicate linking to treatment failure, as antibiotics are often prescribed for other infectious conditions. Once again, use of truncated ICD-9-CM codes to identify other infectious diseases was problematic, as several of the truncated codes identified up to two days prior to an antibiotic claim (Appendices E and F), included a variety of infectious and non-infectious conditions. For example, the ICD-9-CM code 706 (Diseases of sebaceous glands) contains the diagnosis of seborrhea for which antibiotics are not indicated, yet also contains the diagnosis of acne for which antibiotic treatment is commonly prescribed (2). Assignment of additional antibiotics to categories I and/or IV (Section 3.5.11) based on temporal association with ICD-9-CM codes consistent with infectious etiologies unrelated to UTI may have resulted in underestimation of treatment failure. However, the majority of antibiotics assigned to categories I and/or IV were based on associated ICD-9-CM codes which contain largely infectious conditions (Appendices E and F). Thus, the likelihood of underestimating treatment failure using this approach appears low.

Additional antibiotics not temporally associated with a MC or HSA containing ICD-9-CM codes consistent with an infectious etiology (Category VI antibiotics), were also problematic. However, it was recognized that receipt of additional antibiotic treatment despite the lack of an associated physician visit was highly probable, as antibiotic treatment may have been prescribed following telephone consultation or subsequent to a physician visit not captured on the MC. Therefore, subsequent antibiotic prescriptions for TMP-SMX, fluoroquinolones, or nitrofurantoin were included as evidence of treatment failure.

The decision to accept only TMP-SMX, fluoroquinolones, or nitrofurantoin from among the antibiotics assigned to category VI as evidence of treatment failure may also have led to underestimation of treatment failure. However, as these three antibiotics accounted for approximately 87% of initial treatment for pyelonephritis among non-pregnant women, any underestimation was expected to be small. Conversely, given the indication for use of TMP-SMX and fluoroquinolones in non-urinary infections, acceptance of these antibiotics as evidence of treatment failure in the absence of a MC or HSA containing diagnoses of UTI may potentially overestimate the number of treatment failures. As this was considered more likely than the possibility of underestimation a sensitivity analysis was undertaken which excluded all category VI antibiotics from the definition of treatment failure. The implications of this sensitivity analysis are discussed in a later section.

Finally, to avoid erroneous assignment of treatment failure, it was necessary to identify additional antibiotic prescriptions that likely reflected the provision of prophylactic or suppressive therapy for subsequent UTI. Antibiotic prescriptions which included less than two solid dosage units per day were considered prophylactic or suppressive therapy (except for antibiotics for which once daily dosing is standard), rather than evidence of treatment failure. However, this may have resulted in an underestimation of the number of treatment failures, since a single daily dose of TMP-SMX or a fluoroquinolone may be appropriate in situations of reduced renal function. However, underestimation was considered unlikely, since the number of additional antibiotic prescriptions with less than 2 dosing units per day were few (Appendix G). Of the seventeen prescriptions thus identified, sixteen were assigned to category VI,

indicating they were not temporally associated with a MC or HSA containing a diagnosis of infectious etiology. Thus, these prescriptions may have been issued at the time of the initial infection, and reflect the provision of prophylactic or suppressive therapy. In addition, the long durations of treatment provided for many of these prescriptions (30-180 days) is consistent with the assignment of prophylactic or suppressive treatment.

5.2 Empirical Findings

The purpose of the current study was twofold; to examine the effect of subject specific variables on the probability of receipt of a fluoroquinolone for the treatment of pyelonephritis, and to compare outcomes arising from the two recommended treatments (TMP-SMX and fluoroquinolones). Although the study attempted to identify all new episodes of pyelonephritis in Manitoba during the study period, the existence of the non-site-specific ICD-9-CM code for urinary tract infection in all probability prevented complete detection.

Approximately 21% of treated subjects identified were admitted to hospital for initial treatment. The higher incidence of admission to hospital among pregnant subjects and/or those with factors suggestive of underlying comorbidities (e.g., diabetes, recent antibiotic use, recent hospitalization), as seen in the current study, has been previously reported (135, 137). The higher incidence of admission to hospital among subjects presenting to the ER versus physicians' offices (34% versus 16% respectively), was also consistent with earlier studies (136, 137). Given that presentation to an ER may indicate greater severity of symptoms than observed in physicians' offices, this finding was not unexpected.

The rationale for the higher incidence of hospitalization identified for subjects in lower income quintiles may be multifactorial. Lower income quintiles contained a higher proportion of diabetic subjects than higher income quintiles. This was unsurprising given the higher prevalence of diabetes among the First Nations population of Manitoba (an economically disadvantaged group), compared to the general population (208). As previously indicated, diabetes was associated with a higher probability of hospitalization. In addition, lower income is associated with poorer health status overall (186, 209, 210), which may result in the observed increased likelihood of hospitalization. Furthermore, the decision to hospitalize may be made for social reasons, that is, lack of home supports more common among those with low income.

For those subjects treated as out-patients, antibiotic treatments were fairly consistent with current recommendations (11, 12, 139). However, only 58.5% of subjects identified as Winnipeg residents presenting to a non-ER setting provided a urine culture, despite recommendations that this be performed. Approximately 83% of non-pregnant subjects received either TMP-SMX or a fluoroquinolone. Despite reports of increasing resistance to TMP-SMX among uropathogens (7, 162, 163), TMP-SMX accounted for a greater proportion of out-patient antibiotic treatments than fluoroquinolones; 50.1% and 32.8% respectively. Nitrofurantoin use, observed in approximately 4% of non-pregnant subjects, is considered inappropriate treatment for pyelonephritis due to the inability of nitrofurantoin to achieve sufficient serum and tissue concentrations (161). Use of this agent for pyelonephritis may indicate a lack of understanding by physicians, and provides an opportunity for education. Alternately, the prescribing of nitrofurantoin identified in this study, may reflect the inclusion of episodes of cystitis (for which nitrofurantoin is

appropriate treatment) which were erroneously coded as pyelonephritis. However, as non-pregnant subjects treated with nitrofurantoin experienced a higher proportion of treatment failure (27.1%) compared with TMP-SMX or a fluoroquinolone (19.0 and 19.3% respectively), it is probable that many of these subjects received inappropriate treatment, rather than being incorrectly coded as cystitis.

The frequent use of aminopenicillins (33.3%) and cephalosporins (27.8%) in subjects identified as pregnant reflected appropriate treatment for pyelonephritis during pregnancy. However, use of a fluoroquinolone by a further 7% of pregnant subjects was troubling, as fluoroquinolones are contraindicated throughout pregnancy (128). Possible explanations for this finding may include a lack of physician knowledge related to fluoroquinolone toxicity in pregnancy, a lack of early detection of pregnancy by patients and/or physicians, or deficiencies in the method used to define pregnancy status.

Whilst a small proportion of women delay seeking prenatal care until the second or third trimesters (188), receipt of a prescription for a fluoroquinolone necessitated physician contact. Therefore, it is likely that a possible pregnancy would be reported/discovered at this time. In addition, the assignment of pregnancy status was based on the number of weeks of gestation recorded on HSA for hospitalizations which resulted in delivery. Thus, it is unlikely that non-pregnant subjects would be assigned a positive pregnancy status. Therefore, the use of fluoroquinolones during pregnancy likely reflects physicians' inattention to consideration of possible pregnancy and/or a lack of physician knowledge related to the contraindication of fluoroquinolone use in pregnancy. The prescribing of contraindicated antibiotics (tetracycline use in children under the age of eight years) has been previously reported (211).

The proportion of subjects experiencing a treatment duration of fourteen days was lower than expected, given current treatment guidelines (11, 12, 139). However, treatment durations as short as seven days have been advocated by some authors (139, 151). In the current study, 92% of subjects were found to have experienced treatment durations ranging from seven to fifteen days, which is a positive finding. Possible reasons for the shorter durations of treatment experienced by some subjects (i.e., less than seven days), include provision of a short duration of empirical treatment pending culture results, patient request for less than the prescribed quantity due to cost considerations, lack of physician knowledge regarding appropriate duration of treatment, and the inclusion of episodes of cystitis (for which short durations of treatment are appropriate) which were erroneously coded as pyelonephritis. Receipt of relatively long durations of treatment may reflect the provision of drug for treatment of the acute episode in addition to ongoing prophylactic or suppressive therapy. However, in the current study few subjects were prescribed treatment in excess of 15 days.

In summary, while in most cases the out-patient antibiotic treatment of pyelonephritis was consistent with current recommendations, there remain opportunities for improvement in the performance of urine culture, selection of appropriate antibiotics, duration of treatment, and consideration of drug toxicity.

Several subject specific variables were significantly associated with receipt of a fluoroquinolone versus TMP-SMX. Among rural residents, increasing age was significantly associated with receipt of a fluoroquinolone, and a similar (albeit non-significant) trend was observed among urban subjects. The finding that increasing age is associated with the receipt of a fluoroquinolone is consistent with the findings of

McCombs and Nichol, and Strand *et al.* who found that older adults were more likely to receive broad spectrum and/or second-line agents (174). In addition, this finding echoes that of Huang *et al.* who reported a higher proportion of fluoroquinolone use for the treatment of cystitis among older, compared with younger, adults (201). This finding may be due to the recognition by physicians of the positive association between increasing age and infection caused by antibiotic-resistant pathogens.

Rural residents were identified as being more likely than urban residents to receive a fluoroquinolone, which was consistent with the findings of Strand *et al.* and McCombs and Nichol who reported rural physician practice, and rural residence of patient, respectively, to be associated with an increased probability of receipt of a broad spectrum antibiotic (173, 174). Possible reasons for this include comparatively reduced availability of laboratory services to ensure the susceptibility of pathogens to TMP-SMX, and/or the difficulty of providing follow-up care in situations of treatment failure, due to geographic location or physician workload. Thus, the reported increased prevalence of antibiotic-resistant pathogens in older adults (166, 171, 172) may be of greater concern in rural areas, resulting in the observed higher probability of fluoroquinolone use among older subjects in the rural setting.

In the current study, the effect of income on the probability of being prescribed a fluoroquinolone was consistent with the findings of Henricson *et al.* These researchers indicated that higher socio-economic status (SES) was associated with an increased probability of receipt of broad spectrum antibiotics (190). Interaction effects with subject variables, in the current study, complicated the interpretation of this association. The probability of receipt of a fluoroquinolone increased as income increased, and this effect

was greater for those subjects presenting to the ER. It is improbable that subjects in the higher income quintiles were more likely to harbour resistant organisms, or were clinically more ill than subjects in the lower income quintiles. The propensity for persons of higher SES to receive more specialized or higher cost health services than persons of lower SES, irrespective of need, has been previously reported (186, 188).

The cost of pharmaceuticals for Manitoba residents is borne in part by the provincial government, with the proportion of the cost borne based on family income. As income increases the proportion of pharmaceutical costs borne by the government decreases (189). However, coverage of fluoroquinolone treatment is provided only where documented resistance or allergy to alternative agents is identified (Appendix A). Therefore, much empirical treatment of pyelonephritis will not meet these criteria, and patients will be responsible for the full cost of treatment. The differential ability of patients to absorb this cost, likely impacts treatment decisions. Physicians' recognition of the inability of low income patients to afford what they perceive as required treatment (i.e., a fluoroquinolone), may partially explain the higher incidence of hospitalization among subjects in the lower income quintiles. For subjects who were not hospitalized, the ability to absorb the cost of fluoroquinolone treatment was a significant determinant of receipt of a fluoroquinolone.

The positive association between presentation to an ER and receipt of a fluoroquinolone is consistent with the findings of Pennie, who reported urgent care physicians were more likely than family physicians to prescribe second line antibiotics (212). This finding was not unexpected since it was assumed that subjects presenting to an ER would be more clinically ill than those presenting to a physician's office.

However, the effect of presentation to an ER on the probability of receipt of a fluoroquinolone was not as pronounced for the lower income quintiles. The disparity may reflect differences in the way ER services are used by persons in high, versus low income quintiles. Mustard *et al.* reported low neighbourhood income to be positively associated with use of ER services, yet this was not perceived to be due to increased need or acuity of illness (187). Rather, several authors suggest the disproportionate use of ER services may be due to living situations associated with low SES (186, 187, 213). That is, the inability to make and keep appointments due to work/family considerations, geographic distribution of primary care providers, a lack of transportation, and cultural preference. These independently, or in combination, may lead to use of ER services for non-emergent/urgent care by persons with low SES. Conversely, persons of higher SES may be likely to utilize ER for urgent/emergent care than those of lower SES. Thus, it is possible that subjects in higher income quintiles presenting to an ER were more acutely ill, resulting in the greater probability of receipt of a fluoroquinolone by high compared with low income subjects in this setting.

In contrast, the significant association between income and receipt of a fluoroquinolone, observed in non-diabetics, was not demonstrated for diabetic subjects. It appears physicians may ignore cost considerations when making treatment decisions for subjects with diabetes due to either the increased probability of antibiotic-resistant pathogens, or the implications of possible treatment failure in this patient population. Similarly, the positive association between both recent antibiotic use and recent hospitalization with receipt of a fluoroquinolone, may be due to recognition of these variables as risk factors for antibiotic-resistant organisms. There was no evidence of an

association between recent UTI and receipt of a fluoroquinolone. This may be explained by the paucity of evidence of the association between recent UTI and infection caused by antibiotic-resistant pathogens.

Sensitivity analyses, using both an expanded and restrictive cohort, produced results similar to those discussed above. However, the interaction between diabetes and income was not significant for the restrictive cohort, indicating that the effect of income on the probability of receipt of a fluoroquinolone was the same for both diabetic and non-diabetic subjects. This may be explained by the higher proportion of subjects with diabetes, excluded from the restrictive cohort. The lack of a significant association between recent antibiotic use and receipt of a fluoroquinolone, using the restrictive cohort, was also not surprising given the exclusion of a large proportion of subjects with recent antibiotic use. In addition, the effect of recent antibiotic use on the probability of harbouring antibiotic-resistant pathogens decreases as the time since antibiotic use increases (199). However, the possibility exists that this lack of association in the restrictive cohort was due to the elimination of subjects with unrecognized earlier treatment and treatment failure. Thus, the finding that recent antibiotic use is associated with an increased probability of receipt of a fluoroquinolone is equivocal.

The proportion of subjects experiencing treatment failure was not significantly different between the TMP-SMX and fluoroquinolone groups; approximately 19%. These data compare favourably to the clinical failure at late follow-up reported by Mouton *et al.*; 44% and 50% for TMP-SMX and lomefloxacin respectively (150). However, Talan *et al.* reported clinical failure of 9% and 23%, for ciprofloxacin and TMP-SMX respectively (151). The few available RCTs comparing TMP-SMX and a fluoroquinolone

in pyelonephritis, provide little data regarding the effect of subject variables on treatment outcome, rather subjects with diabetes, recent antibiotic use, or other complicating factors were commonly excluded from study (141, 148, 150, 151). Thus, the results of the current study provide new insight into subject variables which may affect treatment outcomes.

Subject variables were chosen based on their reported association with infection by antibiotic-resistant pathogens. Due to differences in resistance to TMP-SMX and fluoroquinolones among uropathogens, the subject variables were expected to have a varying effect on the likelihood of treatment failure dependent upon the initial antibiotic received. Thus, an interaction between each subject variable and the initial antibiotic was hypothesized. For example, increasing age is associated with a greater probability of infection with an antibiotic-resistant pathogen (166, 171, 172), and resistance to TMP-SMX is more common than resistance to fluoroquinolones (10). Therefore, it was hypothesized that while increasing age would result in an increase in the probability of treatment failure overall, the effect would be more pronounced for subjects receiving TMP-SMX compared with fluoroquinolones. The same rationale resulted in the hypothesized interactions between initial antibiotic, and other subject specific variables associated with infection with antibiotic-resistant pathogens (e.g., recent antibiotic use, recent hospitalization).

In the multivariate model, evaluating the effect of initial antibiotic treatment and subject specific variables on the probability of treatment failure, the only interaction which achieved statistical significance was that between age and initial antibiotic. Based on these data, it appears fluoroquinolones are superior to TMP-SMX for treatment of

pyelonephritis in younger women, while no significant difference exists between the two agents in older women. This finding does not support the hypothesis that older women treated with TMP-SMX experience more treatment failure due to an increased propensity to harbour resistant organisms (166, 171, 172).

This unexpected result may be explained by the way physicians make prescribing decisions; thus, creating a systematic bias in the study. As observed in the earlier analysis, older subjects were more likely to receive fluoroquinolones than younger subjects. This difference was controlled by the inclusion of age in the multivariate model. However, the possibility that physicians' prescribing decisions, based on severity of illness, may differ by age is difficult to control in the analysis, as healthcare claims do not provide clinical measures of severity of illness. Thus, if physicians made the decision to treat all but the least clinically ill older subjects with TMP-SMX, yet made no such distinction among younger subjects, this may "stack the odds" in favour of TMP-SMX producing successful outcomes in older subjects; producing the observed result. The difficulty in controlling confounding by indication was previously discussed.

The effects of age and initial antibiotic treatment on outcome, were further examined in the sensitivity analysis. The effects of age and initial antibiotic, as described above, remained consistent for the restrictive cohort (exclusion of subjects with antibiotic use in the previous three weeks, to minimize the possibility of a follow-up visit being erroneously identified as the initial visit). However, when the effects of age and initial antibiotic were examined using the restrictive definition of treatment failure (no category VI antibiotics in definition of treatment failure), fluoroquinolones appeared superior over all age groups, and the probability of failure decreased with age for both drugs. The lack

of a significant interaction effect may have been due to disproportionate exclusion of older subjects on application of the restrictive definition of treatment failure.

No other subject specific variables evidenced differential effects on the relationship between initial antibiotic treatment and treatment outcome. That is, no other interactions between initial antibiotic and subject variables achieved significance in the multivariate model. However, several subject variables were independent risk factors for treatment failure. Evidence of a recent UTI increased the odds of a patient experiencing treatment failure by approximately 100%. The effect was consistent in sensitivity analyses, using both the restrictive cohort and restrictive definition of treatment failure, and was consistent with data reported by Fihn *et al.* (152). That the effect of a recent UTI on treatment outcome was unrelated to the initial antibiotic treatment may reflect the difficulty in eradicating infection in women who are predisposed to UTI due to structural/functional abnormalities, rather than any difference in the resistance profile of infecting organisms.

Recent antibiotic use increased the odds of treatment failure by a factor of 1.4, however, in the sensitivity analysis it failed to achieve significance when the restrictive definition of treatment failure was employed. Once again, this may be due to the disproportionate exclusion of older subjects who were more likely to be recent antibiotic users. In addition, recent antibiotic use was not a significant contributor to treatment failure when subjects taking antibiotics within the previous three weeks were excluded (restrictive cohort; N=960).

The intention of the current study was not to examine the effect of differences in treatment duration on treatment outcome. Rather, duration of treatment was included in

the multivariate model to control for possible differences in treatment durations between the two agents under investigation. Indeed, duration of treatment was significantly shorter among subjects treated with a fluoroquinolone versus TMP-SMX. However, treatment duration (less than 10 days) was identified as an independent risk factor for treatment failure; increasing the odds of treatment failure by approximately 100% irrespective of the choice of initial antibiotic. The effect of treatment duration on treatment outcome was robust to changes in the definition of treatment failure and study cohort, consistently producing an increase in the odds of treatment failure of approximately 100%.

The increased likelihood of failure observed with shorter treatment durations provided some reassurance regarding the validity of the diagnosis. For example, if subjects received shorter durations of treatment because they had cystitis (erroneously coded as pyelonephritis), treatment failure would be expected to be less frequent among these subjects, as suggested by RCT (Tables 2 and 3). As, this was not observed in the current study, the probability of contamination of the study cohort by episodes of cystitis was considered low.

There are few data in the literature regarding the optimal duration of treatment for pyelonephritis. Recommendations for treatment durations of 14 days appear to be based on an early study which reported that 14 days provided as efficacious a treatment as 6 weeks (141). Subsequent to that report, few studies have addressed treatment durations for this indication. Talan *et al.* recently reported that seven days of ciprofloxacin was superior to fourteen days of TMP-SMX in pyelonephritis (151). However, the current study indicates that 14 days of a fluoroquinolone would also be superior to seven days of a fluoroquinolone. Based on the results of the current study, a treatment duration of at

least ten days is advisable, regardless of the initial antibiotic; TMP-SMX or a fluoroquinolone.

There was little evidence of an association between diabetes and treatment failure; either in the original analysis, or in sensitivity analysis using the restrictive cohort. However, when the restrictive definition of treatment failure was used, an increase in the odds of treatment failure was identified for diabetics in income quintiles 4 and 5. The reason for this is unclear, furthermore the estimates of effect lacked precision due to the small number of subjects with diabetes in the upper income quintiles. None of the reviewed studies of UTI reported differences in outcome associated with diabetes, however, many of these studies excluded subjects with diabetes (144, 146, 151, 153, 155). Thus, the hypothesized association between diabetes and treatment failure was based on the reported relationship between diabetes and UTI caused by antibiotic-resistant organisms. However, the current study did not support this hypothesis. Similarly, there was no significant association between recent hospitalization and treatment failure, either in the original analysis, or in sensitivity analysis. This despite reports of an association between recent hospitalization and UTI caused by resistant pathogens (169, 176, 177, 184).

The lack of a significant association between known risk factors for UTI caused by resistant pathogens (e.g., diabetes, recent hospitalization), and treatment failure may be due to a low incidence of UTI caused by resistant pathogens in the study cohort. Recently, approximately 19% of uropathogens in Canada were reported resistant to TMP-SMX, compared to only 2% to fluoroquinolones (10). The difference in the prevalence of resistance to the two agents under investigation was expected to impact comparative

treatment outcomes. However, as with other studies reporting the prevalence of antibiotic-resistant pathogens (7, 162, 163), the Canadian study relied upon examination of physician-ordered urine cultures, and included both male and female subjects of varying ages. As urine cultures are expected to be reserved for patients likely to have resistant organisms or difficulty eradicating infections, the prevalence of antibiotic resistance based on these cultures may not reflect the true prevalence of resistance in the general population. Since the current study utilized young females, the prevalence of resistant organisms among study subjects may have been too low to exert any significant effect on treatment outcome.

5.3 Implications for clinical practice

The present study provides a measure of the effectiveness of current antibiotic use in the treatment of pyelonephritis. As previously discussed, effective drug use consists of several components; the most basic of which is the use of drugs known to be safe and efficacious for a given indication. The receipt of nitrofurantoin by a small proportion of subjects with pyelonephritis constituted ineffective drug use, as nitrofurantoin is not efficacious in pyelonephritis due to its inability to achieve adequate serum/tissue concentrations (161). The use of fluoroquinolones by a small proportion of pregnant subjects constituted unsafe drug use, due to the potential for toxic effects on the developing fetus. Education of physicians on these issues, as subsequently discussed, is desirable to minimize unsafe and ineffective drug use.

The majority of subjects received either TMP-SMX or a fluoroquinolone, both of which have been shown to be efficacious in the treatment of pyelonephritis (141, 148,

150, 151). In an attempt to minimize treatment costs and the potential for selection of fluoroquinolone resistant organisms, Manitoba Health restricts coverage of fluoroquinolone treatment to situations of resistance or intolerance to alternative agents (Appendix A). Given that empiric treatment is required prior to knowledge of culture results, it is clear these conditions are infrequently met. Yet, approximately one-third of non-pregnant subjects received initial treatment with a fluoroquinolone. This study sought to determine subject variables associated with receipt of a fluoroquinolone, and further determine the appropriateness of prescribing decisions based on treatment effectiveness.

The current study provides evidence that physicians appear to consider known risk factors for antibiotic resistance when selecting initial treatment, since increasing age, recent antibiotic use, and recent hospitalization were associated with an increased probability of receipt of a fluoroquinolone. However, an examination of treatment outcomes revealed little justification for consideration of several of these subject variables in the selection of initial antibiotic treatment. Subjects with recent antibiotic use were more likely to experience treatment failure, however, this was true regardless of initial antibiotic. Other subject variables which were hypothesized to differentially affect treatment outcome (e.g., recent hospitalization and diabetes) were not substantiated. Thus, there appears little justification for preferential prescribing of fluoroquinolones based on the presence of the above variables.

Fluoroquinolones appear to provide a superior outcome, in comparison to TMP-SMX for the treatment of pyelonephritis, at least in young women. However, for several reasons, wholesale treatment of pyelonephritis with fluoroquinolones cannot be

recommended. First, TMP-SMX use resulted in favourable treatment outcome in over 80% of subjects treated in the current study. Second, the cost of treatment with fluoroquinolones is approximately 20 times that of TMP-SMX, thus increasing healthcare expenditures for limited gain. Third, increased use of fluoroquinolones may potentiate the selection of pathogens resistant to this class of agents. Fluoroquinolones are increasingly advocated for treatment of community-acquired infections, often due to increasing resistance to older agents (7). However, unlike other infectious etiologies, such as community-acquired pneumonia, where collection of sputum samples is problematic and cultures frequently fail to identify causative pathogens, urine samples are easily obtained and cultured. Thus, where laboratory services are readily available, and out-patient antibiotic use is suitable, use of TMP-SMX, in combination with urine culture, continues to be appropriate treatment. The provision of urine culture by only 58.5% of Winnipeg residents presenting to a non-ER setting, in the current study, indicates an opportunity for improved practice. Where laboratory services are not readily available, or the ease of patient follow-up is questionable, initial treatment with a fluoroquinolone may be justified.

The conflict between theory and the results of this study regarding the relationship between age and initial antibiotic treatment, and the probability of treatment failure, indicates the need for further study before recommendations regarding choice of initial treatment for pyelonephritis based on age may be made. The effect of treatment duration on outcome was an important finding. Irrespective of initial antibiotic (TMP-SMX or fluoroquinolone), treatment durations of ten to fourteen days are recommended.

Finally, it is important to translate the results of studies of drug effectiveness into initiatives to promote optimal drug use through the reduction of unnecessary or inappropriate use. Such educational initiatives commonly focus on clinicians, however, education of the public has also been used in an attempt to decrease unnecessary antibiotic use through reduced demand.

Raisch has divided methods to influence prescribing into direct and indirect approaches (214). Direct approaches include administrative policies such as prescribing restrictions and financial incentives. Reports indicate that such approaches have met with success in lowering drug costs and improving prescribing (71, 215, 216). However, Raisch noted that administrative policies do nothing to change physicians' underlying beliefs and intentions regarding prescribing, and suggests that once restrictions are eased, physicians will revert to inappropriate prescribing. This was confirmed by Himmelberg *et al.* who observed an increase in inappropriate antibiotic use following removal of prescribing restrictions in a hospital setting (216).

In Manitoba, the conditional coverage of fluoroquinolone prescriptions by Manitoba Health is an attempt to optimize fluoroquinolone use. However, no policy precludes the prescribing of fluoroquinolones to subjects able and willing to pay for them, regardless of their appropriateness for a given indication. Therefore, the willingness or ability of a patient to pay for fluoroquinolones in essence acts as an easing of the restrictive policy. Higher use of fluoroquinolones among subjects in higher income quintiles was observed in the present study, confirming that prescribing behaviour will change upon removal of restrictions. For this reason, Raisch's suggestions that indirect methods of changing

prescribing behaviour be used concurrently with direct methods becomes more relevant (214).

Indirect methods to influence prescribing practices include educational initiatives such as the provision of one-on-one consultation and printed material by academic detailers, peer counseling, and information regarding prescribing practices in relation to peers (214). Whilst the above methods have been reported to improve prescribing to varying degrees (72, 211, 217-219) Raisch's suggestion that such educational initiatives must be maintained to achieve long-term results becomes more salient (214).

5.4 Future Research

In this study the utility of the healthcare claims from the Manitoba Health database to answer questions about drug effectiveness was as much of interest as the drug/disease questions to which it was applied. Therefore recommendations for further investigation include additional research questions related to the treatment of pyelonephritis, the assessment and improvement of the database for future research, and selection of drugs and/or disease states for additional effectiveness research. The following are suggested areas for further investigation.

1. A study of the effect of Manitoba's prescribing restrictions for fluoroquinolones on the selection of initial treatment of pyelonephritis; in-hospital or out-patient antibiotic treatment. In chapter 2 it was noted that one of the components of effective drug use was equity of distribution. That is, are all patients eligible to receive a drug able to receive it? The current study suggests that there is a disparity in the ability to receive fluoroquinolone treatment based on income, with

subjects with higher income more likely to receive such treatment. This situation is created by restrictions put in place by Manitoba Health, which are not absolute restrictions on prescribing but restrictions on payment, thus restricting access based on ability to pay. Given that subjects in the higher income quintiles were more likely to receive a fluoroquinolone and subjects in lower income quintiles were more likely to be hospitalized, it is worthwhile to examine the possibility that prescribing restrictions simply shift the cost of treatment for low income residents to the hospital setting; a more costly alternative. This is particularly important in view of the fact that subjects in the lowest income quintiles accounted for the majority of pyelonephritis cases.

2. Additional investigation related to the completeness and validity of the healthcare data are suggested. The final goal of such studies is eventual improvement of the data for research purposes. Possible areas for further study include the following, which were of particular importance to the current study.

    (i) Determine the proportion of services provided by salaried physicians which are submitted to Manitoba Health and encourage policy changes to maximize the submission of healthcare claims.

    (ii) Determine the extent of non-specific coding within disease states. For example, what proportion of claims containing the ICD-9-CM code 599 might be more accurately classified as 590 (pyelonephritis) or 595 (cystitis). Minimizing use of non-specific codes, through education of clinicians and other responsible personnel, may assist in establishing

the burden of illness for many disease states and may result in larger cohorts for study.

(iii) Exploration of methods to facilitate the submission of diagnostic information with pharmaceutical claims.

3. Adapting the methodology from the current study to other drugs and other disease states (infectious and non-infectious). Diseases states with a high incidence/prevalence, and where drug use and drug costs are high, would be of particular interest. In the area of infectious diseases, studies of antibiotic treatment of cystitis and otitis media are suggested. Both infectious conditions are commonly treated in community practice, and have experienced increasing antibiotic resistance among causative pathogens that has led to the promotion of expensive broad spectrum antibiotics as treatment choices.

Appendices

Appendix A.

Antibiotic prescribing restrictions

Prescriptions issued, which do not meet one or more of the criteria listed below are not eligible for coverage by Manitoba Health (98).

1. Amoxicillin-Clavulanic Acid

(i) for treatment of patients not responding to alternative antibiotics (e.g., amoxicillin).

(ii) for treatment of infections caused by organisms known to be resistant to alternative antibiotics (e.g., amoxicillin).

2. Azithromycin

(i) for treatment of patients not responding to or intolerant of alternative antibiotics (e.g., amoxicillin and erythromycin).

(ii) mycobacterial infections due to mycobacterium avium and mycobacterium intracellulare.

(iii) sexually transmitted diseases due to Chlamydia

3. Cefaclor/Cefuroxime/Cefprozil/Cefixime

(i) step-down care following hospital separation in patients treated with intravenous cephalosporins.

(ii) treatment of patients with infections not responding to alternative antibiotics (e.g., amoxicillin).

(iii) treatment of infections caused by organisms known to be resistant to alternative antibiotics (e.g., amoxicillin).

(iv) treatment of patients known to be allergic or unresponsive to alternate antibiotics (e.g., penicillins or sulfonamides).

4. Ciprofloxacin/Ofloxacin

(i) step-down care following hospital separation in patients treated with parenteral antibiotics.

(ii) treatment of Pseudomonal infections or resistant gram-negative infections.

(iii) treatment of resistant Gonococcal infections.

(iv) treatment of infections in persons allergic to alternative agents (e.g., penicillins, cephalosporins and sulfonamides).

(v) treatment of infections in immunocompromised patients.

(vi) treatment of diabetic foot infections and complications of orthopedic surgery.

(vii) treatment of chronic bacterial prostatitis.

5. Clarithromycin

(i) infections not responding or intolerant of alternative antibiotics (e.g., amoxicillin and erythromycin).

(ii) mycobacterial infections due to mycobacterium avium and mycobacterium intracellulare.

(iii) in combination therapy in the treatment of *H. pylori* where the patient is intolerant or allergic to amoxicillin.

6. Erythromycin-Sulfisoxazole

(i) for pediatric respiratory (upper and lower) infections or otitis media unresponsive or allergic to penicillins.

7. Minocycline

(i) for treatment of acne unresponsive to tetracycline or erythromycin.

8. Nitrofurantoin Macrocrystals

(i) for patients not tolerant of microcrystalline nitrofurantoin.

9. Norfloxacin

(i) for treatment of urinary tract infections caused by *Pseudomonas aeruginosa.*

(ii) for treatment of urinary tract infections not responding to alternative therapy (e.g., penicillins, cephalosporins and sulfonamides.

(iii) -for treatment of chronic bacterial prostatitis.

10. Vancomycin

(i) for treatment of pseudomembranous colitis unresponsive to metronidazole.

Appendix B.

ATC Codes for systemic antibiotics available in Canada(78)

* Indicates antibiotics for which once daily dosing is standard

J01A – Tetracyclines

- J01AA02 Doxycycline*
- J01AA07 Tetracycline
- J01AA08 Minocycline

J01B – Amphenicols

- J01BA01 Chloramphenicol

J01C – Beta-lactam antibacterials, penicillins

J01CA – penicillins with extended coverage

- J01CA01 ampicillin
- J01CA02 pivampicillin
- J01CA03 carbenicillin
- J01CA04 amoxicillin
- J01CA06 bacampicillin
- J01CA08 pivmecillinam
- J01CA12 piperacillin
- J01CA13 ticarcillin

J01CE – beta-lactamase sensitive penicillins

- J01CE01 benzylpenicillin
- J01CE02 phenoxymethylpenicillin
- J01CE08 benzathine benzylpenicillin
- J01CE09 procaine penicillin

J01CF – beta-lactamase resistant penicillins

- J01CF02 cloxacillin
- J01CF05 flucloxacillin

J01CG – beta-lactamase inhibitors

- J01CG02 tazobactam

J01CR – combinations of penicillins incl. Beta-lactamase inhibitors

- J01CR02 amoxicillin and enzyme inhibitor
- J01CR03 ticarcillin and enzyme inhibitor
- J01CR05 piperacillin and enzyme inhibitor

J01D – Other Beta-lactam Antibacterials

J01DA – cephalosporins and related substances

J01DA01 cephalexin
J01DA04 cefazolin
J01DA05 cefoxitin
J01DA06 cefuroxime
J01DA08 cefaclor
J01DA10 cefotaxime
J01DA11 ceftazidime
J01DA13 ceftriaxone*
J01DA14 cefotetan
J01DA22 ceftizoxime
J01DA23 cefixime*
J01DA24 cefipime
J01DA32 cefoperazone
J01DA33 cefpodoxime
J01DA41 cefprozil*

J01E – Sulfonamides and Trimethoprim

J01EA – trimethoprim and derivatives

J01EA01 trimethoprim

J01EE – combinations of sulfonamides and trimethoprim, incl derivatives

J01EE01 sulfamethoxazole and trimethoprim
J01EE02 sulfadiazine and trimethoprim

J01F – Macrolides and Lincosamides

J01FA – macrolides

J01FA01 erythromycin
J01FA09 clarithromcyin
J01FA10 azithromycin*

J01FF – lincosamides

J01FF01 clindamycin

J01G – Aminoglycoside Antibacterials

J01GA – Streptomycins

J01GA01 streptomycin

J01GB – Other aminoglycosides

J01GB01 tobramycin
J01GB02 gentamicin
J01GB04 kanamycin
J01GB05 neomycin
J01GB06 amikacin

J01M – Quinolone Antibacterials

J01MA Fluoroquinolones

J01MA01 ofloxacin
J01MA02 ciprofloxacin
J01MA06 norfloxacin
J01MA11 grepafloxacin*
J01MA12 levofloxacin*
trovafloxacin*

J01R Combinations of antibacterials

J01RA02 sulfonamide comb. with other antibacterials (excl trimethoprim)

J01X Other antibacterials

J01XA Glycopeptide antibacterials

J01XA01 Vancomycin
J01XA02 teicoplanin

J01XB Polymyxins

J01XB polymyxin B

J01XC Steroid antibacterials

J01XC01 fusidic acid

J01XD Imidazole derivatives

J01XD01 metronidazole

J01XX Other antibacterials

J01XX01 fosfomycin*
J01XX04 spectinomycin

G04A Urinary antiseptics and antibacterials

G04AA Methenamine preparations

G04AA01 methenamine

G04AB Quinolone derivatives (excl. J01M)

G04AB01 nalidixic acid

G04AC Nitrofurantoin derivatives

G04AC01 nitrofurantoin

G04AG Other urinary antiseptics and anti-infectives

G04AG05 Mandelic acid

Appendix C.

Initial antibiotic treatment provided to 17 subjects receiving more than one antibiotic on the same date.

Subject Number	Antibiotics	Duration of treatment
1	TMP-SMX	7 days
	Cephalexin	7 days
2	Amoxicillin	7 days
	Amoxicillin	7 days
3	Cephalexin	10 days
	Cefuroxime	10 days
4	TMP-SMX	14 days
	Amoxicillin	14 days
5	Cephalexin	10 days
	Norfloxacin	10 days
6	Ciprofloxacin	2 days
	Ciprofloxacin	5 days
7	Amoxicillin	10 days
	TMP-SMX	10 days
8	TMP-SMX	14 days
	TMP-SMX	100 days
9	Ceftriaxone	10 days
	Ciprofloxacin	10 days
10	TMP-SMX	10 days
	Ciprofloxacin	10 days
11	Amoxicillin	10 days
	Norfloxacin	10 days

Subject number	Antibiotics	Duration of treatment
12	Cloxacillin	7 days
	TMP-SMX	14 days
13	Cephalexin	7 days
	Ciprofloxacin	7 days
14	Ciprofloxacin	10 days
	Ciprofloxacin	14 days
15	Ciprofloxacin	14 days
	Ciprofloxacin	14 days
16	TMP-SMX	7 days
	Cephalexin	7 days
17	TMP-SMX	5 days
	TMP-SMX	5 days
	TMP-SMX	5 days

Appendix D.

Alternative diagnosis codes submitted on HSA and/or MC within two days of initial antibiotic. X indicates diagnoses considered to be of infectious etiology unrelated to the urinary tract and which resulted in a subject being excluded from the final cohort

ICD-9-CM code		Infectious etiology
008	Intestinal Infections due to other organisms	X
041	Bacterial infection in conditions classified elsewhere and of unspecified site	X
162	Malignant neoplasm of trachea, bronchus/lung	
218	Uterine leiomyoma	
220	Benign neoplasm of ovary	
250	Diabetes Mellitus	
272	Disorders of lipid metabolism	
276	Disorders of fluid, electrolyte and acid-base balance	
280	Iron deficiency anemias	
281	Other deficiency anemias	
285	Other and unspecified anemias	
300	Neurotic disorders	
305	Nondependent abuse of drugs	
307	Special symptoms/syndromes not classified elsewhere	
311	Depressive disorder not classified elsewhere	
314	Hyperkinetic syndrome of childhood	
346	Migraine	
367	Disorders of refraction and accommodation	
369	Blindness and low vision	
372	Disorders of conjunctiva	
396	Diseases of mitral and aortic valves	
401	Essential hypertension	
410	Acute myocardial infarction	
427	Cardiac dysrhythmias	
462	Acute pharyngitis	X
463	Acute tonsillitis	X
464	Acute laryngitis	X
465	Acute upper respiratory tract, multiple/unspecified sites	X
466	Acute bronchitis and bronchiolitis	X
473	Chronic sinusitis	X
476	Chronic laryngitis and laryngotracheitis	
477	Allergic rhinitis	
486	Pneumonia, organism unspecified	X
487	Influenza	
490	Bronchitis, not specified as acute or chronic	X

493	Asthma	
496	Chronic airway obstruction, not classifed elsewhere	
518	Other diseases of lung	
524	Dentofacial anomalies, including malocclusion	
530	Diseases of esophagus	
535	Gastritis and duodenitis	
536	Disorders of function of stomach	
537	Other disorders of stomach and duodenum	
541	Appendicitis, unqualified	X
553	Other hernia of abdominal cavity without mention of obstruction or gangrene	
558	Other non-infectious gastroenteritis and colitis	
574	Cholelithiasis	
575	Other disorders of gallbladder	
578	Gastrointestinal hemorrhage	
585	Chronic renal failure	
592	Calculus of kidney and ureter	
593	Other disorders of kidney and ureter	
598	Urethral stricture	
611	Other disorders of breast	X
614	Inflammatory disease of ovary/fallopian tube/pelvic/ cellular tissue/peritoneum	X
616	Inflammatory disease of cervix, vagina, and vulva	X
617	Endometriosis	
621	Disorders of uterus not classified elsewhere	
622	Noninflammatory disorders of cervix	
625	Pain and other symptoms associated with female genital organs	
626	Disorders of menstruation and other abnormal bleeding from female genital organs	
634	Spontaneous abortion	
635	Legally induced abortion	
640	Hemorrhage in early pregnancy	
643	Excessive vomiting in pregnancy	
644	Early or threatened labour	
645	Prolonged pregnancy	
646	Other complications of pregnancy, not classified elsewhere	
648	Other conditions in mother classified elsewhere but complicating pregnancy, childbirth or the puerperium	
655	Known or suspected fetal abnormality affecting management of mother	

656	Other fetal and placental problems affecting management of mother	
670	Major puerperal infection	X
682	Other cellulitis and abscess	X
719	Other and unspecified disorders of joint	
724	Other and unspecified disorders of back	
726	Peripheral enthesopathies and allied syndromes	
728	Disorders of muscle, ligament and fascia	
729	Other disorders of soft tissue	
780	General symptoms	
784	Symptoms involving head and neck	
786	Dyspnea and respiratory abnormalities	
787	Symptoms involving digestive system	
788	Symptoms involving urinary system	
789	Other symptoms involving abdomen and pelvis	
845	Sprains and strains of ankle and foot	
847	Sprains and strains of other and unspecified parts of back	
874	Open wound of neck	
879	Open wound of other and unspecified sites, except limbs	
995	Certain adverse effects not elsewhere classified	
998	Other complications of procedures not elsewhere classified	
E92	Accidents caused by cutting and piercing instruments or objects	
V22	Normal pregnancy	
V24	Postpartum care and examination	
V25	Encounter for contraceptive management	
V27	Outcome of delivery	
V72	Special investigations and examinations	

Appendix E.

Alternative diagnosis codes associated with Medical Claims which preceded DPIN claims for additional antibiotics by up to two days. X indicates diagnoses which resulted in an antibiotic being placed in Category I with regard to assignment of failure status

ICD-9-CM	Infectious Etiology
054 Herpes Simplex	
070 Viral hepatitis	
078 Other diseases due to viruses and chlamydia	X
132 Pediculosis and phthirus infestation	
174 Malignant neoplasm of female breast	
250 Diabetes mellitus	
296 Affective psychoses	
300 Neurotic disorders	
311 Depressive disorder, not elsewhere classifed	
382 Suppurative and unspecified otitis media	X
411 Other acute and subacute forms of ischemic heart disease	
451 Phlebitis and thrombophlebitis	
461 Acute sinusitis	X
462 Acute pharyngitis	X
463 Acute tonsilitis	X
465 Acute upper respiratory infections of multiple or unspecified sites	X
466 Acute bronchitis and bronchiolitis	X
473 Chronic sinusitis	X
483 Pneumonia due to other specified organism	X
486 Pneumonia, organism unspecified	X
487 Influenza	
490 Bronchitis, not specified as acute or chronic	X
493 Asthma	
522 Disease of pulp and periapical tissues	X
558 Other non-infectious gastroenteritis and colitis	
562 Diverticula of intestine	X
564 Functional digestive disorders, not elsewhere specified	
574 Cholelithiasis	
577 Diseases of pancreas	X
583 Nephritis and neuropathy	
590 Infections of kidney	
592 Calculus of kidney and ureter	
593 Other disorders of kidney and ureter	
594 Calculus of lower urinary tract	
595 Cystitis	
599 Other disorders of urethra and urinary tract	

614 Inflammatory disease of ovary, fallopian tube, pelvic cellular tissue, and peritoneum	X
616 Inflammatory disease of cervix, vagina, and vulva	X
618 Genital prolapse	
623 Noninflammatory disorders of ovary, fallopian tube, and broad ligament	
625 Pain and other symptoms associated with female genital organs	
626 Disorders of menstruation and other abnormal bleeding from female genital tract	
681 Cellulitis and abscess of finger and toe	X
682 Other cellulitis and abscess	X
684 Impetigo	X
692 Contact dermatitis and other eczema	
704 Diseases of hair and hair follicles	
706 Diseases of sebaceous glands	X
719 Other and unspecified disorders of joint	
729 Other disorders of soft tissue	
780 General symptoms	
786 Symptoms involving respiratory system and other chest symptoms	
787 Symptoms involving digestive system	
788 Symptoms involving urinary system	
789 Other symptoms involving abdomen and pelvis	
790 Nonspecific findings on examination of blood	
945 Burn of lower limbs	
995 Certain adverse effects not elsewhere classified	
V72 Special investigations and examinations	

Appendix F.

Alternative diagnosis codes associated with HSA which preceded DPIN claims for additional antibiotics by up to two days. X indicates diagnoses which resulted in an antibiotic being placed in Category IV with regard to assignment of failure status.

ICD-9-CM code	**Infectious Etiology**
041 Bacterial infection in conditions classified elsewhere and of unspecified site	X
112 Candidiasis	
131 Trichomoniasis	X
218 Uterine leiomyoma	
250 Diabetes mellitus	
296 Affective psychoses	
346 Migraine	
357 Inflammatory and toxic neuropathy	
382 Suppurative and unspecified otitis media	X
401 Essential hypertension	
455 Hemorrhoids	
486 Pneumonia, organism unspecified	X
490 Bronchitis, not specified as acute or chronic	X
491 Chronic bronchitis	X
493 Asthma	
524 Dentofacial anomalies, including malocclusion	
530 Disease of esophagus	
583 Nephritis and neuropathy, not specified as acute or chronic	
590 Infection of kidney	
592 Calculus of kidney and ureter	
599 Other disorders of urethra and urinary tract	
617 Endometriosis	
620 Noninflammatory dissorder of ovary, fallopian tube, and broad ligament	
625 Pain and other symptoms associated with female genital organs	
784 Symptoms involving head and neck	
785 Symptoms involving cardiovascular system	
786 Symptoms involving respiratory system and other chest symptoms	
788 Symptoms involving urinary system	
V12 Personal history of certain other diseases	
V45 Other postsurgical states	

Appendix G.

Antibiotic prescriptions designated as prophylaxis or suppressive therapy due to a dispensed quantity of less than two solid dosage forms per day.

Antibiotic	Prescription quantity	Days supply	Units per day
TMP-SMX	15	30	0.5
TMP-SMX	30	30	1.0
TMP-SMX	30	30	1.0
TMP-SMX	30	30	1.0
TMP-SMX	30	30	1.0
TMP-SMX	30	25	1.2
TMP-SMX	60	60	1.0
TMP-SMX	60	60	1.0
TMP-SMX	90	180	0.5
Trimethoprim	60	60	1.0
Nitrofurantoin	60	60	1.0
Nitrofurantoin	90	90	1.0
Norfloxacin	10	7	1.4
Ciprofloxacin	7	7	1.0
Ciprofloxacin	10	10	1.0
Ciprofloxacin	14	14	1.0
Cefuroxime axetil	21	11	1.9

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