Antimicrobial Resistance Trends in the Province of British Columbia

2011

Communicable Disease Prevention and Control Services

British Columbia Centre for Disease Control

BC Centre for Disease Control

An agency of the Provincial Health Services Authority

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Executive Summary

Objective

The purpose of this report is to provide a comprehensive overview of antimicrobial resistance (AMR) trends in the province of British Columbia (BC) and to correlate these trends with antibiotic utilization.

Methods

Data were obtained from various provincial and national collaborators for a broad-spectrum view of clinically relevant bacteria. Rates of antimicrobial utilization were available through analysis of BC PharmaNet data. Data were analyzed in Microsoft Excel and SPSS; significance is based on a two-sided Spearman Rank test.

Results

- According to BCAMM, which represents both hospital and community isolates, the percent of *Staphylococcus aureus* isolates that are methicillin-resistant (MRSA) decreased between 2006 to 2010 (23% to 17.1%). BC Biomedical Laboratories, which represents community isolates in the Lower Mainland, reports a variable increase between 2008 and 2011 (16.1% to 24.9%), but an overall decrease from 30.5% in 2007. The overall decrease in non-susceptibility rate for clindamycin, erythromycin and trimethoprim-sulfamethoxazole (TMP-SMX) reflects an increase in community-associated (CA) MRSA strains.
- *Streptococcus pneumoniae* isolates have demonstrated a stable rate of resistance to erythromycin since 2007, with 31.4% of all tested isolates demonstrating resistance against erythromycin in 2011. Approximately one sixth to one fourth of *Streptococcus pneumoniae* isolates have also demonstrated non-susceptibility against clindamycin (14.9%), penicillin (18.0%) and trimethoprim-sulfamethoxazole (TMP-SMX) (23.8%).
- From 2007 to 2010, resistance rates to erythromycin and clindamycin decreased in *Streptococcus pyogenes* isolates, but then increased in 2011. All isolates remain highly susceptible to penicillin and vancomycin (>99%).
- *Enterococcus* spp. isolates remain highly susceptible to vancomycin, ampicillin and nitrofurantoin (>97%). Approximately one fourth of all isolates tested are resistant to ciprofloxacin (24.7%), largely due to the high amount of resistance in those greater than 70 years of age. The percent of *Enterococcus* spp. isolates demonstrating resistance against vancomycin (VRE) has remained below or near 1% for all years.
- Data from BC Biomedical Laboratories indicated the percent of *H. influenzae* isolates resistant to ampicillin decreased from 18.4% in 2008 to 14.3% in 2011. Data from CBSN indicated the percent of β-lactamase-producing *Haemophilus influenzae* isolates showed a significant increase in 2008, with approximately 40% of isolates testing positive. This discrepancy may be due to the different nature of data sources.

- *Escherichia coli* resistance to ciprofloxacin sits at 26.8% as it continues to increase. Much of this resistance comes from those greater than 70 years of age.
- Urinary tract pathogens such as *Escherichia coli* and *Klebsiella pneumoniae* have shown increasing resistance to ciprofloxacin, although the increase is much less prevalent and consistent in *K. pneumoniae*, while *Proteus mirabilis* isolates have shown varying resistance to ciprofloxacin after a peak in 2008. *E. coli* and *P. mirabilis* isolates demonstrate high levels of resistance to trimethoprim-sulfamethoxazole (TMP-SMX) for all years available, including 26.0% in 2011 for *E. coli* and 30.5% for *P. mirabilis*, while a relatively lower resistance rate was found for *K. pneumoniae* (8.5%). Nitrofurantoin remains highly effective for *E. coli* isolates with over 96% of isolates showing susceptibility. This is reassuring as 85% to 90% of all uncomplicated UTI infections are caused by *E. coli*.
- According to data from the BCAMM 2010 report, the percent of Enterobacteriaceae spp. producing extended spectrum β-lactamases (ESBL) remained low for BC communities, including *Escherichia coli* (0.7% – 2.5%) and *Klebsiella pneumoniae* (0.5%).
- *Salmonella* enteriditis resistance to ampicillin, tetracycline, and chloramphenicol remains low (<3%).
- Resistance rates for *Pseudomonas aeruginosa* isolates to ciprofloxacin continue to decline, reaching 10.1% in 2011. *P. aeruginosa* isolates continue to be highly susceptible (>95%) to tobramycin, piperacillin, ceftazidime and gentamicin.
- *Mycobacterium tuberculosis* isolates that demonstrate multiple-drug resistance (MDR; resistance to both isoniazid and rifampin) were found in 10 cases over 6 years, representing 0.7% of cases. Mono-resistance occurred in 8.6% of cases while poly-resistance was noted in 2.2% of cases over all years. There are no cases of extensively drug resistant TB (XDR) cases in BC from 2005 to 2010.
- The overall antibiotic utilization rate has decreased after 2005, due to drops in 2006 and 2009, arresting an upward trend seen between 2002 and 2005.
- Penicillins constitute the majority of antimicrobial prescriptions with a rate of 5.3 defined daily doses (DDD)/1000 inhabitant-days in 2010. Penicillins are followed by macrolides, tetracyclines, quinolones, cephalosporins, other antibacterials and finally sulfonamides and trimethoprim.
- Within the β-lactam class, there had been a significant increase in the use of penicillins with β-lactamase inhibitors until the rate plummeted in 2010. β-lactamase resistant penicillins decreased from 1996 to 2009, but saw a small increase in 2010. β-lactamase sensitive penicillins have continued the decreasing trend with a large drop in 2010. Cephalosporin utilization rate remains high, although the rate has been decreasing since 2007. Although first and second generation cephalosporins have decreased since 2007, third generation cephalosporins had a large percentage increase in 2010; however, the rate remains low.
- Macrolide utilization of clarithromycin continues to increase while erythromycin utilization has significantly decreased since 1996. Utilization of azithromycin has decreased since 2007, reversing the increasing trend seen since 1996. Lincosamide utilization of clindamycin has increased consistently since 1996, despite stabilization from 2007 to 2009.

- The fluoroquinolones subclass continues to be the major contributor to the increase in quinolone utilization. Ciprofloxacin remains the most common within the fluoroquinolones subclass. The utilization rate for fluoroquinolones has decreased since 2007; however, even though all other fluoroquinolones have decreased in utilization since 2007 (disregarding ciprofloxacin the use of fluoroquinolones has been decreasing since 2004), moxifloxacin has consistently increased since introduction in 2000, and has had the second highest quinolone utilization since 2003.
- Combinations of sulfonamides and trimethoprim, including derivatives, saw a 59% decrease in utilization from 1996 to 2010.

Conclusion

In the past year, antimicrobial utilization remained relatively stable; however, continued surveillance of this, as well AMR trends in BC are necessary to ascertain the trend and to guide control efforts. The compilation of this report would not be possible without the provision of data from both provincial and national collaborators. Continued collaboration with these and additional data providers will be necessary to monitor changes in AMR trends in subsequent years.

Introduction

Objective

This report aims to describe trends in antimicrobial resistance (AMR) in the province of British Columbia (BC) for all years where data are available. For specific antimicrobial classes, data are also presented for antimicrobial utilization rates.

Background

Bacterial strains that acquire resistance to one or more first-line antimicrobials pose numerous challenges to healthcare, including: increased patient morbidity and mortality, increased drug costs, prolonged illness duration, and more expensive disease control measures (1). These antimicrobial resistant (AMR) strains arise, in part, as a result of antimicrobial use that selects for resistant organisms (1). Inappropriate antimicrobial use therefore contributes unnecessarily to the rise in resistance. In addition to the use of antimicrobials in the human population, the use of antimicrobials in food-producing animals for prophylaxis, treatment, and growth promotion purposes also contributes to the growing antimicrobial selection pressure on the microbial community (1).

Because AMR genes can be readily transmitted through a bacterial population, surveillance of AMR trends is critical for the rapid detection of new isolates and continuous monitoring of disease prevalence (1). This report aims to provide a comprehensive overview of AMR prevalence in BC and to correlate the trends with antimicrobial utilization rates. It is an update of the annual report “Antimicrobial Resistance Trends in the Province of British Columbia” prepared at the BC Centre for Disease Control since 2006. Data presented in this report may differ from previous years due to additional information regarding changes in testing methods or number of isolates tested. The most current report should be considered the most accurate.

Methods

The data sources used for the compilation of this report are discussed below. The specific bacterial species provided by each data source are indicated. With the exception of BC Biomedical Laboratories and the BCCDC Public Health and Reference Microbiology Laboratory (BCCDC PHRML), all data sources used the microbroth dilution method in accordance with the Clinical Laboratory Standards Institute (CLSI) guidelines. BC Biomedical Laboratories used a combination of agar dilution, Kirby-Bauer, Etest, and D-test methods in accordance with current CLSI guidelines. BCCDC PHRML uses the Etest method in accordance with current CLSI guidelines.

Wherever possible, data are presented for both resistant and intermediate isolates. Unless otherwise indicated, all other presented data combine both resistant and

intermediate percentages, and are referred to as the percent of isolates non-susceptible to the specific antimicrobial.

Data were analyzed using Microsoft Office Excel 2003 and SPSS 14.0 for Windows. Where appropriate, correlations between AMR trends and antimicrobial utilization were determined using the two-sided Spearman Rank test. The significance level for this report was set at α=0.05. Antimicrobial utilization typically precedes the selection of AMR phenotypes. Some literature correlates resistance data to utilization data from 1-24 months prior to account for this lag; however, the data presented in this report are not lagged due to the lack of information necessary to make specific claims. This potential lag time should be kept in mind when interpreting correlations between AMR trends and antimicrobial utilization.

Data Sources

BC Biomedical Laboratories

***Escherichia coli, Enterococcus* spp.*, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia* spp.*, Providencia* spp.*, Morganella* spp.*, Citrobacter* spp.*, Enterobacter* spp.*, Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus,* methicillin-resistant *Staphylococcus aureus* (MRSA), *Haemophilus influenzae*, *E. coli* and *K. pneumoniae* isolates with phenotype compatible with ESBLs**

BC Biomedical Laboratories collected isolates from 45 community-based patient service centres located throughout the Lower Mainland of BC. Due to the clustering of patient services centres in the Vancouver Coastal and Fraser Health Authorities, isolates may not be representative of the entire province. BC Biomedical Laboratories published empiric therapy antibiograms from which earlier data for this report were obtained. For years 1999 and 2002, the percent of isolates for each organism susceptible to a particular antimicrobial was reported in yearly aggregated form. If susceptibility data are similar between years, a new antibiogram is not published for the subsequent year. Therefore antibiograms were only available for years 1999, 2002, 2007 and 2011. The 2011 empiric therapy antibiogram is currently available on the BC Biomedical Laboratories' website (2). Since 2007, anonymous monthly datasets which included all tested isolates were provided to the DBND program in BC for analysis. The data shown for *E. coli* and *K. pneumoniae* isolates with phenotype compatible with ESBLs in the present report were not provided directly from the BC Biomedical Laboratories. Instead, these isolates were identified based on resistance to third generation cephalosporins (e.g. ceftriaxone, cefotaxime, ceftazidime, or cefixime). However, because cephamycin results were not available, true identification of ESBL producing *E. coli* and *K. pneumoniae* isolates was not possible and an overestimation is expected. With this in mind, isolates identified based on these assumptions will be referred to as "isolates with phenotype compatible with ESBLs."

BC Association of Medical Microbiologists (BCAMM)

Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBL producing Enterobacteriaceae)

The BC Association of Medical Microbiologists (BCAMM) collects data from a representative sample of community-based and hospital-based laboratories in BC. Refer to

the BCAMM 2010 Report for a complete list of all participating laboratories (3). Note that the participating community-based laboratories include BC Biomedical Laboratories and Life Labs, which provide most of the out-patient coverage for the province. Limitations of the BCAMM data include possibly more than one isolate from the same patient being tested and included by different participating sites, re-testing of isolates at certain sites, the lack of denominator data for enterococci as they are part of normal enteric flora and often non-pathogenic, and the inability to differentiate community-acquired and hospital-acquired infections. Aggregated data were provided for years 2002 to 2010.

Canadian Bacterial Surveillance Network (CBSN)
Streptococcus pneumoniae, Haemophilus influenzae

The Canadian Bacterial Surveillance Network (CBSN) received isolates from one or more hospitals located in BC each year (nine different hospitals in total). From participating hospitals, CBSN collects a set of consecutive clinically relevant *Streptococcus pneumoniae* isolates (from any site) as well as isolates from a sterile site. Similarly, a consecutive set of *Haemophilus influenzae* isolates were collected from 2001 to 2008. Limitations that may affect the data are the collection method being from any site, and isolate submission being voluntary with only two hospitals having submitted isolates for 2010 and one for 2011. Aggregated data were available for years 1994 to 2011 for *Streptococcus pneumoniae* and 2001 to 2008 for *Haemophilus influenzae*.

Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)
Salmonella *enteritidis*

Salmonella isolates from the BC Centre for Disease Control Public Health and Reference Microbiology Laboratory (BCCDC PHRML) were forwarded to the National Microbiology Laboratory (NML) in Winnipeg, Manitoba for susceptibility testing. Only isolates from the first two weeks of each month were sent to CIPARS; consequently, the tested isolates represent approximately half of all *Salmonella* cases in BC. The twelfth edition of the Performance Standards for Antimicrobial Resistance Testing from the CLSI was used to classify minimum inhibitory concentration (MIC) breakpoints for resistance (4). Aggregated data were available for years 2003 to 2008. Data for years 2008 and 2009 were obtained from preliminary reports as final reports were not available at the time of writing.

BCCDC Public Health Microbiology & Reference Laboratory
***Neisseria gonorrhoeae,* methicillin-resistant *Staphylococcus aureus* (MRSA), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBL producing Enterobacteriaceae)**

Invasive meningococcal disease and *gonorrhoea*e infection are both reportable to the BCCDC (5). Due to the increased use of molecular methods to detect *Neisseria gonorrhoeae* infections, not all reported cases of *N. gonorrhoeae* infections are tested for antimicrobial susceptibility. In the present report, data for *N. gonorrhoeae* are based on cultures submitted for gonorrhea testing from 1991 to 2011. There was a change in reporting systems in 2006, so data from 1991-2005 are from a different system than data from 2006-2010. Data from 2006 are missing for January 1 – March 8. Susceptibility testing for *N. gonorrhoeae* is performed at BC PHMRL using the Etest assay (bioMérieux).

Since the fall of 2010, the BCCDC Public Health Microbiology & Reference Laboratory implemented genotypic methods for testing Enterobacteriaceae isolates in order to confirm antibiotic susceptibility profiles for isolates with unusual phenotypic profiles submitted from front-line microbiology laboratories. In particular, the BCCDC PHRML looks for gene targets associated with ESBL (SHV, TEM, CTX-M and OXA-1), AmpC (CMY-2, CMY-1/MOX, CMY-2/LAT, DHA, ACC, MIR/ACT and FOX) and carbapenem (KPC, NDM, IMP and VIM) resistance. These data are reported in the BCAMM report.

Clinical Prevention Services, BC Centre for Disease Control (BCCDC)
Public Health Microbiology & Reference Laboratory (PHMRL)
Mycobacterium tuberculosis

Data from 2005 to 2008 are obtained from the 2005-2008 Tuberculosis Report (6), and data from 2006 to 2010 are provided by PHMRL via Clinical Prevention Services. The Clinical Prevention Services division at the BCCDC is informed of tuberculosis cases directly from providers and laboratories throughout the province. All new cases of TB with confirmatory testing in BC and bacterial isolate available (approximately 80% of all cases) are tested for susceptibility against anti-tuberculosis agents. Data used for analysis are extracted from iPHIS (Integrated Public Health Information System). Drug resistance is noted for isolates that were mono-resistant, multi-drug resistant (MDR-TB) and poly-resistant.

National Centre for Streptococcus (NCS)
Integrated Public Health Information System (iPHIS)
***Streptococcus pyogenes* (Group A Streptococcus)**

In BC, all reported cases of invasive streptococcal disease were documented in the Integrated Public Health Information System (iPHIS) at the BCCDC. 2009 NCS susceptibility data for *Streptococcus pyogenes* were linked to cases documented in iPHIS. *S. pyogenes* isolates were classified as invasive based on assigned disease code from the iPHIS database.

PharmaNet
Antimicrobial Utilization Data

PharmaNet collects all the individual prescription medications dispensed to BC residents by retail pharmacies, including online pharmacies. This provides the ability to analyze the utilization at population level. Anonymized antimicrobial utilization data were analyzed by a BCCDC statistician. Antimicrobial utilization was measured as the defined daily dose (DDD) per 1000 inhabitants per day in accordance with World Health Organization (WHO) guidelines using the Anatomical Therapeutic Classification (ATC) 2011 Index. BC population estimates and projections were obtained from BC Stats, the BC Ministry of Labour and Citizens' Services. Population estimates were prepared using the Generalized Estimation System (GES) and population projections were prepared from the Population Extrapolation for Organizational Planning with Less Error Projection 35 (P.E.O.P.L.E. 35). Data were available from January 1996 to December 2010 and were aggregated by year.

Antimicrobial Resistance (AMR) Trends

Gram-positive Organisms

1.1. Staphylococcus aureus

Data Source(s)

BC Biomedical Laboratories

BC Association of Medical Microbiologists (BCAMM)

Canadian Nosocomial Infection Surveillance Program (CNISP)

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are the most prevalent and most clinically important form of antimicrobial resistance among the staphylococci. MRSA existence was reported as early as 1964 in the United States and United Kingdom, and nosocomial outbreaks were becoming common by the late 1970's (7). The first major report of MRSA in BC was an outbreak in a Vancouver teaching hospital in 1981 (7). Although MRSA infections were traditionally only acquired in the hospital setting, community-associated MRSA (CA-MRSA) strains have become prevalent in recent years (8). Hospital-associated MRSA (HA-MRSA) infections are typically resistant to multiple classes of antimicrobials in addition to β-lactam antimicrobials due to the presence of multiple antimicrobial resistance (AMR) genes in their SCCmec gene cassette (8-13). CA-MRSA and HA-MRSA strains are microbiologically different and both strains are now transmitted in both settings (11;12). The setting of infection was not determined for the purpose of this report. This report refers to methicillin-susceptible *S. aureus* as MSSA, which represents all strains of *S. aureus* that are susceptible to the β-lactam class of antibiotics.

In Canada, the Canadian Nosocomial Infection Surveillance Program (CNISP) has monitored the prevalence of MRSA from 1995 to 2007. CNISP reports that the overall incidence of both MRSA colonization and MRSA infection increased from 0.65 to 11.04 cases per 10,000 patient-days during the 1995-2007 period (10). CNISP also reports that infection with community associated MRSA strains rose significantly from 6 percent in 1995 to 23 percent in 2007 (10). In the CANWARD study, 18,538 isolates were collected from Canadian tertiary hospitals from 2007 to 2009 (8). Of the 18,538 isolates, 3589 were *S. aureus*, 899 (25.0%) were identified as MRSA, and of those 224 (25.2%) were found to be CA-MRSA, while 644 (72.4%) were found to be HA-MRSA (8). CANWARD found that in BC and Alberta, the proportion of CA-MRSA is even higher at 34% with HA-MRSA at 66% (8). Treatment options for MRSA strains are both clinically and economically challenging. Goetghebeur *et al.* estimated that the total cost of controlling MRSA infections in Canada averaged $82 million in 2004 and could reach $129 million in 2010 (14).

Studies have shown that MRSA positive for the Panton-Valentine leukocidin (PVL) genes are more virulent than their hospital-associated counterparts (8;11-13). According to the CANWARD study, 98.2% of CA-MRSA contained the SCC*mec* type IVa gene, while 89.7% of CA-MRSA were positive for the PVL gene out of 224 CA-MRSA isolates in 2007-2009 (8). The same study found that only 1.9% of HA-MRSA contained the SCC*mec* type IVa gene, while 0.5% of HA-MRSA were positive for the PVL gene out of 644 HA-MRSA isolates (8). According to CANWARD, the majority of CA-MRSA isolates have a pulse-field gel electrophoresis (PFGE) pattern corresponding to the CMRSA-10 (USA300) group with a small proportion of the isolates having a PFGE pattern corresponding to the CMRSA-7 (USA400) group (8). CANWARD also found that 83.5% of HA-MRSA had a PFGE corresponding with the CMRSA-2 group (8).

Results

According to data from BC Biomedical Laboratories, the proportion of all *S. aureus* isolates resistant to methicillin (MRSA) steadily increased from 7.2% in 2002 to a peak of 30.5% in 2007 (*Figure 1*). The percent of MRSA isolates dropped to 16.1% in 2008, but has since fluctuated between 23.9% and 27.9% (*Figure 1*). According to the BCAMM data, which includes both hospital and community laboratory data, the proportion of MRSA in all *S. aureus* isolates increased from 9.1% in 2002 to a peak of 23.0% in 2006 (*Figure 1*). This figure lowered to 17.1% in 2010 (*Figure 1*). Data from both the BC Biomedical Laboratories and BCAMM show similar MRSA proportions until 2009, after which BCAMM shows a continued decrease, while BC Biomedical Laboratories reports an increasing proportion through 2010. This may in part be due to the increased prevalence of community associated MRSA, which is likely represented in greater proportions within the BC Biomedical Laboratories' dataset.

According to data from BC Biomedical Laboratories, the proportion of isolates resistant to clindamycin, erythromycin, and trimethoprim-sulfamethoxazole (TMP-SMX) was considerably higher for MRSA isolates compared to methicillin-susceptible *S. aureus* (MSSA) isolates (*Figure 2*). Among MRSA, resistance to clindamycin and to TMP-SMX declined from 2002 to 2011, in keeping with the increasing role of CA-MRSA (*Figure 2*). Resistance to erythromycin has also decreased from 2005 to 2011. In 2011, more than 95% of MRSA isolates continued to be susceptible to vancomycin and mupirocin (data not shown). Among MSSA, resistance to clindamycin and erythromycin has stayed stable from 2002 to 2011, but resistance to TMP-SMX decreased during this period, reaching 0.8% in 2011 (*Figure 2*). In 2011, as expected, MRSA isolates were 99.9% resistant to cephalothin, while MSSA isolates were 99.8% susceptible.

Cellulitis and Abscess

The age standardized rate of physician visits for skin infections and cellulitis and abscess decreased between 1997-2000, subsequently increased until a peak of 73.8 visits/1000 population in 2006, and afterwards decreased slightly through 2008 (*Figure 3*). The most likely explanation for such an increase is the spread of CA-MRSA during this decade. These data were provided by BC Ministry of Health and were derived from MSP billings coded for 682 – cellulitis and abscess.

Discussion

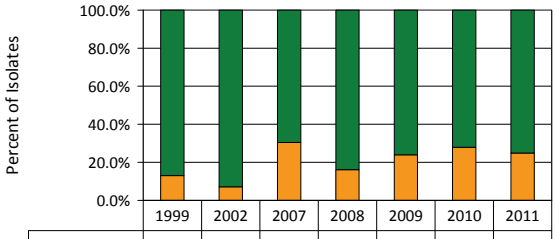
MRSA now makes up 24.9% of all *S. aureus* isolates according to data from BC Biomedical Laboratories and 17.1% in both BC community and hospital labs, according to the BCAMM report. The decrease in non-susceptibility rates for most of the tested antimicrobials between 2002 to 2010 reflects an increased proportion of CA-MRSA strains, which are typically more susceptible to antimicrobials than their hospital-associated counterparts (8-13). The CANWARD study found that while 85.6% and 27.8% of HA-MRSA were susceptible to TMP-SMX and clindamycin respectively, 100% and 86.1% of CA-MRSA were susceptible to the same drugs (8;15). Similar relations were found with several other antibiotics (8;15).

β-lactamase resistant penicillins remain an effective treatment option for MSSA infections. The majority of MSSA isolates remain susceptible to TMP-SMX while resistance trends for clindamycin and erythromycin remain relatively stable since 2002.

Treatment options for MRSA isolates are more limited; however, the majority of MRSA isolates remain susceptible to vancomycin, mupirocin as well as TMP-SMX. CA-MRSA isolates should be managed according to susceptibility results if antibiotic treatment is required.

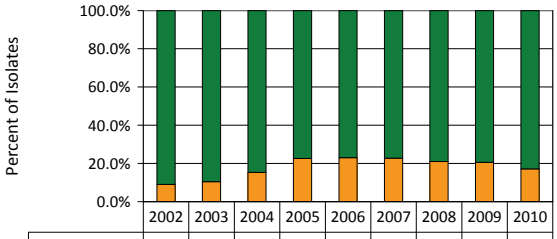
The rate of physician visits for cellulitis and abscess should continue to be watched as the general increasing trend may be attributed to CA-MRSA prevalence.

BC Biomedical



	1999	2002	2007	2008	2009	2010	2011
MSSA	87.0%	92.8%	69.5%	83.9%	76.1%	72.1%	75.1%
MRSA	13.0%	7.2%	30.5%	16.1%	23.9%	27.9%	24.9%
Total Isolates	NA	4587	2336	1070	1676	1880	1464

BCAMM



	2002	2003	2004	2005	2006	2007	2008	2009	2010
MSSA	90.9%	89.6%	84.7%	77.4%	77.0%	77.3%	79.0%	79.4%	82.9%
MRSA	9.1%	10.4%	15.3%	22.6%	23.0%	22.7%	21.0%	20.6%	17.1%
Total Isolates	27641	29991	33079	39471	43694	50226	52604	48126	47220

Figure 1 Percent of *Staphylococcus aureus* isolates methicillin-sensitive (MSSA) and methicillin-resistant (MRSA)

Source: BC Biomedical Laboratories; BCAMM (3)

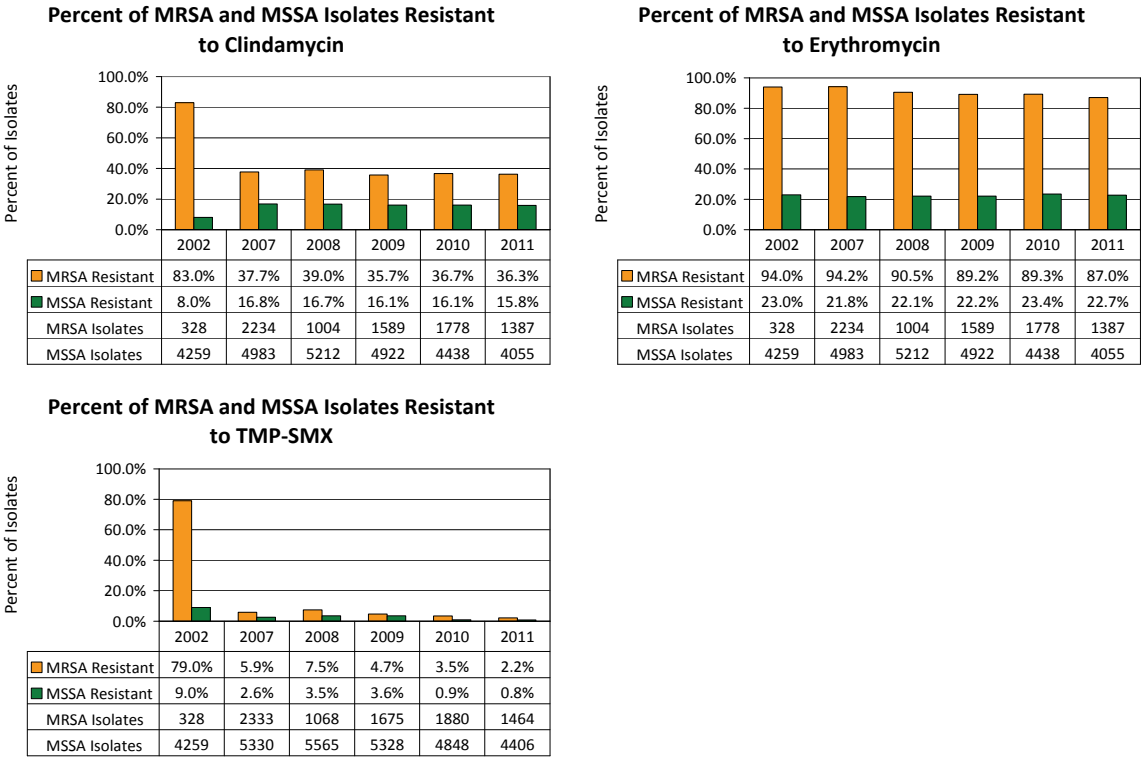


Figure 2 Percent of MRSA and MSSA isolates resistant to clindamycin, erythromycin and trimethoprim-sulfamethoxazole (TMP-SMX)

Source: BC Biomedical Laboratories

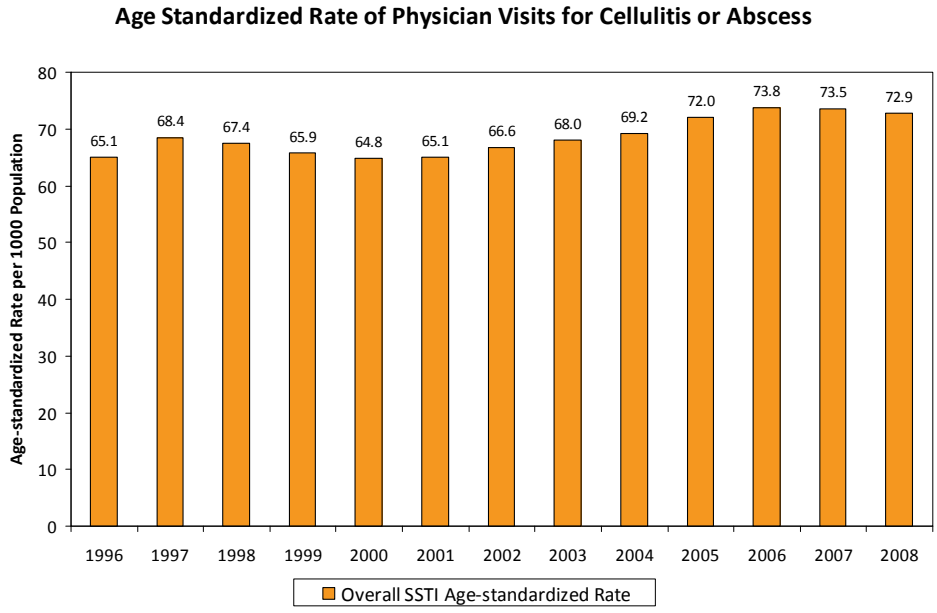


Figure 3 Age standardized rate of physician visits for patients presenting with cellulitis or abscess

Source: BC Ministry of Health, MSP Claims Data

1.2. Streptococcus pneumoniae

Data Source(s)

BC Biomedical Laboratories

Canadian Bacterial Surveillance Network (CBSN)

Background

Streptococcus pneumoniae (pneumococcus) is the leading cause of community acquired pneumonia (CAP), but also commonly presents as acute otitis media, bacteremia, and meningitis. Treatment for pneumococcal infections typically includes β-lactams, macrolides and tetracycline (See Bugs & Drugs 2006 edition for the full list) (16). Resistance to penicillin first began to emerge in the mid-1960s, with the first penicillin-resistant isolate in BC being reported in 1993 (17). Resistance to these drug classes is now prevalent in Canada, particularly in children under the age of five and adults over the age of sixty-five(16;18;19).

Results

According to BC Biomedical Laboratories data, 3.0% of *Streptococcus pneumoniae* were resistant to penicillin in 2011 despite a drop from 6.5% 2007 to 0.9% 2010, while isolates testing intermediate decreased to 15.0% in 2011 after reaching a peak of 20.7% in 2010 (*Figure 4*). Therefore, although *S. pneumoniae* non-susceptibility remained high, the percent of isolates that were resistant to penicillin actually decreased significantly since 2002. The proportion of *S. pneumoniae* non-susceptible to erythromycin remained stable around 30% from 2007 to 2011 (*Figure 4*). A large but inconsistent increase in non-susceptibility was observed for clindamycin from 2.0% in 1999 to 19.7% in 2009, but has dropped to 14.9% in 2011 (*Figure 4*). Meanwhile, non-susceptibility towards TMP-SMX decreased from a peak of 66% in 2008 to 16.1% in 2007, but inconsistently increased since then to 23.8% in 2011 (*Figure 4*).

Data from the CBSN indicated a substantial overall increase in the percent of isolates non-susceptible to clindamycin, ceftriaxone (non-meningitis breakpoint), tetracycline, and erythromycin between the years 1994 to 2009. Since then, there has been an increase in susceptibility to ceftriaxone and clindamycin, while erythromycin and tetracycline non-susceptibility dropped slightly, but remained relatively high in 2011 (*Figure 5*). From 2006 to 2009, using the oral penicillin breakpoints, an increase was observed in the percent of isolates non-susceptible to penicillin, followed by a large decrease in 2010 and 2011 (*Figure 5*). TMP-SMX non-susceptibility remained stable just above 25.0% in 2011 (*Figure 5*). Resistance to moxifloxacin was similar, but slightly less than resistance to levofloxacin for most years with nearly 1.5% of *S. pneumoniae* isolates showing resistance to moxifloxacin and to levofloxacin in 2011 (*Figure 5*).

Discussion

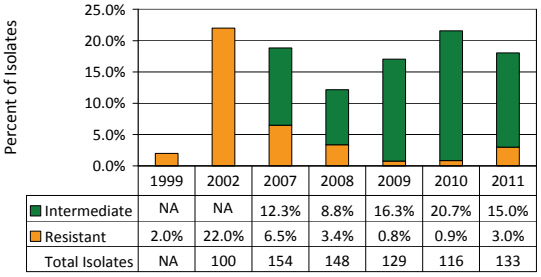
CBSN data indicate that *S. pneumoniae* isolates demonstrated overall increasing resistance trends to erythromycin and clindamycin until 2009, but since then both rates have decreased. CBSN data also showed an increasing trend for resistance to ceftriaxone and tetracycline from 1994 to 2010, followed by sharp decreases in 2011, while TMP-SMX

non-susceptibility remained stable. Even though penicillin non-susceptibility rates have fluctuated in earlier years, recent years displayed an increasing trend to 2009 followed by a sharp decline in 2010 and 2011.

BC Biomedical Laboratories data indicated that penicillin non-susceptibility have oscillated over recent years. TMP-SMX resistance has remained relatively constant since a large drop after 1999, erythromycin has stabilized and clindamycin resistance is beginning to drop after an increasing trend; these data are semi-consistent with CBSN data.

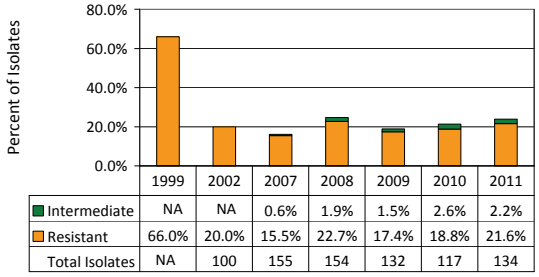
Discrepancies between the two sources may be due to the differences in the site of data collection. BC Biomedical Laboratories collects isolates from community sources throughout the Lower Mainland of BC while CBSN obtains isolates from several hospitals inside and outside the Lower Mainland. For 2010 and 2011, susceptibility results from one and two hospitals were available at time of publication for CBSN. Intermediate data previous to 2007 were unavailable from BC Biomedical Laboratories.

Percent of *S. pneumoniae* Isolates Non-Susceptible to Penicillin



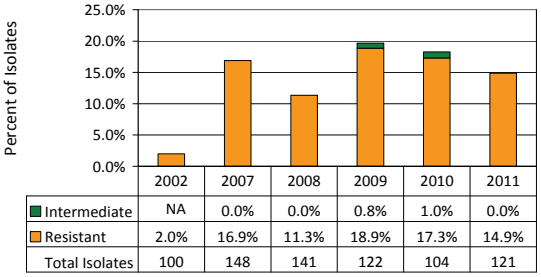
	1999	2002	2007	2008	2009	2010	2011
Intermediate	NA	NA	12.3%	8.8%	16.3%	20.7%	15.0%
Resistant	2.0%	22.0%	6.5%	3.4%	0.8%	0.9%	3.0%
Total Isolates	NA	100	154	148	129	116	133

Percent of *S. pneumoniae* Isolates Non-Susceptible to TMP-SMX



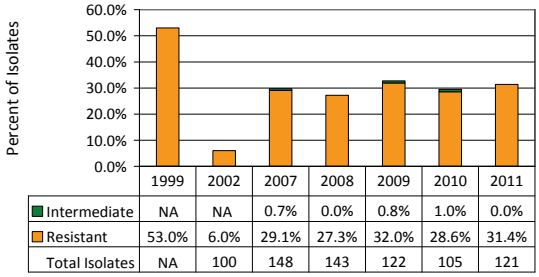
	1999	2002	2007	2008	2009	2010	2011
Intermediate	NA	NA	0.6%	1.9%	1.5%	2.6%	2.2%
Resistant	66.0%	20.0%	15.5%	22.7%	17.4%	18.8%	21.6%
Total Isolates	NA	100	155	154	132	117	134

Percent of *S. pneumoniae* Isolates Non-susceptible to Clindamycin



	2002	2007	2008	2009	2010	2011
Intermediate	NA	0.0%	0.0%	0.8%	1.0%	0.0%
Resistant	2.0%	16.9%	11.3%	18.9%	17.3%	14.9%
Total Isolates	100	148	141	122	104	121

Percent of *S. pneumoniae* Isolates Non-Susceptible to Erythromycin

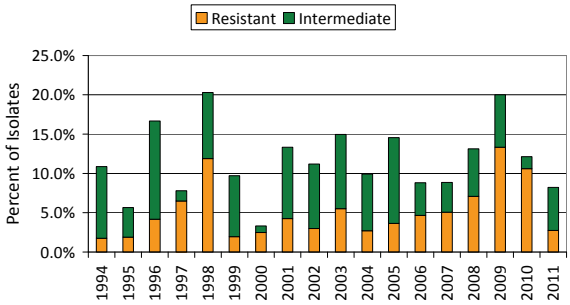


	1999	2002	2007	2008	2009	2010	2011
Intermediate	NA	NA	0.7%	0.0%	0.8%	1.0%	0.0%
Resistant	53.0%	6.0%	29.1%	27.3%	32.0%	28.6%	31.4%
Total Isolates	NA	100	148	143	122	105	121

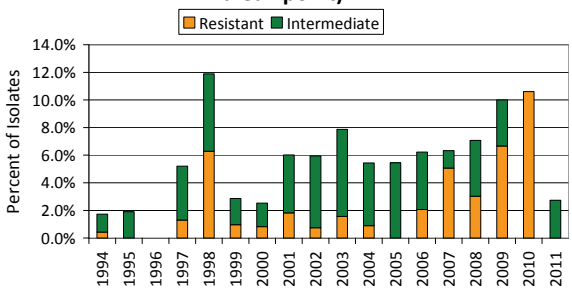
Figure 4 Percent of *Streptococcus pneumoniae* isolates non-susceptible to penicillin, trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, and erythromycin

Source: BC Biomedical Laboratories

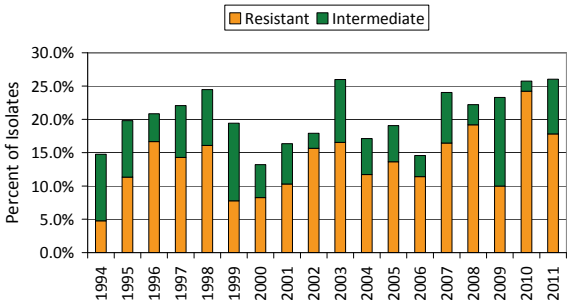
Percent of *S. pneumoniae* Isolates Non-susceptible to Penicillin



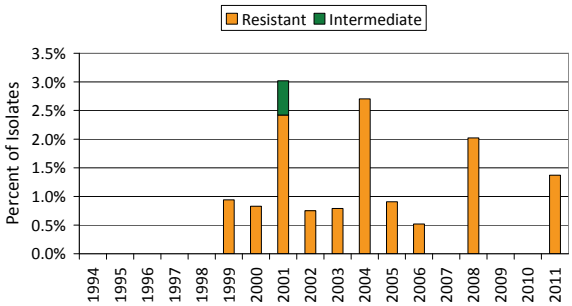
Percent of *S. pneumoniae* Isolates Non-susceptible to Ceftriaxone (non-meningitis break point)



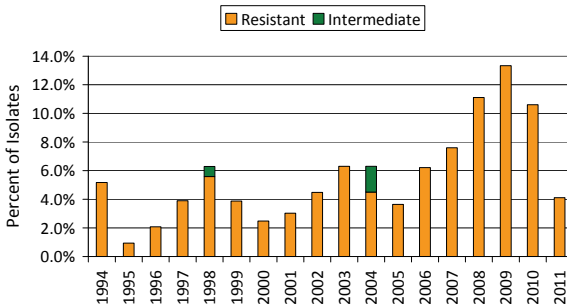
Percent of *S. pneumoniae* Non-susceptible to TMP-SMX



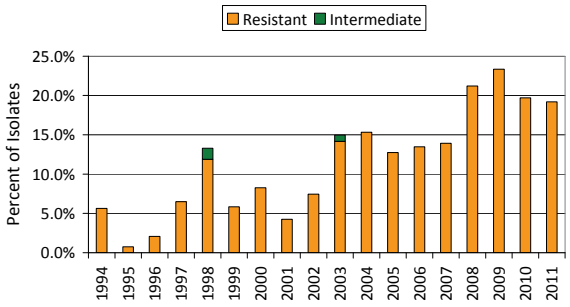
Percent of *S. pneumoniae* Isolates Non-susceptible to Levofloxacin



Percent of *S. pneumoniae* Isolates Non-susceptible to Clindamycin



Percent of *S. pneumoniae* Non-susceptible to Erythromycin



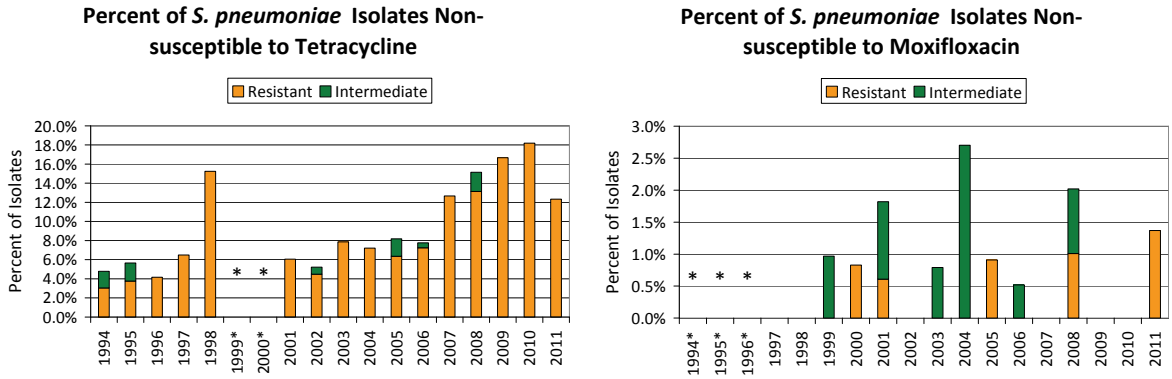


Figure 5 Percent of *Streptococcus pneumoniae* isolates non-susceptible to penicillin, ceftriaxone, ciprofloxacin, levofloxacin, TMP-SMX, erythromycin, clindamycin, moxifloxacin and tetracycline

*Fewer than 40 isolates tested

Source: CBSN

Table 1 Number of *Streptococcus pneumoniae* Isolates Tested Against Antibacterial Agents

Year	All Other Antibacterials†	Ciprofloxacin and Levofloxacin	Moxifloxacin	Tetracycline	Clindamycin
1994	230	224	0	230	58
1995	106	106	0	106	106
1996	48	48	0	48	48
1997	77	77	77	77	77
1998	143	143	143	118	143
1999	103	103	103	0	103
2000	121	121	121	1	121
2001	165	165	165	165	165
2002	134	134	134	134	134
2003	127	127	127	127	127
2004	111	111	111	111	111
2005	92	92	92	92	92
2006	189	189	189	189	189
2007	79	79	79	79	79
2008	100	100	100	100	100
2009	95	95	95	95	95
2010	66	66	66	66	66
2011	73	73	73	73	73

†"All Other Antibacterials" includes penicillin, ceftriaxone, erythromycin, and trimethoprim-sulfamethoxazole

Source: CBSN

1.3. Streptococcus pyogenes

Data Source(s)

BC Biomedical Laboratories

National Centre for Streptococcus (NCS) and integrated Public Health Information System (iPHIS) linked dataset

Background

Streptococcus pyogenes, also known as β-hemolytic Group A Streptococci (GAS), typically presents as a relatively mild, non-invasive throat infection ("Strep throat"), but can also cause more serious invasive infections including necrotizing fasciitis and toxic shock syndrome. Recommended therapies for GAS infections include penicillin, erythromycin, and clindamycin (15). Erythromycin-resistant isolates of *S. pyogenes* were first documented in the United Kingdom during the 1950s (20).

Two main *S. pyogenes* phenotypes are typically associated with resistance against macrolide (e.g. erythromycin) antimicrobials. MLS_B strains encode a ribosomal modification gene (*erm*) that confers decreased susceptibility to macrolides, lincosamides, and streptogramin B (21;22). A second resistance mechanism against macrolides is associated with the M phenotype, which encodes an efflux system (*mef*) for macrolide antimicrobials (21;22). Due to the duplicate resistance mechanisms against macrolides, it is not surprising that erythromycin is the most documented antimicrobial for which GAS acquires resistance.

Results

BC Biomedical Laboratories data include both invasive and non-invasive GAS isolates for all years available. All isolates remained susceptible to penicillin as of 2011 (data not shown). The percent of isolates non-susceptible to erythromycin decreased since 2007, but jumped to a peak of 14.7% in 2011 (*Figure 6*). Clindamycin non-susceptibility has been very similar to erythromycin non-susceptibility for all years, although the increase in 2011 was more modest and so remains at 11.9% as determined by the double disk diffusion test (D-test) (*Figure 6*). The D-test determines whether clindamycin non-susceptibility can be induced when *S. pyogenes* bacteria are grown in the presence of erythromycin.

Due to withdrawal of federal funding, data from the National Centre for Streptococcus (NCS) were unavailable at time of writing. Therefore, linking of NCS data to integrated Public Health Information System (iPHIS) was not possible. No other provincial sources of susceptibility data specifically for invasive GAS were available for 2010 or 2011. As such, this report only shows invasive GAS data prior to 2010.

From previous years' data, it was found that 100% of invasive isolates remained susceptible to vancomycin and chloramphenicol (data not shown). Resistance to erythromycin peaked in 2005 at 26.4% before decreasing to 5.4% in 2009 (*Figure 7*). After displaying consecutive decreases in previous years, resistance to clindamycin increased in 2009 to 4.6% (*Figure 7*). The increase in clindamycin resistance does not resonate with the decrease in clindamycin resistance observed from the BC Biomedical Laboratories data.

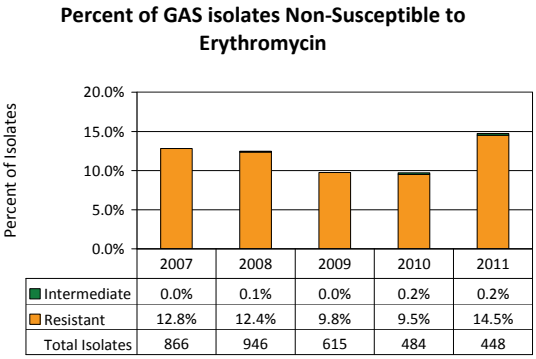
Although the NCS implemented the D-test for inducible clindamycin resistance, results were not included within the provided dataset.

Discussion

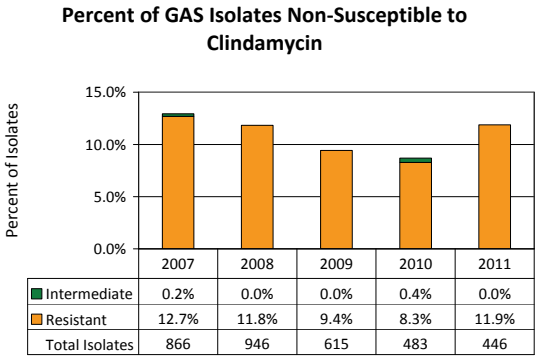
According to data from BC Biomedical Laboratories, until a spike in 2011 erythromycin-inducible clindamycin non-susceptibility rates had witnessed a decreasing trend amongst *S. pyogenes* isolates. All isolates remain susceptible to penicillin in 2011.

Both the BC Biomedical Laboratories data and the NCS-iPHIS linked data show decreased erythromycin resistance in 2009. The decreasing trend observed may be due to increased usage of newer macrolides in replacement of erythromycin, an older macrolide.

There are several observable differences between the BC Biomedical Laboratories data and the NCS-iPHIS linked data. Observable differences may be due to the fact that BC Biomedical Laboratories data include both invasive and non-invasive GAS isolates while the NCS-iPHIS data only included invasive GAS data. Also, the number of isolates from the NCS-iPHIS source is much lower compared to the BC Biomedical Laboratories data. Literature frequently reports higher resistance among non-invasive streptococci (23). Moreover, BC Biomedical Laboratories clindamycin susceptibility rates were determined using the D-test method which was not available in the NCS dataset.



	2007	2008	2009	2010	2011
Intermediate	0.0%	0.1%	0.0%	0.2%	0.2%
Resistant	12.8%	12.4%	9.8%	9.5%	14.5%
Total Isolates	866	946	615	484	448

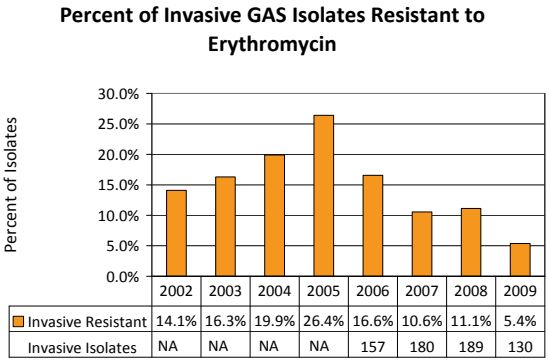


	2007	2008	2009	2010	2011
Intermediate	0.2%	0.0%	0.0%	0.4%	0.0%
Resistant	12.7%	11.8%	9.4%	8.3%	11.9%
Total Isolates	866	946	615	483	446

Figure 6 Percent of *Streptococcus pyogenes* isolates resistant to erythromycin and with inducible clindamycin non-susceptibility (as determined by the D-test in the presence of erythromycin)

Note: Sample size for years 1999 and 2002 were not sufficient due to a change in BC Biomedical Laboratories GAS testing procedure.

Source: BC Biomedical Laboratories



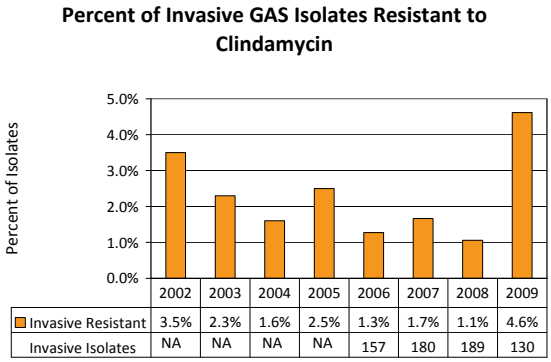


Figure 7 Percent of invasive Group A Streptococcus (iGAS) isolates non-susceptible to erythromycin and clindamycin

Source: NCS and iPHIS linked dataset

1.4. Enterococcus Spp.

Data Source(s)

BC Biomedical Laboratories

BC Association of Medical Microbiologists (BCAMM)

Background

A prominent nosocomial pathogen, enterococci, more specifically *Enterococcus faecalis* and *Enterococcus faecium*, are normal enteric flora bacteria that may cause urinary tract infections (UTIs), intra-abdominal infections, and bacteremia. Most enterococci strains are intrinsically resistant to macrolides, lincosamides, trimethoprim-sulfamethoxazole (TMP-SMX), and β-lactams including cephalosporins and some penicillins (24).

Vancomycin-resistant *Enterococcus* (VRE) was first reported in Canada in the early 1990s, with the first outbreak of VRE in Canada occurring in an Ontario hospital in 1995 (25). The Canadian Nosocomial Infection Surveillance Program (CNISP) reported that although the incidence of VRE in Canada is low, rates of VRE detection, infection, and the percentage of VRE within *Enterococcus* genus continued to increase as of 2005 (26). The CANWARD 2007-2009 study reports that Canadian VRE rates increased from 1.8% in 2007 to 4.6% in 2009 (15). Of particular concern is the increasing prevalence of VRE in the United States, as well as the ability of *Enterococcus* spp. to spread antimicrobial resistance genes to other bacterial species including methicillin-resistant *Staphylococcus aureus* (MRSA).

Results

According to BC Biomedical Laboratories data, the proportion of *Enterococcus* spp. isolates resistant to vancomycin and nitrofurantoin remained under 2% (*Figure 8*). After 2002 very little vancomycin resistance was observed until 2010 when the rate increased to 1.0% and reached a peak of 1.1% in 2011 (*Figure 8*). From 2008 to 2011, resistance towards ampicillin increased from 1.0% to 2.4% (*Figure 8*), which may be due to the increased number of *E. faecium* isolates resistant to vancomycin as these are also resistant to ampicillin. Non-susceptibility to ciprofloxacin decreased progressively from a peak of 47.0% in 2002 to 24.8% in 2011 (*Figure 8*). Nitrofurantoin resistance remained low with 1.7% of isolates displaying resistance in 2011 (*Figure 8*). All isolates are intrinsically resistant to TMP-SMX.

Between years 2002 and 2007, BCAMM estimated that the proportion of vancomycin-resistant *Enterococcus* (VRE) in BC remained less than 1% (3). While an estimate is not available for 2008-2010 due to uncertainty in the denominator, estimates for VRE in BC remained very low. BCAMM reported a 24% decrease in the number of new patients with VRE from 2008 to 2010 (3).

When resistance to ciprofloxacin of urinary *Enterococcus* isolates is broken down by age, one observes an interesting correlation; generally, as the age of the patient increases, the proportion of resistance increases (*Figure 9*). This is the same trend observed in *E. coli,* and could be explained by the general tendency that those of greater age have usually had more exposure to ciprofloxacin and other antibiotics, and therefore have had greater selection for resistance.

Discussion

The majority of *Enterococcus* spp. isolates remain susceptible to vancomycin, ampicillin and nitrofurantoin. Even though resistance towards ciprofloxacin is decreasing, approximately a fourth of *Enterococcus* spp. isolates still demonstrate ciprofloxacin non-susceptibility. The prevalence of VRE infections in BC remains very low.

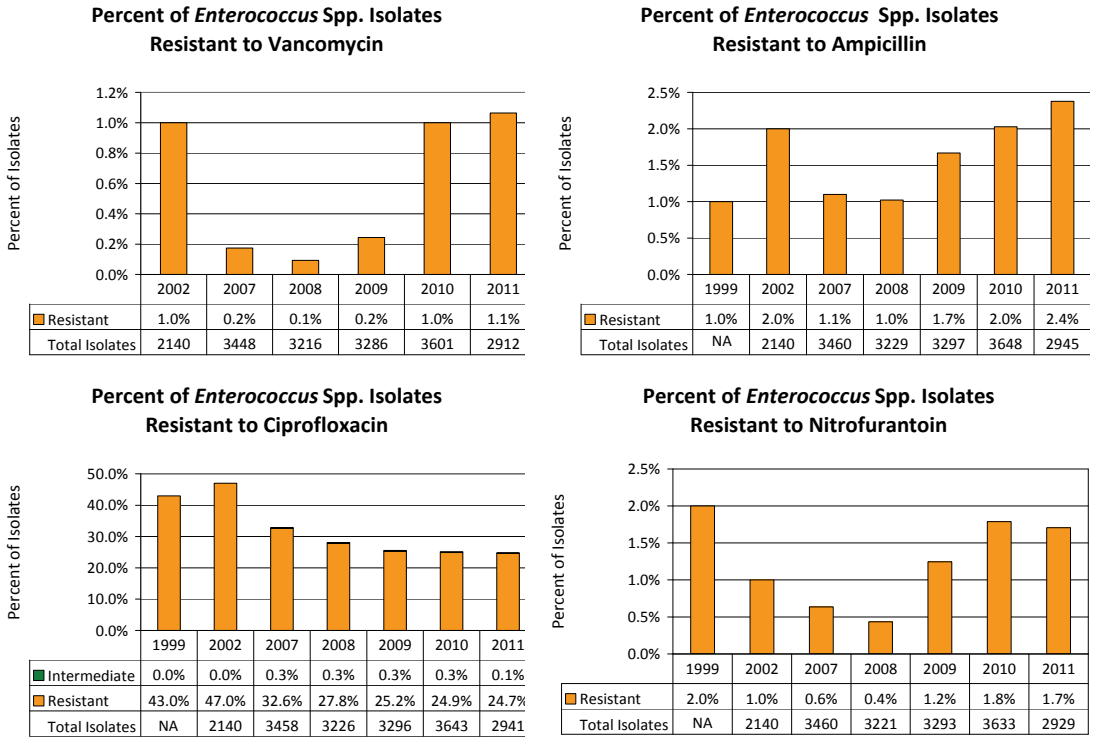
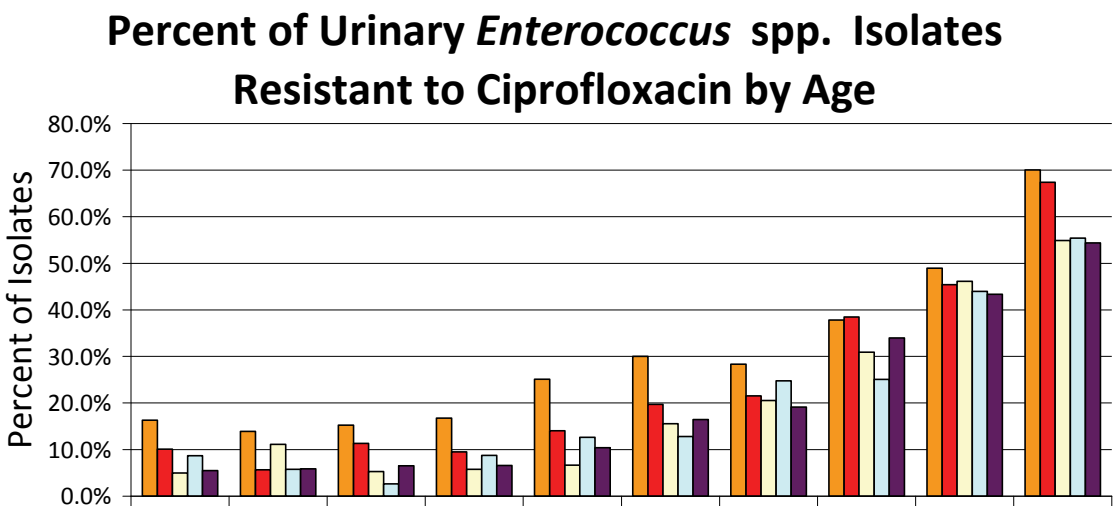


Figure 8 Percent of *Enterococcus* spp. isolates resistant to vancomycin, ampicillin and nitrofurantoin and non-susceptible to ciprofloxacin

Source: BC Biomedical Laboratories



	<10	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
2007	16.3%	13.9%	15.2%	16.8%	25.1%	30.0%	28.3%	37.8%	48.9%	70.1%
2008	10.1%	5.7%	11.4%	9.5%	14.0%	19.7%	21.5%	38.5%	45.4%	67.4%
2009	5.0%	11.1%	5.3%	5.8%	6.7%	15.6%	20.5%	30.9%	46.1%	54.9%
2010	8.7%	5.8%	2.6%	8.7%	12.7%	12.8%	24.8%	25.1%	43.9%	55.4%
2011	5.5%	5.9%	6.5%	6.6%	10.4%	16.5%	19.1%	34.0%	43.4%	54.4%

Figure 9 Percent of *Enterococcus* spp. urinary isolates non-susceptible to ciprofloxacin by age of patient

Source: BC Biomedical Laboratories

Gram-negative Organisms

1.5. Escherichia coli

Data Source(s)

BC Biomedical Laboratories

Background

Escherichia coli is a pathogen that causes sepsis, gastrointestinal infections, and approximately 85-90% of urinary tract infections (UTIs) (27). Treatment for *E. coli* infections usually consists of nitrofurantoin, TMP-SMX, fluoroquinolones or aminoglycosides (16;28). Strains of *E. coli* that produce extended spectrum beta-lactamases (ESBL), conferring resistance to the penicillins and cephalosporins, may also harbor resistance to other classes of antibiotics. In Canada, the first reported outbreak of multidrug-resistant ESBL-producing *E. coli* strains occurred in Ontario in 2000 (29). The North American Urinary Tract Infection Collaborative Alliance (NAUTICA) reports resistance against β-lactam antimicrobials, fluoroquinolones, and TMP-SMX, suggesting that alternate treatment regimes may be necessary (30).

Results

The number of *E. coli* isolates resistant to ampicillin, ciprofloxacin, TMP-SMX, and gentamicin significantly increased between years 1999 and 2011 (*Figure 10*). Among these, the highest proportion of non-susceptible isolates occurred for ampicillin, with 45.8% of isolates showing non-susceptibility in 2011 (*Figure 10*). A high proportion of non-susceptible isolates also occurred for ciprofloxacin (26.8%) and TMP-SMX (26.0%). The proportion of isolates resistant to nitrofurantoin remains near the 4.0% mark at 3.8% in 2011 (*Figure 10*).

The most noticeable increase in resistance among *E. coli* isolates occurred with ciprofloxacin, of which an almost 9-fold increase was demonstrated between 1999 and 2011 (*Figure 10*). Although the resistance rate seemed to have stabilized from years 2007 to 2009 at around 22%, the rate has since risen to 26.8% in 2011 (*Figure 10*).

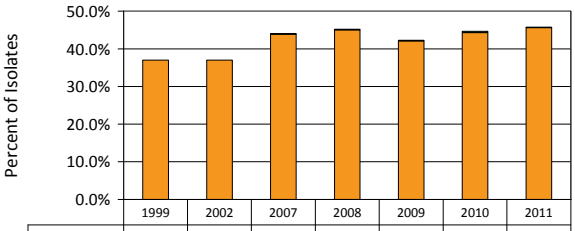
When resistance to ciprofloxacin of urinary *E. coli* isolates is broken down by age, one observes an interesting correlation; generally, as the age of the patient increases, the proportion of resistance increases (*Figure 11*). This is the same trend observed in *Enterococcus,* and could be explained by the general tendency that those of greater age have usually had more exposure to ciprofloxacin and other antibiotics, and therefore have had greater selection for resistance. The increasing E. coli resistance to ciprofloxacin is most prevalent in those above the age of 70 (*Figure 11*).

Discussion

The highest proportion of non-susceptible isolates occurred for ampicillin in 2011, but resistance has remained quite stable since 2008. Even though resistance rates have stabilized in recent years, more than 1 in 4 isolates displays resistance towards TMP-SMX. The relatively high proportion of isolates resistant to fluoroquinolone antimicrobials is a

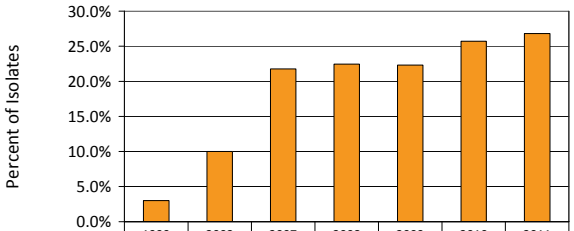
concern, most notably in those over the age of 70 years. The percent of isolates resistant to nitrofurantoin however, continues to be stable and low.

Percent of *E. coli* Isolates Non-Susceptible to Ampicillin



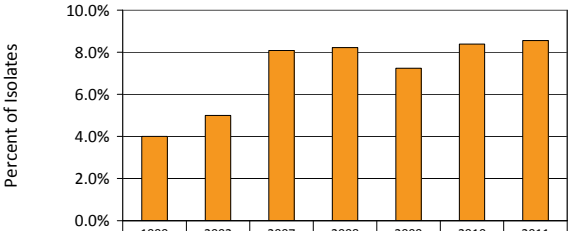
	1999	2002	2007	2008	2009	2010	2011
Intermediate	0.0%	0.0%	0.2%	0.2%	0.2%	0.3%	0.2%
Resistant	37.0%	37.0%	43.9%	45.1%	42.1%	44.3%	45.6%
Total Isolates	NA	15,000	24,363	24,568	24,849	27,511	24,444

Percent of *E. coli* Isolates Resistant to Ciprofloxacin



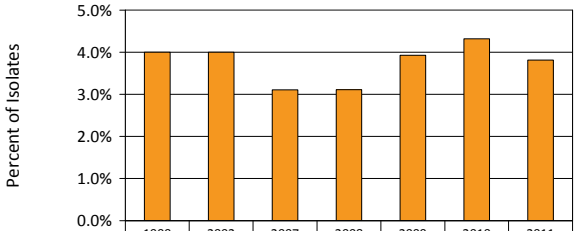
	1999	2002	2007	2008	2009	2010	2011
Resistant	3.0%	10.0%	21.8%	22.5%	22.3%	25.7%	26.8%
Total Isolates	NA	15,000	24,362	24,568	24,848	27,511	24,439

Percent of *E. coli* Isolates Resistant to Gentamicin



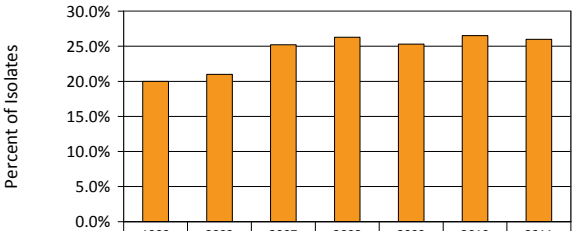
	1999	2002	2007	2008	2009	2010	2011
Resistant	4.0%	5.0%	8.1%	8.2%	7.2%	8.4%	8.6%
Total Isolates	NA	15,000	24,361	24,565	24,847	27,511	24,446

Percent of *E. coli* Isolates Resistant to Nitrofurantoin



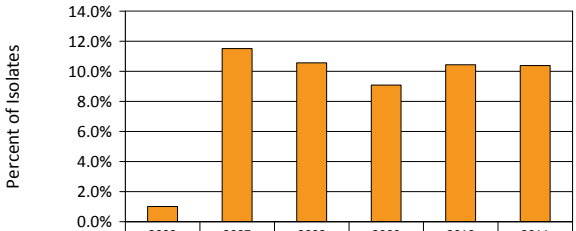
	1999	2002	2007	2008	2009	2010	2011
Resistant	4.0%	4.0%	3.1%	3.1%	3.9%	4.3%	3.8%
Total Isolates	NA	15,000	24,344	24,553	24,833	27,489	24,433

Percent of *E. coli* Isolates Resistant to TMP-SMX



	1999	2002	2007	2008	2009	2010	2011
Resistant	20.0%	21.0%	25.2%	26.3%	25.3%	26.5%	26.0%
Total Isolates	NA	15,000	24,364	24,568	24,848	27,512	24,447

Percent of *E. coli* Isolates Resistant to Third Generation Cephalosporins*

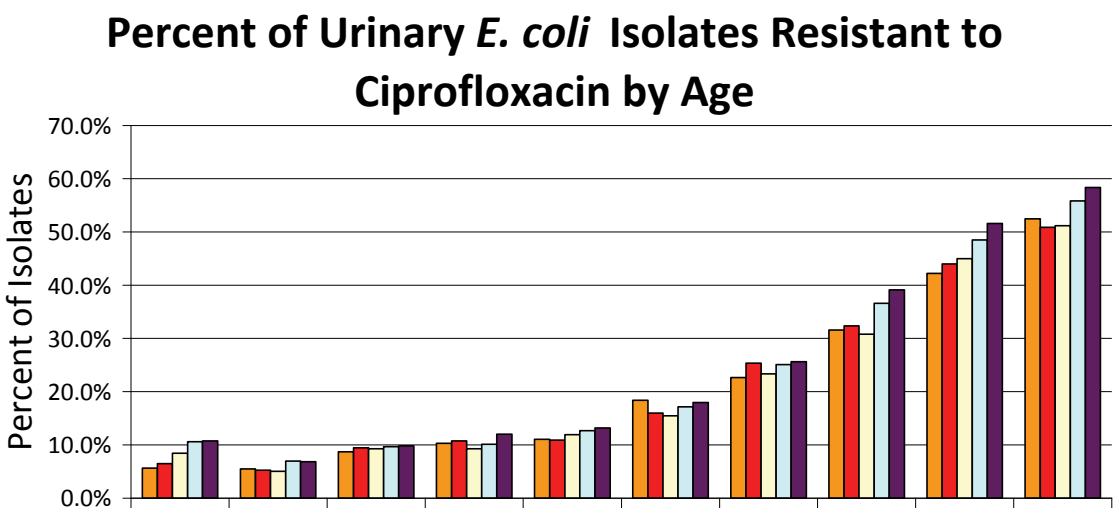


	2002	2007	2008	2009	2010	2011
Resistant	1.0%	11.5%	10.6%	9.1%	10.4%	10.4%
Total Isolates	15,000	24,348	24,560	24,848	27,510	24,448

Figure 10 Percent of *Escherichia coli* isolates resistant to ciprofloxacin, gentamicin, nitrofurantoin, TMP-SMX and third generation cephalosporins, and non-susceptible to ampicillin

*The third generation cephalosporin tested in 2002 was cefixime, while in all other years it was cefotaxime

Source: BC Biomedical Laboratories



	<10	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
2007	5.7%	5.5%	8.7%	10.3%	11.1%	18.4%	22.7%	31.6%	42.2%	52.5%
2008	6.5%	5.3%	9.5%	10.7%	10.9%	16.0%	25.3%	32.4%	44.0%	50.8%
2009	8.4%	5.0%	9.3%	9.3%	11.9%	15.5%	23.4%	30.8%	45.0%	51.2%
2010	10.6%	7.0%	9.7%	10.1%	12.7%	17.2%	25.1%	36.6%	48.5%	55.8%
2011	10.8%	6.9%	9.8%	12.0%	13.2%	18.0%	25.6%	39.1%	51.6%	58.4%

Figure 11 Percent of *Escherichia coli* urinary isolates non-susceptible to ciprofloxacin by age of patient

Source: BC Biomedical Laboratories

1.6. Klebsiella pneumoniae

Data Source(s)

BC Biomedical Laboratories

Background

Klebsiella pneumoniae, another cause of UTIs after *Escherichia coli*, can also lead to pneumonia, bacteremia, and skin and soft tissue infections (31). The majority of *K. pneumoniae* isolates associated with pneumonia remain susceptible to β-lactams, carbapenems (e.g. meropenem and imipenem), aminoglycosides (e.g. gentamicin), and fluoroquinolones (e.g. ciprofloxacin) (32). As of 2002, approximately 5% of *K. pneumoniae* isolates produced an extended spectrum β-lactamase (ESBL), conferring resistance to the penicillins and cephalosporins (32;33). *K. pneumoniae* isolates demonstrated moderate resistance to combinations of β-lactams and β-lactamase inhibitors (e.g. amoxicillin-clavulanic acid and piperacillin-tazobactam) as well as gentamicin, nitrofurantoin, and TMP-SMX (31;34).

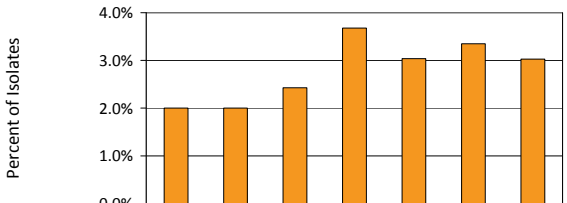
Results

The percent of isolates resistant to ciprofloxacin increased from 2.0% in 1998 to 3.7% in 2008, but that percentage has since stabilized near 3% (*Figure 12*). The percent of isolates resistant to gentamicin remained low at 1.5% in 2011 (*Figure 12*). Isolates resistant to TMP-SMX continued the decreasing trend that has occurred since 2008 to a value of 8.5% in 2011, a nadir for all available years (*Figure 12*). Resistance to nitrofurantoin decreased from a peak of 76.0% in 1999 to 50.1% in 2011 (*Figure 12*).

Discussion

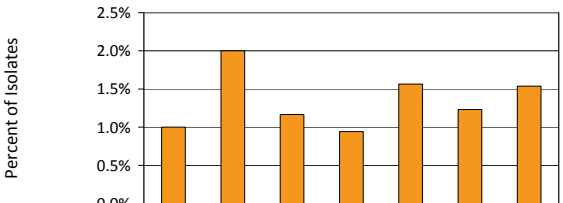
Approximately half of *Klebsiella pneumoniae* isolates tested are resistant to nitrofurantoin even though a declining trend has occurred since 1999. The percent of *K. pneumoniae* resistant to TMP-SMX have decreased in the last four years. Ciprofloxacin and gentamicin resistance remain low.

Percent of *K. pneumoniae* Isolates Resistant to Ciprofloxacin

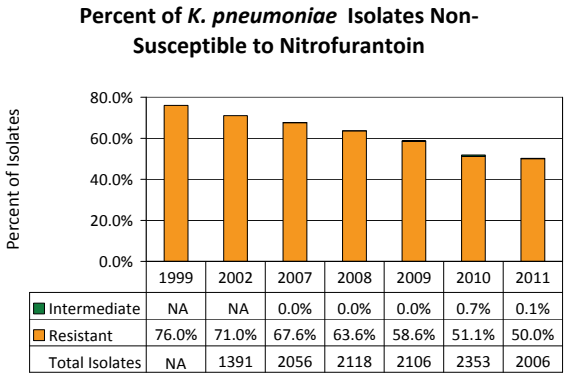


	1999	2002	2007	2008	2009	2010	2011
Resistant	2.0%	2.0%	2.4%	3.7%	3.0%	3.4%	3.0%
Total Isolates	NA	1391	2059	2121	2108	2358	2015

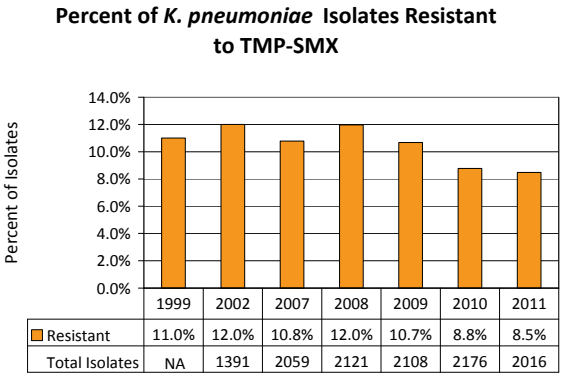
Percent of *K. pneumoniae* Isolates Resistant to Gentamicin



	1999	2002	2007	2008	2009	2010	2011
Resistant	1.0%	2.0%	1.2%	0.9%	1.6%	1.2%	1.5%
Total Isolates	NA	1391	2059	2121	2107	2358	2016



	1999	2002	2007	2008	2009	2010	2011
Intermediate	NA	NA	0.0%	0.0%	0.0%	0.7%	0.1%
Resistant	76.0%	71.0%	67.6%	63.6%	58.6%	51.1%	50.0%
Total Isolates	NA	1391	2056	2118	2106	2353	2006



	1999	2002	2007	2008	2009	2010	2011
Resistant	11.0%	12.0%	10.8%	12.0%	10.7%	8.8%	8.5%
Total Isolates	NA	1391	2059	2121	2108	2176	2016

Figure 12 Percent of *Klebsiella pneumoniae* isolates resistant to ciprofloxacin, gentamicin, nitrofurantoin, and TMP-SMX

Source: BC Biomedical Laboratories

1.7. Serratia, Providencia, Morganella, Citrobacter, and Enterobacter spp.

Data Source(s)

BC Biomedical Laboratories

Background

Serratia spp., *Providencia* spp., *Morganella* spp., *Citrobacter* spp., and *Enterobacter* spp. are collectively referred to as the SPICE organisms. Along with *Escherichia*, *Proteus*, *Klebsiella*, and *Salmonella*, these organisms belong to the *Enterobacteriaceae* family of bacteria. Most SPICE organisms are opportunistic nosocomial pathogens that commonly cause urinary tract or respiratory infections (2). SPICE organisms can produce inducible β-lactamases.

Results

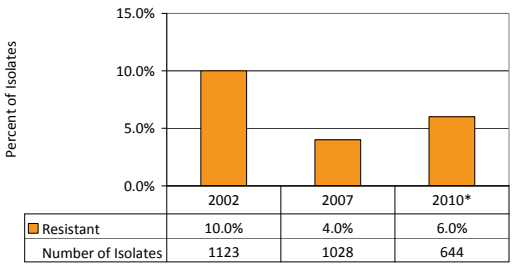
The number of SPICE organism isolates resistant to the tested antimicrobials with the exception of nitrofurantoin, have remained relatively low during the testing period, aside from a peak in resistance during the 2007 testing period for tobramycin and 2002 testing period for other antimicrobials (*Figure 13*). Resistance towards nitrofurantoin displayed the most fluctuation and occurred most frequently, with 61% of isolates demonstrating non-susceptibility in 2010 (*Figure 13*). All tested isolates were non-susceptible to β-lactams and cephalexin in 2010 (data not shown). Data for 2010 were available from July to December 2010 in the 2011 BC Bio Empiric Therapy Antibiogram (2), which can be found online at:

http://www.bcbio.com/images/pdfs/antibiogram2011final.pdf.

Discussion

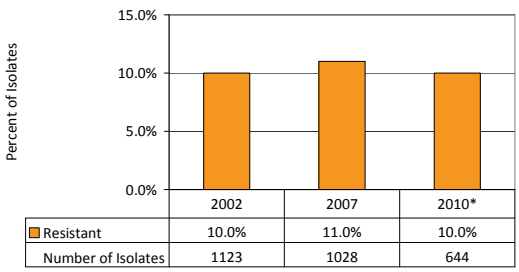
While susceptibility rates varied for the tested antimicrobials, resistance towards nitrofurantoin occurred most frequently. The observation that all SPICE isolates were non-susceptible to cephalexin, however, is not surprising as these organisms have intrinsic cephalosporin resistance.

Percent of SPICE Organisms Resistant to Ciprofloxacin

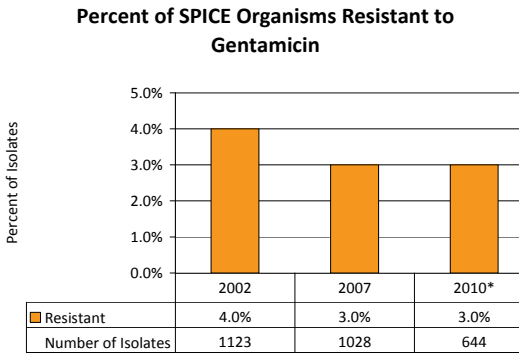


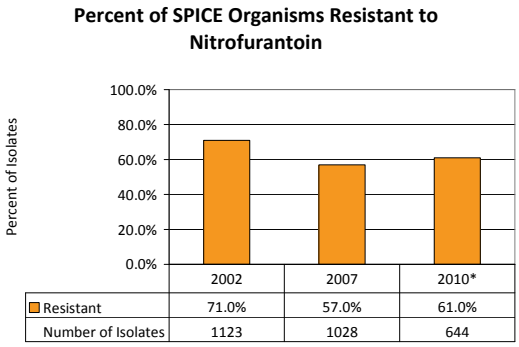
	2002	2007	2010*
Resistant	10.0%	4.0%	6.0%
Number of Isolates	1123	1028	644

Percent of SPICE Organisms Resistant to Tobramycin



	2002	2007	2010*
Resistant	10.0%	11.0%	10.0%
Number of Isolates	1123	1028	644





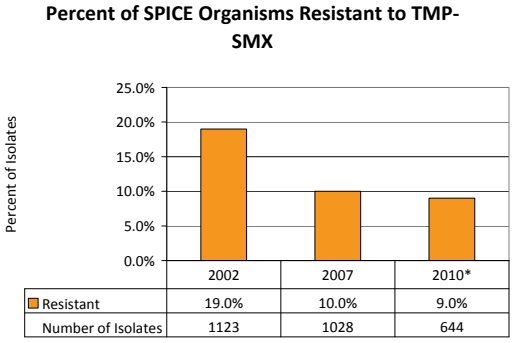


Figure 13 Percent of SPICE (*Serratia*, *Providencia*, *Morganella*, *Citrobacter*, and *Enterobacter*) isolates resistant to ciprofloxacin, tobramycin, gentamicin, nitrofurantoin, and TMP-SMX

Source: BC Biomedical Laboratories

*Represent data from July to December 2010

1.8. Extended spectrum β-lactamase producing Enterobacteriaceae

Data Source(s)

BC Association of Medical Microbiologists (BCAMM)

BC Biomedical Laboratories

Background

Extended spectrum β-lactamases (ESBLs) are enzymes often associated with bacteria within the Enterobacteriaceae family that hydrolyze antibiotics belonging to the penicillin and cephalosporin classes (34). Laboratories detect the presence of ESBLs by evaluating the organism's resistance patterns to different antibiotics (35). An ESBL producing organism must demonstrate resistance to a third generation cephalosporin (e.g. cefotaxime, ceftriaxone or ceftazidime) but not cephamycins (e.g. cefoxitin) and carbapenems (e.g. imipenem, meropenem or ertapenem) (35). In addition, it must also demonstrate a change in susceptibility to third generation cephalosporin in the presence of a β-lactamase inhibitor (e.g. clavulanic acid, tazobactam or sulbactam) (35). The first case of ESBL resistance was reported in Germany in 1983 (36). In 2008, 4% of *E. coli* and *Klebsiella* spp. isolates in the Toronto area were resistant to third generation cephalosporins (37). From 2007 to 2009 in Canada, Zhanel *et al.* showed that the percentage of ESBL-producing *E. coli* increased from 3.4% to 4.3% and ESBL-producing *K. pneumoniae* increased from 1.8% to 3.4% (15). The same study found that BC and Alberta had the greatest increase in both ESBL producing (4.4%, 7.6% and 9.4% in 2007, 2008 and 2009) and AmpC producing (0.3%, 3.8% and 5.4% in 2007, 2008 and 2009) *E. coli* of all provinces tested (38). These percentages have likely increased in the last two years.

The current most common genetic variant of ESBL is CTX-M, which emerged near the end of the 1990s and is the cause of community-acquired infections, most of which are associated with urinary tract infections (UTIs) (39). The most worldwide CTX-M β-lactamase is group 15 (CTX-M-15) (39). CTX-M-15 producing *E. coli* isolates are now frequently isolated in Canada and the presence of this subtype has increased significantly since 2005 (38;39). Because mutations often occur on transferrable plasmids, resistance genes can be readily passed from strain to strain (36). It has also been observed that ESBL-producing bacteria are frequently resistant to other classes of antibiotics such as quinolones, aminoglycosides and trimethoprim-sulfamethoxazole due to co-resistance genes being passed on the transferrable plasmid (36). Resistance to β-lactamase inhibitors are also beginning to emerge due to production of AmpC β-lactamases, which hydrolyze the inhibitors (39). Carbapenem Resistant Enterobacteriaceae (CRE) organisms are also beginning to emerge around the world (35).

Treatment of ESBL-producing organisms has become limited by increasing resistance. However, over 95% of ESBL-producing Enterobacteriaceae are still susceptible to certain antibiotics, including carbepenems, amikacin, tigecycline and β-lactam/β-lactamase inhibitor combinations (39). In some clinical studies, fosfomycin and nitrofurantoin prove to be good alternatives for urinary tract infections (39).

Results

In BC, laboratory testing for ESBL-producing *E. coli* and *K. pneumoniae* is done routinely by phenotypic methods. An approximate percentage of ESBL-producing *E. coli* and *K. pneumoniae* was given in the BCAMM report. These percentages represent the range of ESBL-producing *E. coli* and *K. pneumoniae* observed in all BC Biomedical Laboratories and Life Labs community laboratories, and 23 health organizations' hospital laboratories across BC (3). The results are presented for both community and hospital settings in 2009 and 2010, in order to reflect the potential differences in prevalence within the respective settings. Although the size of the range varied, the estimated number of ESBL-producing organisms appeared stable (*Table 2*). The percentage varied from 0.7% - 10% for *E. coli* and 0 - 8% for *K. pneumoniae*, and was less for community laboratories than hospital laboratories (*Table 2*).

Data from BC Biomedical Laboratories were used to estimate possible *E. coli* and *K. pneumoniae* isolates demonstrating ESBLs. In particular, isolates were identified based on resistance to third generation cephalosporins (e.g. ceftriaxone, cefotaxime, ceftazidime, or cefixime). However, as cephamycin results are not available, true identification of ESBLs will not be possible. As a result, an overestimation will be expected. With this in mind, these isolates will be referred to as "isolates with phenotype compatible with ESBLs" for the rest of the report. Although data from BC Biomedical Laboratories would represent an overestimation of true ESBL numbers, the data are still useful because they will include all possible ESBL-producing *E. coli* and *K. pneumoniae* isolates. Thus, it is still meaningful to represent the data in this report in order to use this denominator to identify multi-drug resistance patterns associated with *E. coli* and *K. pneumoniae* isolates with phenotype compatible with ESBLs, and to monitor for any changing trends.

Data from BC Biomedical Laboratories show that the percent of *E. coli* isolates with phenotype compatible with ESBLs slightly decreased from 11.5% in 2007 to 9.1% in 2009, but then increased to 12.4% in 2011 (*Figure 14;Table 3*). The percent of *K. pneumoniae* isolates with phenotype compatible with ESBLs decreased substantially from 8.5% in 2007 to 3.3% in 2011 (*Figure 14;Table 3*). These numbers were significantly higher than what was estimated in the BCAMM 2010 report; this may be due to a higher prevalence of ESBLs in areas that BC Biomedical Laboratories operates in, or may simply be due to the overestimation of this data because of the lack of cephamycin results.

Data for *E. coli* and *K. pneumoniae* isolates with phenotype compatible with ESBLs were analyzed for their resistance to one other antibiotic, two other antibiotics, and three other antibiotics. The antibiotics used in this analysis include quinolones (e.g. ciprofloxacin or levofloxacin), aminoglycosides (e.g. gentamicin, amikacin or tobramycin) and sulfonamides and trimethoprim (e.g. trimethoprim-sulfamethoxazole) (*Figure 14;Table 3*). An interesting trend is that the percent of *E. coli* isolates with phenotype compatible with ESBLs that were resistant to one antibiotic, two antibiotics, and three antibiotics decreased from 2007 to 2009, rose again in 2010, and varied depending on the antibiotic in 2011 (*Figure 14;Table 3*). For *E. coli* isolates with phenotype compatible with ESBLs resistant to one antibiotic, the resistance percentage was highest for quinolones, with 9.4% of *E. coli* isolates with phenotype compatible with ESBLs resistant to quinolones in 2011 (*Figure 14;Table 3*). The percent of *K. pneumoniae* with phenotype compatible with ESBLs that are resistant to two antibiotics and three antibiotics stayed relatively constant from 2007 to 2011. However,

there was a significant decrease in the percent of *K. pneumoniae* with phenotype compatible with ESBLs that are resistant to TMP-SMX from 2007 to 2011 (*Figure 14;Table 3*). Percent of *E. coli* and *K. pneumoniae* with phenotype compatible with ESBLs that were resistant to all three antibiotics was 2.5% and 0.8% respectively in 2011 (*Figure 14;Table 3*).

The following information is taken directly from pages 6 and 7 of the 2010 BCAMM report (3):

"Phenotypic testing methods cannot always identify specific mechanisms of resistance, i.e., ESBLs, AmpC (also known as cephalosporinases) and carbapenemases; hence, genotypic methods were implemented at the BCCDC Public Health and Reference Laboratory in the fall of 2010. From October 2009 to June 30, 2011, 123 clinical Enterobacteriaceae isolates, (an 84 additional isolates since the last BCAMM ARO report in 2010) were submitted based on unusual phenotypic antibiotic susceptibility profiles that required confirmation. Duplicate isolates from the same source and collection dates were removed for this report. The phenotypic screening methods and decisions for submitting isolates were at the discretion of frontline medical microbiology laboratories. The distribution of isolates included: *E. coli* (41), *K. pneumoniae* (22), *Enterobacter sp (*30), *Serratia sp* (5), *Providencia rettgeri* (2), *Citrobacter sp* (2), *Hafnia alvei* (1), *Morganella morganii* (15), *Proteus sp* (5)

ESBLs

The gene targets associated with ESBL looked for at BCCDC are not comprehensive, but included SHV, TEM, CTX-M, and OXA-1. In the isolates tested, the most common ESBL genes detected were TEM, CTX-M and OXA-1. ESBL resistance genes were the most common resistance mechanism detected amongst all isolates.

AmpC

BCCDC tests for seven gene targets associated with AmpC resistance, including CMY-2, CMY-1/MOX, CMY-2/LAT, DHA, ACC, MIR/ACT and FOX. Only 2 *E. coli* isolates harboured AmpC genes alone. All other AmpC positive *E. coli* strains were also positive for ESBL genes. Some AmpC positive/ESBL positive strains also carried carbapenem resistance genes. Thirteen of the *Morganella morganii* isolates were positive for AmpC and only carried the DHA gene. CMY-2 and CMY-2/LAT were the most common genes detected.

Carbapenem Resistant Enterobacteriaceae (CRE)

BCCDC tests for KPC, NDM, IMP and VIM carbapenem resistance genes. To date, 11 isolates of *E. coli/K. pneumoniae* carrying the NDM gene from 6 patients were identified. In addition, the following CRE's were also identified: 1 case of KPC positive *K. pneumoniae*, 1 case with a *K. pneumoniae* infection that harboured both KPC and VIM, and 1 case with both a *P. aeruginosa* positive VIM and an NDM positive *K. pneumoniae* isolate. These isolates also contained ESBL +/- AmpC genes."

Please refer to the BCAMM 2010 (3) report for the original information.

Conclusion

E. coli ESBL and *K. pneumoniae* ESBL estimates have remained low in BC in 2010, according to the BCAMM 2010 report. Genotypic testing methods for ESBLs were implemented in 2010 by the BCCDC Public Health and Reference Microbiology Laboratory.

For the 123 clinical Enterobacteriaceae isolates received from October 2009 to June 2011, the most common ESBL genes detected were TEM, CTX-M and OXA-1. Most *E. coli* isolates tested were positive for AmpC as well as ESBL genes. By June 20, 2011 the following carbapenem resistant cases had been identified: 1 KPC positive case of *K. pneumoniae*, 1 case with a *K. pneumoniae* infection that harboured both KPC and VIM, and 1 case with both a *P. aeruginosa* positive VIM and an NDM positive *K. pneumoniae* isolate.

According to BC Biomedical Laboratories data, the percent of *E. coli* isolates with phenotype compatible with ESBLs hit 12.4% in 2011, a slight increase since 2007, while *K. pneumoniae* isolates with phenotype compatible with ESBLs decreased significantly since 2007, to 3.3% in 2011. Although these percentages appear significantly higher than what was reported in BCAMM, this is expected because these numbers are only used to identify isolates with a phenotype potentially compatible with ESBLs, not necessarily laboratory confirmed ESBL isolates, which is what the BCAMM report indicates. *E. coli* isolates with phenotype compatible with ESBLs have become increasingly resistant to multiple other drugs, including quinolones, aminoglycosides and sulfonamides and trimethoprim from 2009 to 2011. However, the overall resistance rate of *E. coli* and *K. pneumoniae* isolates with phenotype compatible with ESBLs that are resistant to either one, two or three antibiotics still remains low in BC.

Table 2 Estimation of the percent of *Escherichia coli* and *Klebsiella pneumoniae* isolates demonstrating ESBLs in BC

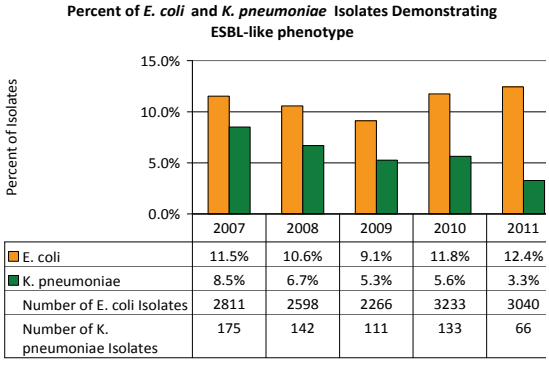
Year	***E. coli* ESBL estimates**	***K. pneumoniae* ESBL estimates**
2007	0.7% – 5%	0% – 3%
2008	1% – 13%	0.3% – 6%
2009 (All laboratories)	1% – 7.8%	0.3% – 6%
2010 (All laboratories)	0.7% – 10%	0% – 8%
2009 (Community laboratories)	1% – 1.7%	0.3% – 1%
2010 (Community laboratories)	0.7% – 2.5%	0.5%

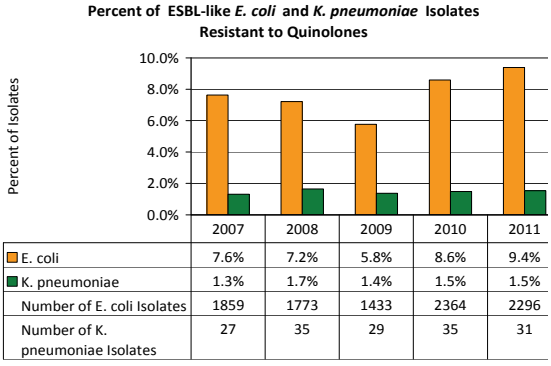
Source: BCAMM 2010 Report (3)

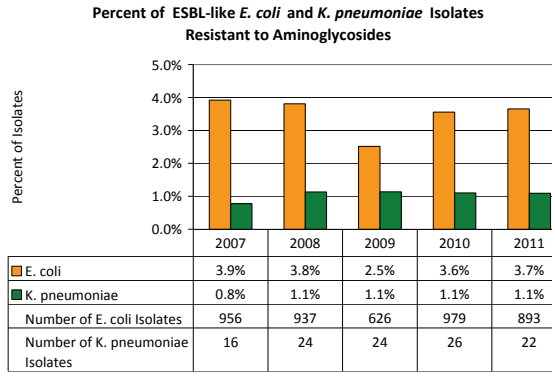
Table 3 Percent of *Escherichia coli* and *Klebsiella pneumoniae* isolates demonstrating ESBL-compatible phenotype and their resistance to one, two and three other antibiotics (quinolones, aminoglycosides and trimethoprim-sulfamethoxazole)

	2007	2008	2009	2010	2011
***E. coli* with phenotype compatible to ESBLs, Total *E. coli* n= ~25000/year**					
Total ESBL-like *E. coli*	11.5% (2811)	10.6% (2121)	9.1% (2108)	11.8% (2358)	12.4% (2016)
ESBL-like *E. coli* resistant to quinolones	7.6% (1859)	7.2% (1773)	5.8% (1433)	8.6% (2364)	9.4% (2296)
ESBL-like *E. coli* resistant to aminoglycosides	3.9% (956)	3.8% (937)	2.5% (626)	3.6% (979)	3.7% (893)
ESBL-like *E. coli* resistant to TMP-SMX	5.6% (1356)	5.5% (1340)	3.8% (935)	6.7% (1843)	7.2% (1750)
ESBL-like *E. coli* resistant to at least 2 of quinolones, TMP-SMX and aminoglycosides	5.6% (1367)	5.5% (1354)	3.9% (961)	6.9% (1898)	7.5% (1840)
ESBL-like *E. coli* resistant to all 3 of quinolones, TMP-SMX and aminoglycosides	2.9% (696)	2.8% (692)	1.7% (411)	2.7% (743)	2.5% (604)
***K. pneumoniae* with phenotype compatible to ESBLs, Total *K. pneumoniae* n= ~2100/year**					
Total ESBL-like *K. pneumoniae*	8.5% (2811)	6.7% (2121)	5.3% (2108)	5.6% (2358)	3.3% (2016)
ESBL-like *K. pneumoniae* resistant to quinolones	1.3% (27)	1.7% (35)	1.4% (29)	1.5% (35)	1.5% (31)
ESBL-like *K. pneumoniae* resistant to aminoglycosides	0.8% (16)	1.1% (24)	1.1% (24)	1.1% (26)	1.1% (22)
ESBL-like *K. pneumoniae* resistant to TMP-SMX	5.2% (108)	4.7% (99)	3.3% (70)	2.2% (52)	2.1% (42)
ESBL-like *K. pneumoniae* resistant to 2 or more of quinolones, TMP-SMX and aminoglycosides	1.4% (28)	1.9% (40)	1.6% (33)	1.4% (32)	1.6% (33)
ESBL-like *K. pneumoniae* resistant to all 3 of quinolones, TMP-SMX and aminoglycosides	0.6% (12)	0.8% (16)	0.8% (16)	0.8% (19)	0.8% (16)

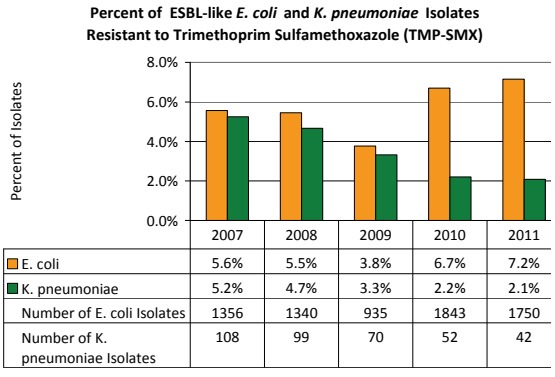
Source: BC Biomedical Laboratories



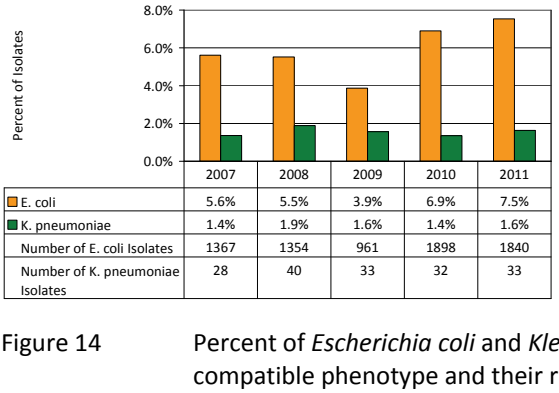




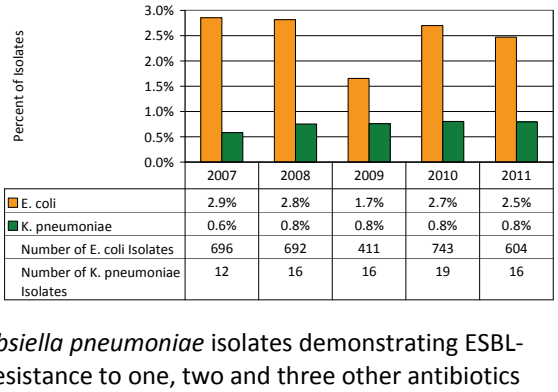
	2007	2008	2009	2010	2011
E. coli	3.9%	3.8%	2.5%	3.6%	3.7%
K. pneumoniae	0.8%	1.1%	1.1%	1.1%	1.1%
Number of E. coli Isolates	956	937	626	979	893
Number of K. pneumoniae Isolates	16	24	24	26	22



	2007	2008	2009	2010	2011
E. coli	5.6%	5.5%	3.8%	6.7%	7.2%
K. pneumoniae	5.2%	4.7%	3.3%	2.2%	2.1%
Number of E. coli Isolates	1356	1340	935	1843	1750
Number of K. pneumoniae Isolates	108	99	70	52	42



	2007	2008	2009	2010	2011
E. coli	5.6%	5.5%	3.9%	6.9%	7.5%
K. pneumoniae	1.4%	1.9%	1.6%	1.4%	1.6%
Number of E. coli Isolates	1367	1354	961	1898	1840
Number of K. pneumoniae Isolates	28	40	33	32	33



	2007	2008	2009	2010	2011
E. coli	2.9%	2.8%	1.7%	2.7%	2.5%
K. pneumoniae	0.6%	0.8%	0.8%	0.8%	0.8%
Number of E. coli Isolates	696	692	411	743	604
Number of K. pneumoniae Isolates	12	16	16	19	16

Figure 14 Percent of *Escherichia coli* and *Klebsiella pneumoniae* isolates demonstrating ESBL-compatible phenotype and their resistance to one, two and three other antibiotics (quinolones, aminoglycosides and trimethoprim-sulfamethoxazole)

Source: BC Biomedical Laboratories

1.9. Pseudomonas aeruginosa

Data Source(s)

BC Biomedical Laboratories

Background

Pseudomonas aeruginosa are predominant nosocomial pathogens that infect numerous sites including the respiratory tract, urinary tract, blood, skin and soft tissue. Treatment for *P. aeruginosa* infections typically includes piperacillin, tobramycin, ceftazidime, carbapenems, fluoroquinolones, and aminoglycosides (16). Although the majority of infections remain susceptible to the antimicrobials listed above, *P. aeruginosa* isolates demonstrated resistance to aminoglycosides, β-lactams and fluoroquinolones during the SENTRY Antimicrobial Surveillance Study (32).

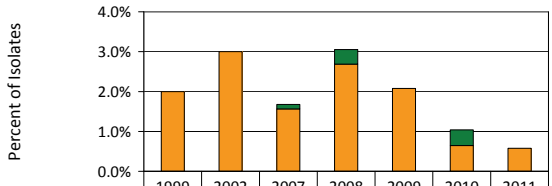
Results

The percent of *P. aeruginosa* isolates non-susceptible to aminoglycosides (tobramycin and gentamicin) remained low in 2011 (*Figure 15*). Tobramycin non-susceptibility fell from 3.1% in 2008 to 0.6% in 2011 (*Figure 15*). Gentamicin resistance decreased from 7.0% in 1999 to 1.9% in 2011 (*Figure 15*). Ciprofloxacin non-susceptibility was 10.1% in 2011 (*Figure 15*). Over the testing period <4% of isolates (1.1% in 2011) were non-susceptible to ceftazidime and ≤3% (1.4% in 2011) to piperacillin (*Figure 15*).

Discussion

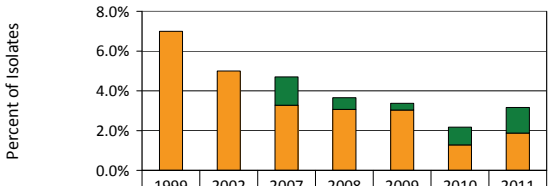
The percentage of isolates non-susceptible to aminoglycosides displayed a decreasing trend compared to its peak in 1998. However, the number of isolates non-susceptible to ciprofloxacin remains steady. Based on high susceptibility rates, treatment with either piperacillin or tobramycin is likely to still be effective.

Percent of *P. aeruginosa* Isolates Non-Susceptible to Tobramycin

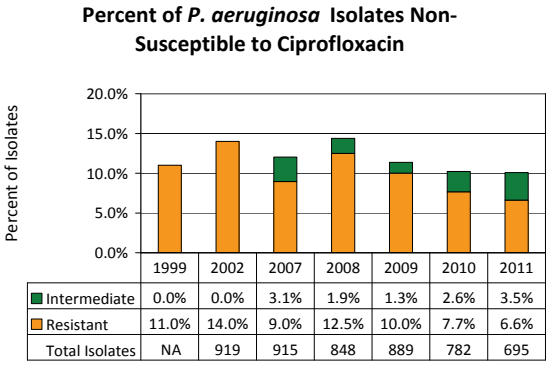


	1999	2002	2007	2008	2009	2010	2011
Intermediate	0.0%	0.0%	0.1%	0.4%	0.0%	0.4%	0.0%
Resistant	2.0%	3.0%	1.6%	2.7%	2.1%	0.6%	0.6%
Total Isolates	NA	919	894	819	865	771	690

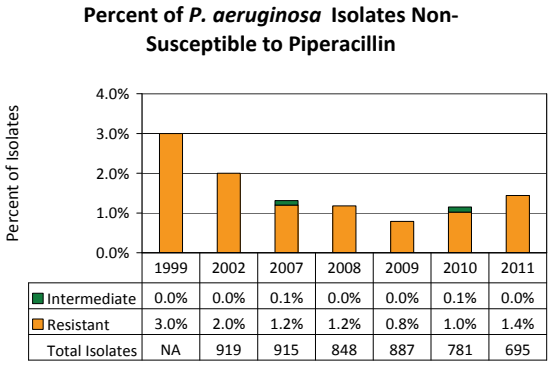
Percent of *P. aeruginosa* Isolates Non-Susceptible to Gentamicin



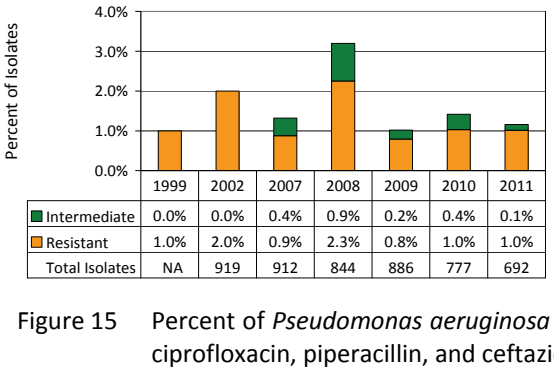
	1999	2002	2007	2008	2009	2010	2011
Intermediate	0.0%	0.0%	1.4%	0.6%	0.3%	0.9%	1.3%
Resistant	7.0%	5.0%	3.3%	3.1%	3.0%	1.3%	1.9%
Total Isolates	NA	919	915	848	889	782	695



	1999	2002	2007	2008	2009	2010	2011
Intermediate	0.0%	0.0%	3.1%	1.9%	1.3%	2.6%	3.5%
Resistant	11.0%	14.0%	9.0%	12.5%	10.0%	7.7%	6.6%
Total Isolates	NA	919	915	848	889	782	695



	1999	2002	2007	2008	2009	2010	2011
Intermediate	0.0%	0.0%	0.1%	0.0%	0.0%	0.1%	0.0%
Resistant	3.0%	2.0%	1.2%	1.2%	0.8%	1.0%	1.4%
Total Isolates	NA	919	915	848	887	781	695



	1999	2002	2007	2008	2009	2010	2011
Intermediate	0.0%	0.0%	0.4%	0.9%	0.2%	0.4%	0.1%
Resistant	1.0%	2.0%	0.9%	2.3%	0.8%	1.0%	1.0%
Total Isolates	NA	919	912	844	886	777	692

Figure 15 Percent of *Pseudomonas aeruginosa* isolates non-susceptible to tobramycin, gentamicin, ciprofloxacin, piperacillin, and ceftazidime

Source: BC Biomedical Laboratories

1.10. Proteus mirabilis

Data Source(s)

BC Biomedical Laboratories

Background

Proteus mirabilis is an enteric bacterium that causes around 2% of UTIs (27). Trimethoprim-sulfamethoxazole (TMP-SMX) used to be the first-line treatment for UTIs; however, use of fluoroquinolones (e.g. ciprofloxacin) and aminoglycosides (e.g. gentamicin) has become more common over the years ((16;28). In Canada, the percent of isolates producing ESBLs is considerably less than other countries (33). The resistance profile of *P. mirabilis* isolates includes resistance against β-lactams, aminoglycosides, ciprofloxacin, TMP-SMX, and nitrofurantoin (15;31;40).

Results

The percent of *P. mirabilis* isolates resistant to TMP-SMX increased between years 1999 to 2009 during which time resistance had more than doubled from 17.0% in 1999 to 34.7% in 2009 (*Figure 16*). The percent of *P. mirabilis* isolates resistant to TMP-SMX saw its first decrease in 2010 to 28.1% followed by a slight increase to 30.5% in 2011 (*Figure 16*). After an increasing trend from 3.0% in 1999 to 23.5% in 2008, non-susceptibility to ciprofloxacin decreased to 14.7% in 2010, then increased to 19.8% in 2011 (*Figure 16*). In addition to the antimicrobials primarily used for UTIs (such as ciprofloxacin and TMP-SMX), the percent of isolates resistant to ampicillin increased from 18.0% 1999 to 33.5% in 2008 (*Figure 16*). However, since 2008 a slight decreasing trend has emerged resulting in a 31.3% resistance rate to ampicillin in 2011 (*Figure 16*). The percent of isolates resistant to gentamicin dramatically decreased from a peak of 11.0% in 2002 to 5.6% in 2007, and has remained stable through to 2011 including 5.4% in 2011 (*Figure 16*). As expected, all isolates were resistant to nitrofurantoin in 2011 according to the BC Biomedical Laboratories data (data not shown).

Discussion

High percentages of *P. mirabilis* isolates demonstrated non-susceptibility against ampicillin, ciprofloxacin, TMP-SMX, and nitrofurantoin. Of particular concern is the high percent of isolates non-susceptible to ampicillin. In 2011, approximately one out of three *P. mirabilis* isolates demonstrated resistance to ampicillin and TMP-SMX. Though both ciprofloxacin and TMP-SMX showed decrease in non-susceptibility for 2010, 2011 demonstrated an increase in non-susceptibility for both of these antibiotics.

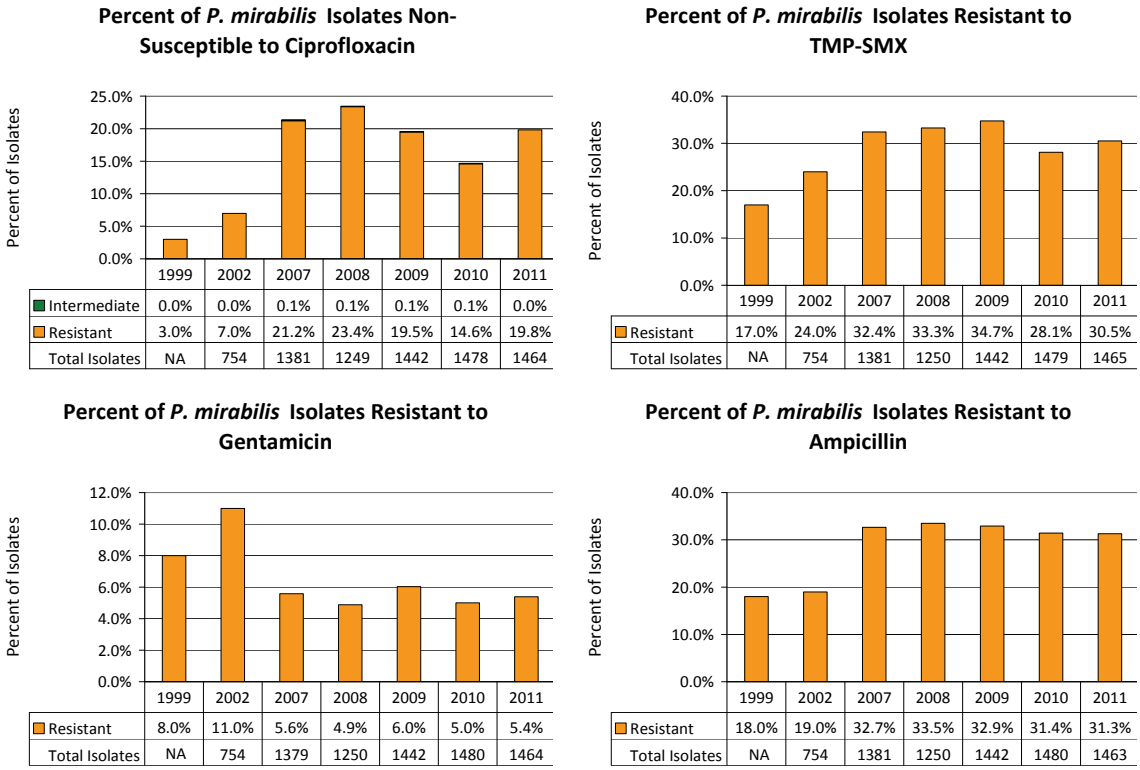


Figure 16 Percent of *Proteus mirabilis* isolates non-susceptible to ciprofloxacin and resistant to TMP-SMX, gentamicin and ampicillin

Source: BC Biomedical Laboratories

1.11. Salmonella Enteritidis

Data Source(s)

Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)

Background

*Salmonell*a is a common cause of gastroenteritis in Canada. *Salmonella* is usually a food-borne pathogen that is transmitted through contaminated or uncooked food products, but can also be transmitted through contaminated water or person-to-person contact (41). *Salmonella* Enteritidis, the most common form of *Salmonella* within Canada, can be transmitted to humans by contaminated eggs (41). While most people do not require antibiotics as illness is self-limited, the elderly, infants and those with weak immune system are more likely to require antimicrobials for treatment (41).

Results

Of the tested antimicrobials, isolates demonstrated 100% susceptibility to ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole (TMP-SMX) as of 2009 (data not shown). Resistance to ampicillin dropped significantly to 1.7% in 2009 compared to 5.2% observed in 2008 (*Figure 17*). Following a large increase from 2.6% in 2005 to 15.5% in 2006, tetracycline resistance rates declined rapidly in the next three years, to 2.5% in 2009 (*Figure 17*). Resistance to chloramphenicol remained below 2.0% since 2004 and no resistance is indicated in any of the tested isolates in 2008 and 2009 (*Figure 17*).

Table 4 displays common *Salmonella* multidrug resistance patterns in BC from years 2003 to 2005. The most frequently observed multidrug resistance pattern was the chromosomally-encoded ACSSuT pattern (i.e. multidrug resistance to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole and tetracycline), which was present in 88 (7.4%) isolates. The ACSSuT multidrug resistance pattern is commonly found in combination with other antimicrobials especially TMP-SMX (41). The A2C pattern (i.e. multidrug resistance to amoxicillin-clavulanic acid, cefoxitin, ceftiofur) and A3C pattern (i.e. the A2C pattern plus cephalothin) were also common with 57 (4.8%) isolates displaying either pattern during the testing period. High frequency of single-drug antimicrobial resistance was found for nalidixic acid (10.4%) and tetracycline (2.4%). In 2007, one isolate from British Columbia with an atypical phage type had an AKSSuT-GEN-NAL (i.e. multidrug resistance to AKSSuT pattern along with gentamicin and nalidixic acid) resistance pattern.

Discussion

Resistance to ampicillin and tetracycline continued to be low. Common antimicrobial resistance patterns include the ACSSuT, A2C, and A3C patterns as well as resistance against nalidixic acid alone and tetracycline alone.

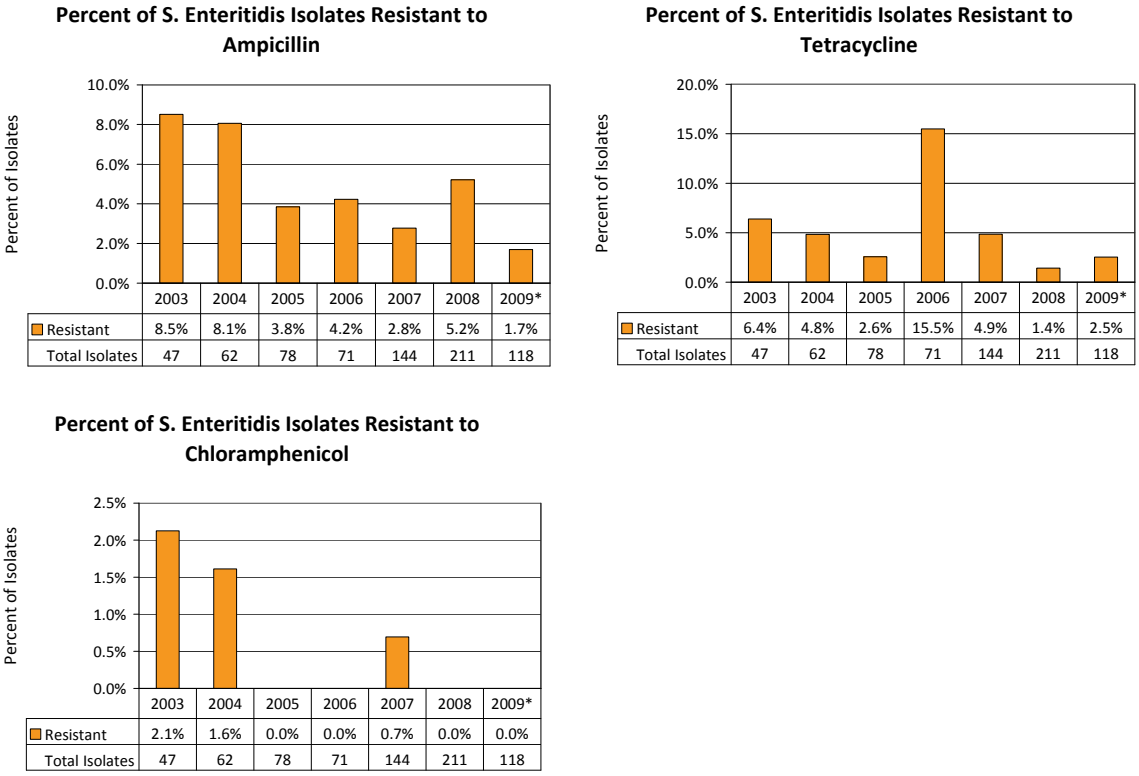


Figure 17 Percent of *Salmonella* Enteritidis isolates resistant to ampicillin, tetracycline, and chloramphenicol

Source: CIPARS

*2009 data is from a preliminary report.

Table 4 Frequently-occurring multidrug resistance patterns in *Salmonella* isolates

Resistance pattern[1,2]	Frequency, n (%)			
	2003, n=395	2004, n=403	2005, n=390	Total, n=1188
NAL	42 (10.6)	40 (9.9)	42 (10.8)	124 (10.4)
TCY	10 (2.5)	12 (3.0)	7 (1.8)	29 (2.4)
AMP	4 (1.0)	5 (1.2)	3 (0.8)	12 (1.0)
STR-TCY	4 (1.0)	6 (1.5)	8 (2.1)	18 (1.5)
AMP-TCY	2 (0.5)	5 (1.2)	3 (0.8)	10 (0.8)
SMX-STR	0 (0.0)	4 (1.0)	4 (1.0)	8 (0.7)
SMX-SXT-TCY	3 (0.8)	3 (0.7)	1 (0.3)	7 (0.6)
SMX-STR-TCY	2 (0.5)	2 (0.5)	3 (0.8)	7 (0.6)
AMP-STR-TCY	1 (0.3)	4 (1.0)	1 (0.3)	6 (0.5)
A2C + AMP	0 (0.0)	16 (4.0)	17 (4.4)	33 (2.8)
ACSSuT	6 (1.5)	5 (1.2)	9 (2.3)	20 (1.7)
ACSSuT + SXT	3 (0.8)	1 (0.2)	2 (0.5)	6 (0.5)
ACSSuT + NAL-SXT	4 (1.0)	3 (0.7)	3 (0.8)	10 (0.8)
ACSSuT + A2C	0 (0.0)	7 (1.7)	2 (0.5)	9 (0.8)
ACKSSuT + SXT	0 (0.0)	15 (3.7)	13 (3.3)	28 (2.4)
ACSSuT + A3C	9 (2.3)	6 (1.5)	0 (0.0)	15 (1.3)

[1] AMP = ampicillin; NAL = nalidixic acid; SMX = sulfamethoxazole; STR = streptomycin; SXT = trimethoprim-sulfamethoxazole; TCY = tetracycline; ACSSuT = ampicillin, chloramphenicol, sulfamethoxazole, streptomycin, tetracycline; ACKSSuT = ampicillin, chloramphenicol, kanamycin, sulfamethoxazole, streptomycin, tetracycline; A2C = amoxicillin-clavulanic acid, cefoxitin, ceftiofur; A3C = amoxicillin-clavulanic acid, cephalothin, cefoxitin, ceftiofur

[2] Cephalothin was not included in the testing panel as of 2004. Cephalothin susceptibility data was available for 109/403 isolates in 2004 and 0/390 isolates in 2005.

Source: CIPARS

1.12. Haemophilus influenzae

Data Source(s)

Canadian Bacterial Surveillance Network (CBSN)

BC Biomedical Laboratories

Background

Haemophilus influenzae is a respiratory tract Gram negative bacteria that causes numerous invasive diseases including bacterial meningitis, bacterial pneumonia, epiglottitis, septic arthritis, cellulitis, and pericarditis. Antimicrobial resistance in *H. influenzae* isolates is mediated by the production of β-lactamases which cleave β-lactam antibiotics (e.g. ampicillin and amoxicillin) and render them ineffective. In Canada, approximately 22% of *H. influenzae* isolates produced β-lactamases in the late 1990s and early 2000s, with sources reporting a decrease in β-lactamase production over their study periods (42;43). In addition to the β-lactam antimicrobials, other antimicrobials to which *H. influenzae* isolates have demonstrated resistance include TMP-SMX, clarithromycin, azithromycin, doxycycline, cefprozil, and cefaclor (34;42;43). The majority of *H. influenzae* isolates remain fluoroquinolone (e.g. ciprofloxacin and levofloxacin) susceptible (15;42;43).

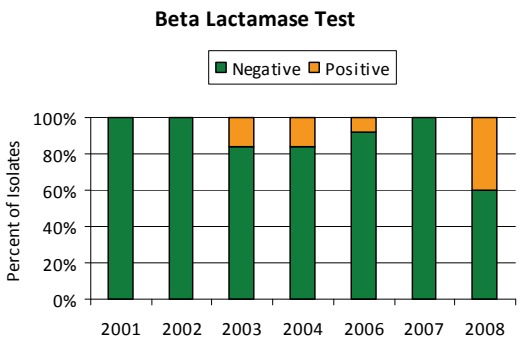
Results

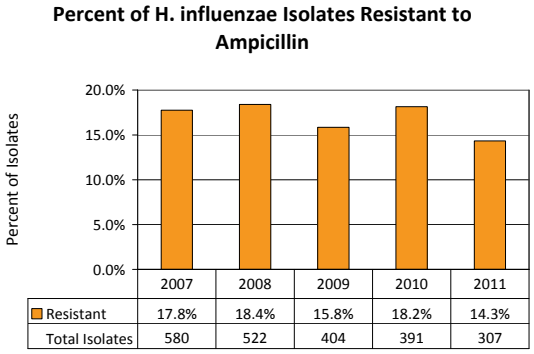
An update on CBSN *H. influenzae* has not been available since 2008. A graph form was provided of β-lactamase test results for years 2001 to 2008. The highest rate of β-lactam resistance which occurred during the testing period was in 2008 with approximately 40% of isolates producing β-lactamases (Figure 18). Between years 2003 and 2006, however, the β-lactam non-susceptibility rates remained relatively stable below 20% (Figure 18). In 2007, β-lactamase results indicated all isolates were negative (Figure 18).

According to BC Biomedical Laboratories results, ampicillin resistance fluctuated around 18% from years 2007 to 2010 with the exception of a temporary drop to 15.8% in 2009, but subsequently decreased to 14.3% in 2011 (Figure 18).

Discussion

The percentage of β-lactamase-producing *H. influenzae* isolates showed a sharp decline during the testing period of 2003 and 2007, but showed a substantial increase in 2008. While this trend is comparable to the reported decline in β-lactam resistance across Canada, the results may be biased due to the voluntary nature of isolate referral to the CBSN (isolates suspected of demonstrating resistance may be submitted more frequently). According to BC Biomedical Laboratories, resistance to ampicillin remained relatively steady from 2007 to 2011, but dropped to 14.3% in 2011.





	2007	2008	2009	2010	2011
Resistant	17.8%	18.4%	15.8%	18.2%	14.3%
Total Isolates	580	522	404	391	307

Figure 18 Percent of β-lactamase producing *Haemophilus influenzae* isolates and the percent of *Haemophilus influenzae* isolates resistant to ampicillin

Source: CBSN, BC Biomedical Laboratories

1.13. Neisseria meningitidis

Data Source(s)

BCCDC Public Health Microbiology & Reference Laboratory

Background

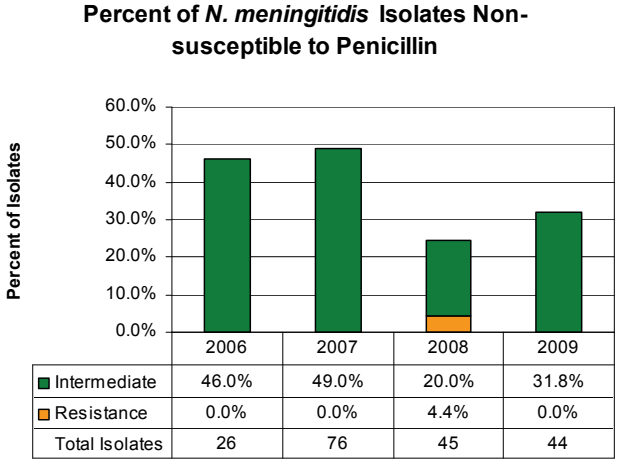
Neisseria meningitidis causes bacterial meningitis and meningococcal septicemia. Due to the routine immunization of children with the meningococcal vaccine, cases of invasive meningococcal disease in BC are rare (4;19). Third-generation cephalosporins, cefotaxime and ceftriaxone, are typically used to treat bacterial meningitis (16). Penicillin-resistant *N. meningitidis* strains first appeared in Europe in the mid-1980s (44). In Canada, antimicrobial resistant *N. meningitidis* strains are rare.

Results

Between years 2006 and 2009, isolates were tested for resistance against the following antimicrobials: penicillin, rifampin, ciprofloxacin, and ceftriaxone. In 2009, non-susceptibility towards penicillin was 31.8%, though full resistance was not seen in any isolates (Figure 19). While isolates showed some resistance towards ciprofloxacin in 2006 (5.3%), no ciprofloxacin-resistant isolates were found from 2007 to 2009 (data not shown). For years 2010 and 2011, no notable changes occurred in resistance pattern. Caution should be taken when inferring data from graph as the number of total isolates is relatively small (*Figure 19*).

Conclusion

Antimicrobial resistant *N. meningitidis* isolates are rare in BC.



	2006	2007	2008	2009
Intermediate	46.0%	49.0%	20.0%	31.8%
Resistance	0.0%	0.0%	4.4%	0.0%
Total Isolates	26	76	45	44

Figure 19 Percent of *Neisseria meningitidis* isolates non-susceptible to penicillin
Source: BCCDC

1.14. Neisseria gonorrhoeae

Data Source(s)

BCCDC Public Health Microbiology & Reference Laboratory

Background

Neisseria gonorrhoeae is the causative agent of gonorrhoea, a sexually transmitted infection of the urethra, cervix, rectum, or pharynx. Due to the increasing prevalence of penicillin, tetracycline and fluoroquinolone resistant *N. gonorrhoeae* strains, third generation cephalosporins (i.e., cefixime or ceftriaxone) are now the recommended treatments (45;46). Co-treatment with azithromycin is recommended for all gonorrhea cases, given high rates of co-infection with Chlamydia trachomatis, and to stem the further emergence of multi-drug resistant *N. gonorrhoeae*. Quinolones such as ciprofloxacin and ofloxacin are not recommended unless susceptibility testing is available or a test of cure is performed (45).

Plasmid-encoded resistance mechanisms in *N. gonorrhoeae* include the production of penicillinases, which cleave the β-lactam ring of penicillin, and expression of the *tetM* gene, which confers resistance against tetracycline (47). Due to increased use of molecular methods (i.e., nucleic acid amplification testing) rather than culture to detect *N. gonorrhoeae* infection, only approximately 22% of *N. gonorrhoeae* detections were tested for antimicrobial susceptibility in recent years (2006-2011).

Results

First-line treatments

According to data from the BCCDC Public Health Microbiology & Reference Laboratory, all isolated *N. gonorrhoeae* tested between 2006 and 2011 were fully susceptible to cefixime and ceftriaxone (MIC [minimum inhibitory concentration] ≤0.25), although the proportion of isolates with elevated MICs just below the expected threshold for susceptibility has increased in the past 6 years (see reference (48) for further information). In response to these findings and similar findings from elsewhere (49), treatment guidelines have been adjusted (as of December 2011) to recommend preferential use of ceftriaxone for some infections and doubling of the dose for cefixime to 800mg for others (45). These trends will be monitored further to detect the emergence of resistance to first-line treatments.

While there are no CLSI criteria for *N. gonorrhoeae* resistance to azithromycin, an MIC ≥2 has been used as a threshold (50;51). Fewer than 3% of isolates have been resistant to azithromycin (MIC ≥2) in recent years *(Table 5)*. This will continue to be monitored carefully. All *N. gonorrhoeae* isolated at the BC PHMRL during this period (2006-2011) remains fully susceptible to spectinomycin.

Other antibiotic monitoring

Non-susceptibility to ciprofloxacin (MIC ≥0.125) increased between 1992 and 2011, and is currently over 30% (*Figure 20*). Non-susceptibility to penicillin (MIC ≥0.125) has increased from 68% in 1991 to 95% in 2011. Non-susceptibility to tetracycline (MIC ≥0.5) has increased from 39% in 1991 to 96% non-susceptibility in 2011.

Discussion

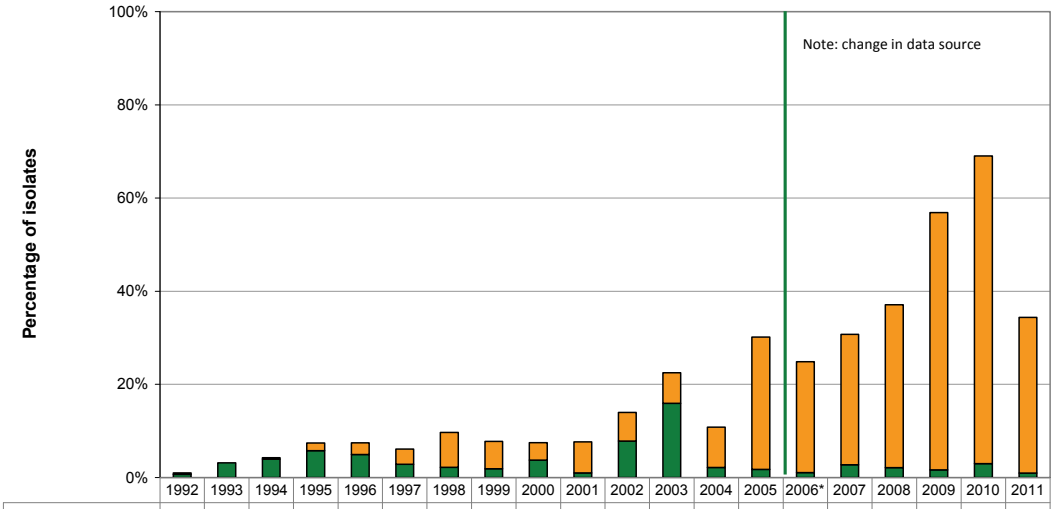
Data from the BCCDC Public Health Microbiology & Reference Laboratory show that *N. gonorrhoeae* resistance to ciprofloxacin continues to increase, despite this drug not being a recommended treatment for gonorrhea infections. No resistance is currently seen for the cephalosporins, though recent rise in MIC just below the threshold of resistance suggests it may emerge. Azithromycin resistance remains low. All of these trends will continue to be monitored carefully.

Table 5 Azithromycin resistance among *N. gonorrhoeae* isolates, March 2006-December 2010

Year	Number isolates tested	Number resistant isolates *	% isolates resistant
2006	193	2	1.0%
2007	230	2	0.8%
2008	244	0	0.0%
2009	302	6	2.0%
2010	336	4	1.2%
2011	501	1	0.2%

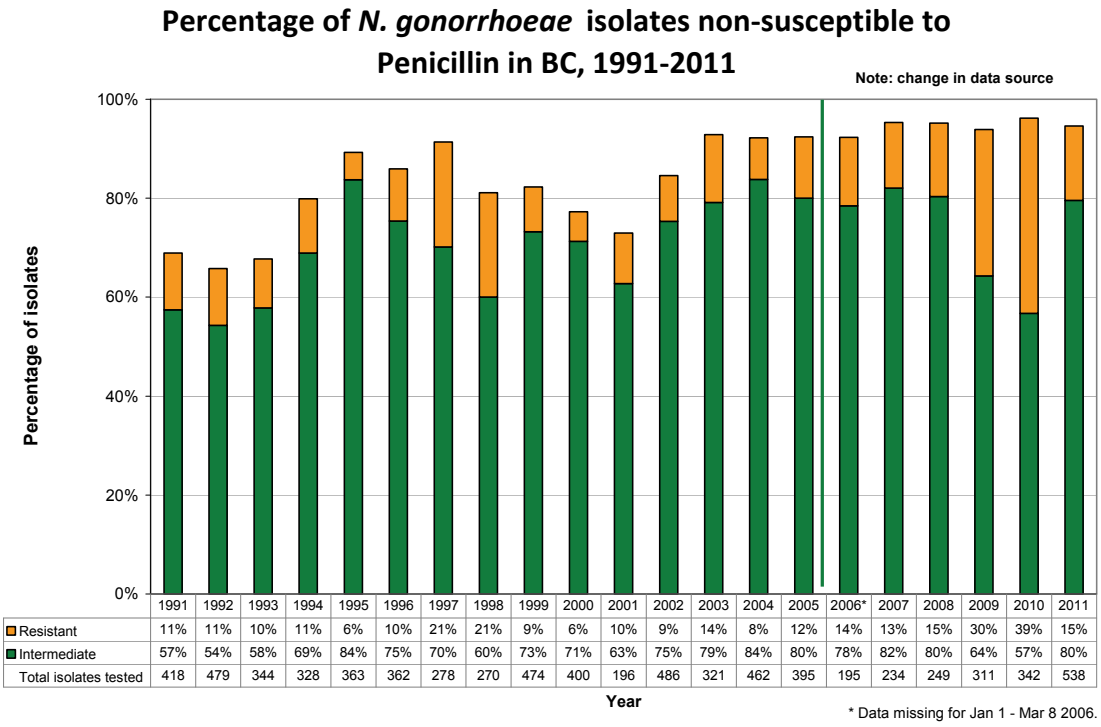
Source: PHMRL via Clinical Prevention Services, BCCDC

Percentage of *N. gonorrhoeae* isolates non-susceptible to Ciprofloxacin in BC, 1992-2011



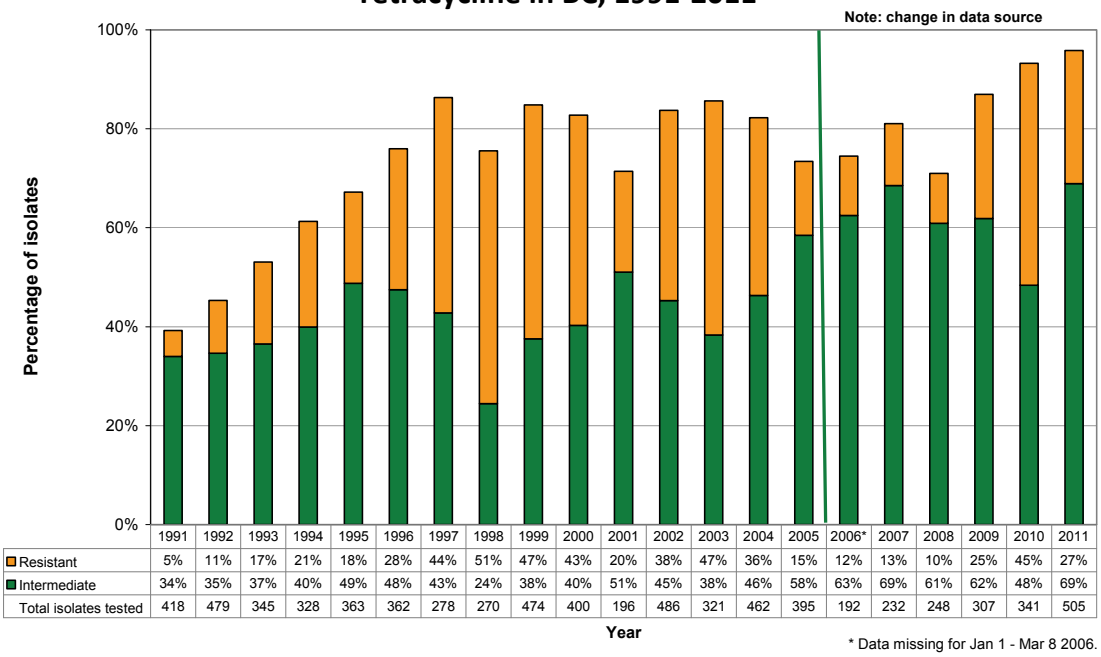
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011
Resistant	0%	0%	0%	2%	2%	3%	7%	6%	4%	7%	6%	7%	9%	28%	24%	28%	35%	55%	66%	33%
Intermediate	1%	3%	4%	6%	5%	3%	2%	2%	4%	1%	8%	16%	2%	2%	1%	3%	2%	2%	3%	1%
Total isolates tested	297	344	328	363	362	278	269	474	400	196	486	320	462	395	185	218	232	299	336	515

* Data missing for Jan 1 - Mar 8 2006.



	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011
Resistant	11%	11%	10%	11%	6%	10%	21%	21%	9%	6%	10%	9%	14%	8%	12%	14%	13%	15%	30%	39%	15%
Intermediate	57%	54%	58%	69%	84%	75%	70%	60%	73%	71%	63%	75%	79%	84%	80%	78%	82%	80%	64%	57%	80%
Total isolates tested	418	479	344	328	363	362	278	270	474	400	196	486	321	462	395	195	234	249	311	342	538

* Data missing for Jan 1 - Mar 8 2006.



	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011
Resistant	5%	11%	17%	21%	18%	28%	44%	51%	47%	43%	20%	38%	47%	36%	15%	12%	13%	10%	25%	45%	27%
Intermediate	34%	35%	37%	40%	49%	48%	43%	24%	38%	40%	51%	45%	38%	46%	58%	63%	69%	61%	62%	48%	69%
Total isolates tested	418	479	345	328	363	362	278	270	474	400	196	486	321	462	395	192	232	248	307	341	505

* Data missing for Jan 1 - Mar 8 2006.

Figure 20 *N. gonorrhoeae* non-susceptibility to ciprofloxacin, penicillin and tetracycline
Source: PHMRL via Clinical Prevention Services, BCCDC

Other organisms

1.15. Mycobacterium tuberculosis

Data Source(s)

Clinical Prevention Services, BC Centre for Disease Control (BCCDC)

Public Health Microbiology & Reference Laboratory (PHMRL)

Background

Mycobacterium tuberculosis (MTB) is a slow-growing, aerobic, acid-fast bacterium that is the causative agent for tuberculosis (TB) (52). The infection usually causes disease in the lungs (pulmonary TB), but the bacteria can travel through the bloodstream to other parts of the body (extrapulmonary TB) (52). Its key virulence factor is its unusual cell wall rich in lipids (mycolic acid) that thickens and changes surface protein and lipid composition under stress (53). In addition, MTB has several mechanisms that prevent acidification of the phagosome during macrophage killing; one of which is the mgtC protein, which is required for the survival of MTB in conditions of low pH as well as growth within human macrophages (53).

In British Columbia, there are about 300 cases of TB disease each year. TB is preventable and curable as there are effective TB medications available for both active and latent TB infections (54). The treatment for active TB is usually given daily for at least 6 months and the patient must follow a strict antibiotic regimen, often under directly observed therapy (54). This standard treatment includes two months with four drugs including isoniazid (INH), rifampin, ethambutol and pyrazinamide, followed by four months of INH and rifampin (54). In bacteriologically confirmed cases, adjustment of the standard treatment should be done as soon as drug susceptibility testing (DST) results are available.

Resistant TB has been a problem since anti-tuberculosis (anti-TB) drugs were first introduced in the mid 1940s (55), and remains a serious threat to TB control efforts (54). Although levels of drug resistance in BC have historically been low, monitoring trends remains a public health priority. Mono-resistant TB is defined as resistance to one drug only, most often Isoniazid (INH). Multi-drug resistant TB (MDR-TB) is caused by MTB resistant to at least isoniazid and rifampin, the most effective anti-TB drugs (56). MDR-TB either results from primary infection with resistant bacteria or may develop in the course of a patient's treatment (acquired resistance). Poly-resistant TB is caused by MTB resistant to more than one anti-TB drug, but not both INH and rifampin (56). Extensively drug-resistant TB (XDR-TB) is a form of TB caused by MTB resistant to INH and rifampin (i.e. MDR-TB), as well as any fluoroquinolone and any of the second-line anti-TB injectable drugs (amikacin, kanamycin or capreomycin) (56).

Results

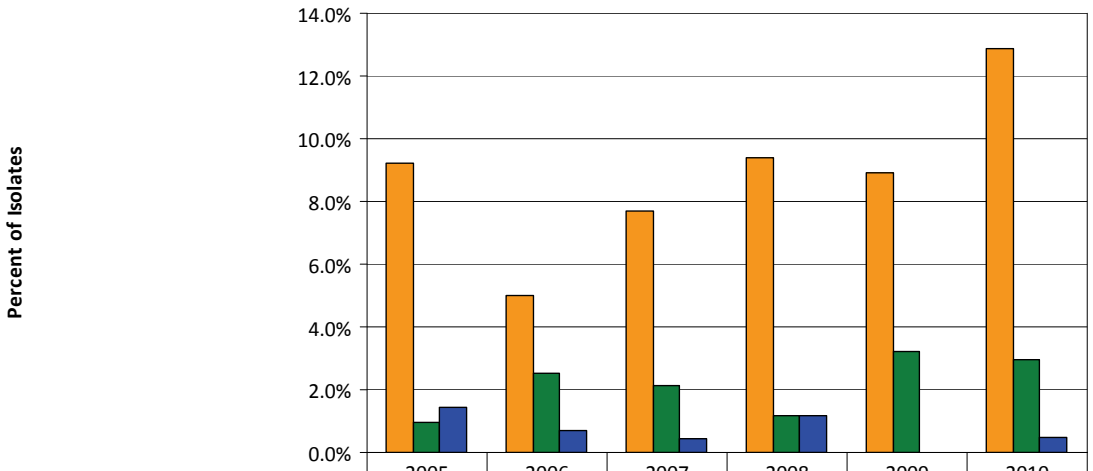
A total of 1424 culture-confirmed TB strains with DST results available were reported between 2005 and 2010 by Clinical Prevention Services, BCCDC. In British Columbia, MDR-TB was found in 0.7% of cases over the 6 years; over the same period in all of Canada, MDR-TB was found in 1.1% of cases (56). Mono-resistance occurred in 8.6% of BC cases while poly-

resistance was noted in 2.2% (*Figure 21*). While the annual proportion of MDR-TB cases has fluctuated over the six-year period, the proportions of poly-resistant and mono-resistant TB cases have increased (*Figure 21*). Seventy-three percent of the MTB strains resistant to at least one drug were in foreign born persons, though this percentage decreased between 2005 and 2010 as a result of an increase in drug-resistant strains from Canadian born persons (3/24 in 2005 versus 12/33 in 2010). There were no cases of extensively drug resistant TB (XDR) diagnosed in BC over the 6 years, but 0.04% of cases in Canada were XDR during that period (56). The commonest single drug resistance was to INH (N=66, 40.2% of those resistant to at least one drug) and nine cases (5.5%) were rifampin mono-resistant.

Discussion

Data from Clinical Prevention Services, BCCDC during the 2005-2010 period indicate that rates of both multi-drug and poly-drug resistant TB remain low (<4%), with no XDR-TB. The increase in mono-resistant TB is largely explained by a cluster of INH-resistant TB in a marginalized/under-housed Canadian born population. For more information on TB, the most recent BCCDC report can be found online at:
http://www.bccdc.ca/dis-cond/a-z/_t/Tuberculosis/statsres/default.htm

Percent and Number of M. Tuberculosis Isolates that are Mono-resistant, Poly-resistant and Multidrug-resistant (MDR-TB) in British Columbia, Canada, 2005-2010



	2005	2006	2007	2008	2009	2010
Mono-resistant	9.2%	5.0%	7.7%	9.4%	8.9%	12.9%
Poly-resistant	1.0%	2.5%	2.1%	1.2%	3.2%	3.0%
Multi-resistant	1.5%	0.7%	0.4%	1.2%	0.0%	0.5%
Number of Mono-resistant strains	19	14	18	24	22	26
Number of Poly-resistant strains	2	7	5	3	8	6
Number of Multi-resistant strains	3	2	1	3	0	1
Total Number of Tested Isolates	206	279	234	256	247	202

Figure 21 Prevalence of drug resistant tuberculosis in British Columbia, Canada 2005-2010
Source: PHMRL via Clinical Prevention Services, BCCDC

Antimicrobial Utilization Rates and Correlations

1. Overall Utilization

Background

Ever since their development, antibiotics have revolutionized medical treatment. However, due to rising trends in antibiotic resistance attributable to the utilization of antimicrobials in humans as well as food producing sources, the consequences of misuse and overuse of these pharmaceuticals must be acknowledged. Specifically, a delicate balance between the risks of the individual and those of the population must be established to optimize the benefits associated with the use of these drugs.

Results

In the late 1990s, consumption of all antimicrobials for systemic use was steadily declining reaching its nadir in 2002 (*Figure 22*); since then, the utilization rate increased until 2005, remained steady until 2008, dropped significantly in 2009, and remained stable in 2010 (*Figure 22*).

The utilization trends of the main classes of antibiotics, as outlined by the Anatomical Therapeutic Chemical (ATC) classification system, are depicted (*Figure 23*). The antibiotic utilization rates in 2010 for most major classes were similar to those of 2009. Utilization of the β-lactam class of antibacterials including penicillins declined from the late 1990s to early 2000s, but has fluctuated at the same level since 2002 (*Figure 23*). Despite an overall decrease, this class remains the most frequently used class of antibacterials in BC. Macrolides, lincosamides and streptogramins utilization rate had been steadily increasing from 1998 to 2005, but has remained relatively steady with a slight decrease since then (*Figure 23*). The increase in utilization rate in the past was primarily attributable to increased utilization of clarithromycin, and in part azithromycin, as erythromycin use has dramatically declined since 1996. Both tetracyclines, and sulfonamides and trimethoprim utilization rates steadily declined since 1996 and remained stable from 2004 to 2009 (*Figure 23*). Despite a remarkable drop in tetracycline drug use, the utilization rate of the tetracyclines class had a greater increase in 2010 than any year recorded due to a dramatic increase in doxycycline and minocycline use (*Figure 23*). The utilization rate for quinolone antibacterials increased from 1996 to 2004, but has since remained steady. Principally due to nitrofurantoin use, the utilization rate of other antibacterials has increased almost every year since 1996, and saw its greatest increase for all years in 2010 (*Figure 23*). The utilization rate of other β-lactam antibacterials increased from 1996 to 2005, but since then has decreased to its lowest point for all years recorded (*Figure 23*).

When compared to that of several European nations, 2009 overall utilization rate in British Columbia is lower than many (12 countries with less utilization and 20 countries with more) (*Figure 24*). For a breakdown of consumption for each class in Europe see (57), and for comparison of BC and European utilization of each class, see the upcoming 2010 Utilization Report published by the BCCDC. When compared to other Canadian provinces,

overall utilization in BC is second lowest (next to Québec), but the overall cost in BC is lowest.

Discussion

The rate of antibiotic utilization remained stable from 2006 to 2008, dropped in 2009 and remained stable in 2010, arresting an upward trend seen between 2002 and 2005.

Some classes of antimicrobials may be starting a decreasing trend in utilization (i.e. other β-lactams, macrolides, lincosamides and streptogramins) while tetracyclines need to be monitored in future years to ensure that the increase observed in 2010 is not the start of a trend. Most other antimicrobial classes seem to be following their previous trends of increasing utilization rates (other antibacterials) and stabilizing utilization rates (quinolones, penicillins, and sulfonamides and trimethoprim).

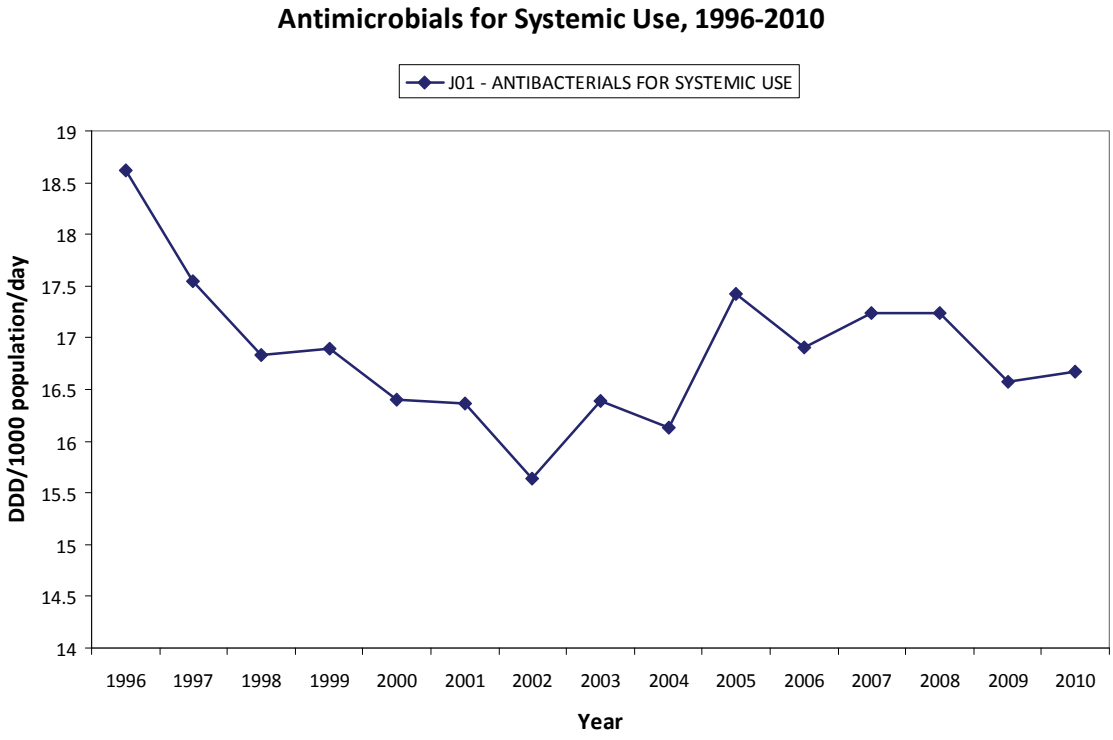


Figure 22 Defined daily rate of all antimicrobials for systematic use
Source: PharmaNet

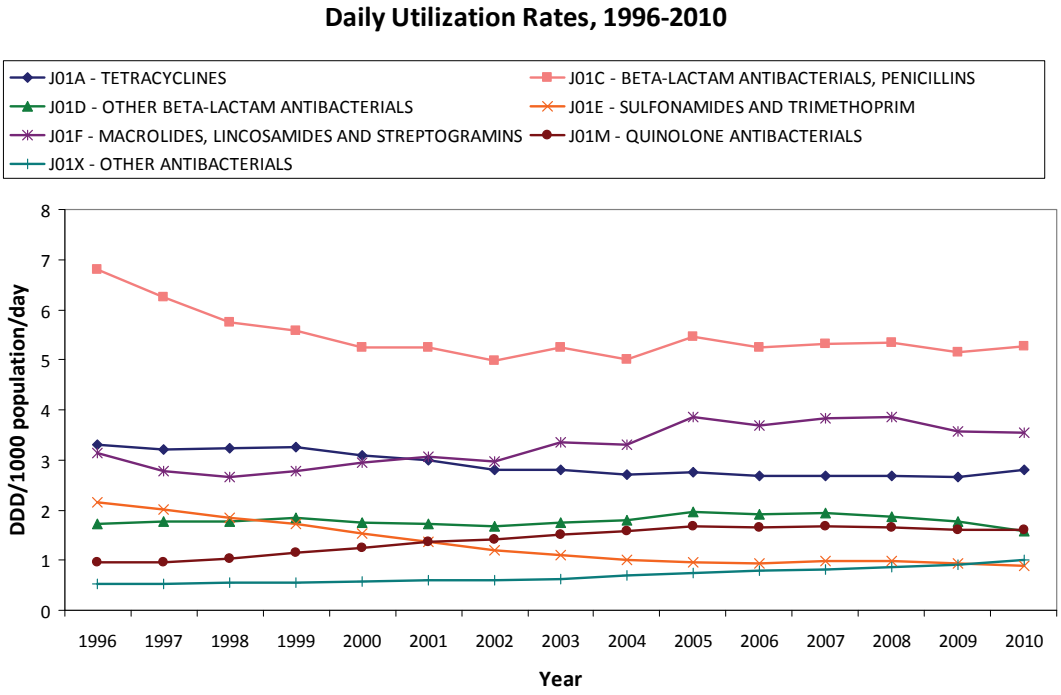


Figure 23 Defined daily rate of antimicrobials utilization by class
Source: PharmaNet

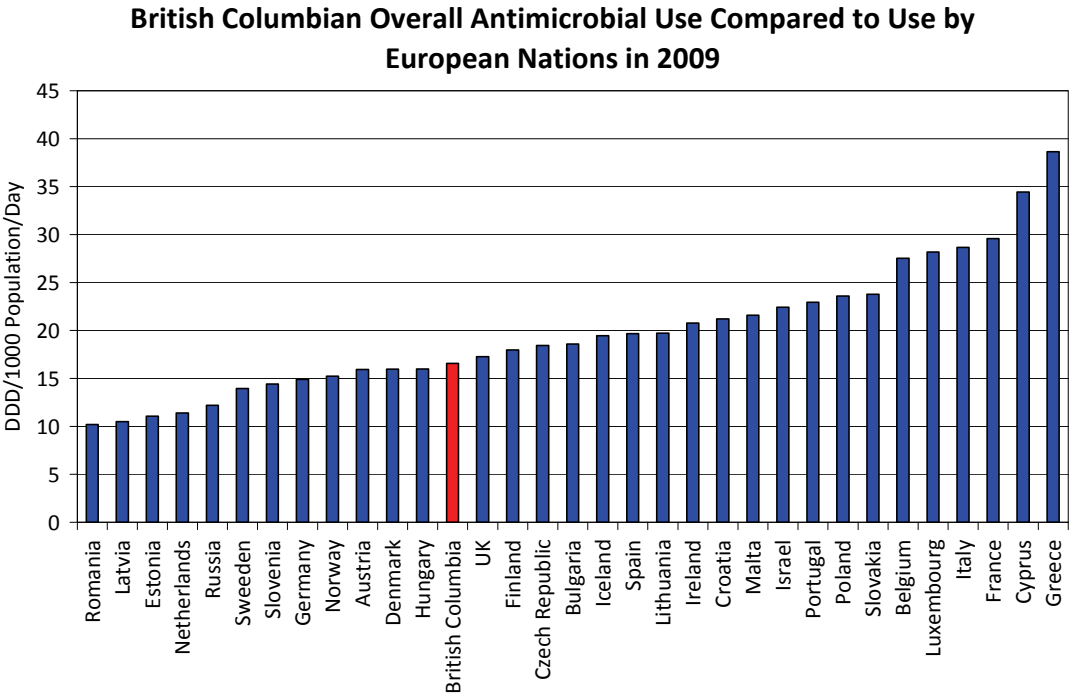


Figure 24 Defined daily rate of all antimicrobials for systematic use in BC and several European nations for 2009
Source: PharmaNet, European Surveillance of Antimicrobial Consumption (ESAC) (57)

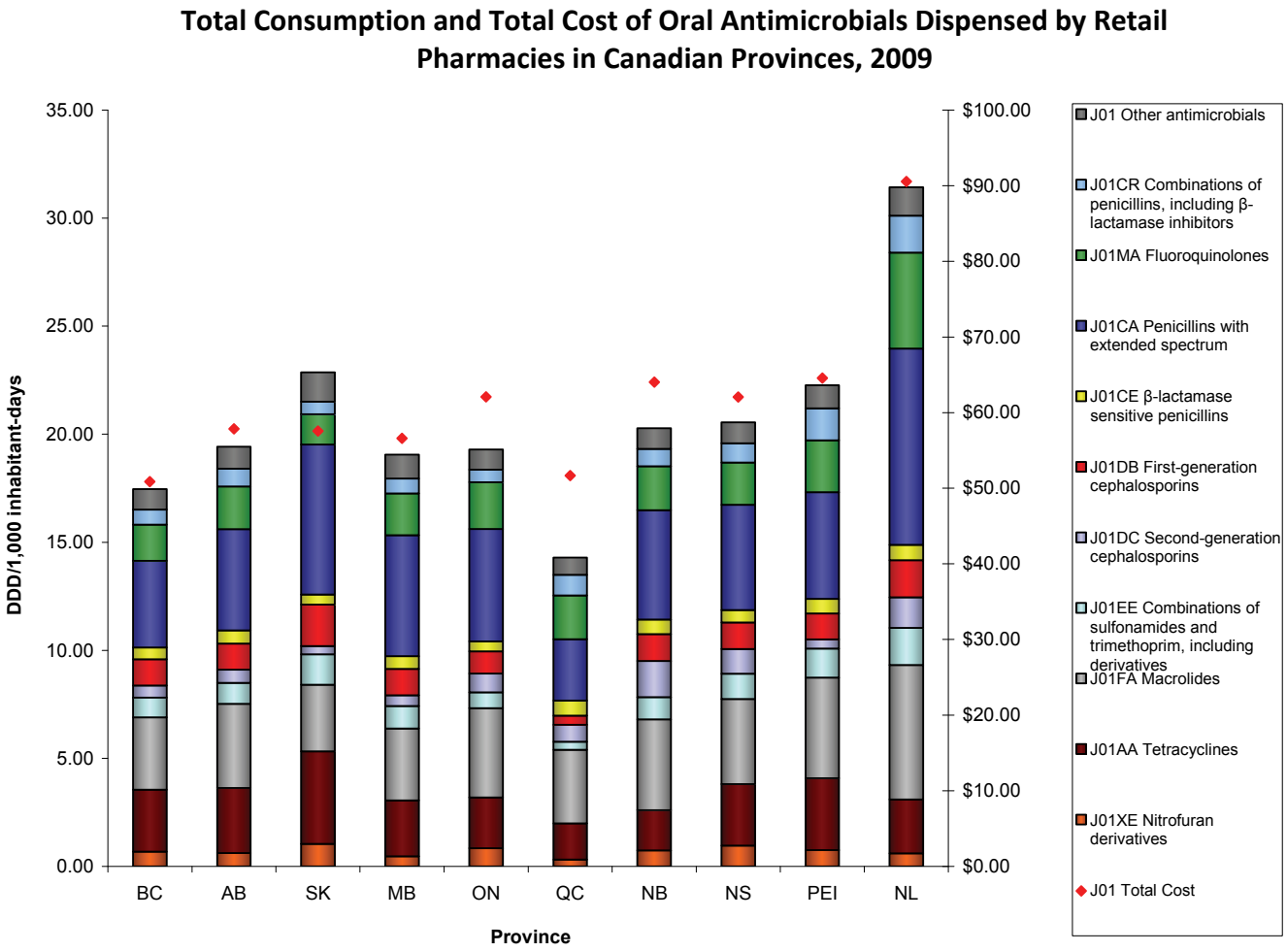


Figure 25 Total consumption (DDD/1,000 inhabitant-days) and total cost of oral antimicrobials dispensed by retail pharmacies in Canadian provinces, 2009 (58)

Source: CIPARS Human Antimicrobial Use Short Report 2000-2009 (58)

2. β-lactams

Examples

Penicillins with extended spectrum – Ampicillin, Amoxicillin

β-lactamase sensitive penicillins – Penicillin V

β-lactamase resistant penicillins – Cloxacillin

Penicillins with β-lactamase inhibitors – Amoxicillin-clavulanic acid

First-generation cephalosporins – Cephalexin

Second-generation cephalosporins – Cefuroxime

Third-generation cephalosporins – Cefixime, Ceftazidime, Ceftriaxone

Background

Penicillin was among the first antibiotics to be produced and marketed for therapeutic use. As such, penicillinase-producing bacterial strains, mainly *Staphylococcus aureus*, were amongst the first examples of documented antimicrobial resistance (9). The class of β-lactam antimicrobials includes penicillins and cephalosporins. These antimicrobials bind to penicillin-binding proteins (PBPs) and prevent cross-linking (transpeptidation) of peptide residues in the cell wall (11;21). Resistance mechanisms include expression of altered PBPs with reduced affinity for β-lactams and production of β-lactamases that cleave β-lactams and render them ineffective (9;11;21). Methicillin-resistant *Staphylococcus aureus* strains (MRSA), for example, express the *mecA* gene, which encodes an altered penicillin-binding protein, PBP2a (11;21).

β-lactam antimicrobials are typically used to treat Gram-positive pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, but are also active against Gram-negative infections (16;21). Newer generation cephalosporins contain modifications that confer increased activity against Gram-negative bacteria, while older generations are active primarily against Gram-positive bacteria. Penicillin antimicrobials are also modified to increase their spectrum of activity (e.g. penicillins with extended spectrum) as well as to circumvent antimicrobial resistance mechanisms (e.g. β-lactamase resistant penicillins and penicillins with β-lactamase inhibitors).

Results

Penicillins remain the most frequently prescribed class of antibiotics in BC. The utilization rate of penicillins showed a decreasing trend from the late 1990s to 2002, but has fluctuated between 5.0 and 5.5 DDD/1000 inhabitant/day (5.27 in 2010) from 2000 to 2010 (*Figure 26*). Penicillins with extended spectrum (e.g. amoxicillin and ampicillin) constitute the majority of penicillin prescriptions; as such, they parallel the increasing trend observed for all penicillin antimicrobials (*Figure 26*). β-lactamase resistant and β-lactamase sensitive penicillins also demonstrated decreasing trends from 1996 to 2009, but while β-lactamase sensitive penicillins continued the trend for 2010, utilization of β-lactamase resistant penicillins increased for the first time in 2010 since first recorded (*Figure 27*). Utilization of penicillins combined with β-lactamase inhibitors demonstrated an increasing trend between years 1996 to 2009, but dropped 20% in 2010 (*Figure 27*).

First generation cephalosporins constituted the majority of cephalosporin prescriptions as the utilization rate of broad spectrum second and third-generation cephalosporins remained below 0.5 DDD/1000 inhabitant/day (*Figure 28*). While third generation cephalosporins saw the largest increase in utilization since first recorded (from 0.07 to 0.11 DDD/1000 inhabitant/day) utilization of second generation cephalosporins saw the largest decrease for all years, following the decreasing trend observed between 1996 and 2010 (*Figure 28*). Although a clear increasing trend of first generation cephalosporins utilization was seen from 1996 to 2005, the trend began to slow until it reversed in 2008 and also witnessed a larger decrease than any other year recorded (*Figure 28*).

Significant positive correlations existed between the percent of MRSA isolates and the utilization of penicillins combined with β-lactamase inhibitors (e.g. amoxicillin-clavulanic acid) and first-generation cephalosporins (e.g. cephalexin) from 2002 to 2010, according to BCAMM data (*Figure 29*).

According to the CBSN data, there is no significant correlation between the percent of *S. pneumoniae* isolates non-susceptible to penicillin and utilization of β-lactamase sensitive penicillin from years 1996 to 2010 (*Figure 30*).

Discussion

Penicillin remains the most frequently prescribed antibiotic class in BC. Although the usage rate fluctuated in previous years, it has been stable in the last five years. The utilization of penicillin antimicrobials is predominantly driven by the utilization of penicillins with extended spectrum.

Significant positive correlations were found between MRSA and the use of first generation cephalosporins and of penicillins combined with β-lactamase inhibitors, from 2002 to 2010. First generation cephalosporin continues to be the most frequently used cephalosporin. While these results do not indicate the appropriateness of particular treatments for MRSA infections (indeed, both of the classes reported here are not effective for MRSA), they do describe the correlation between use and resistance as seen in the community.

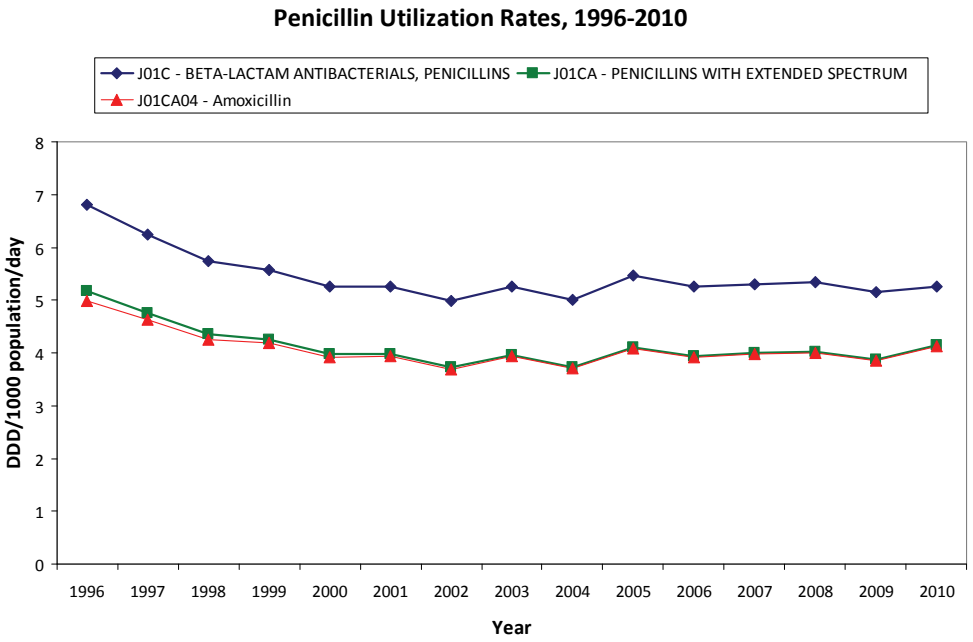


Figure 26 Defined daily rate of all penicillins, penicillins with extended spectrum and amoxicillin utilization

Source: PharmaNet

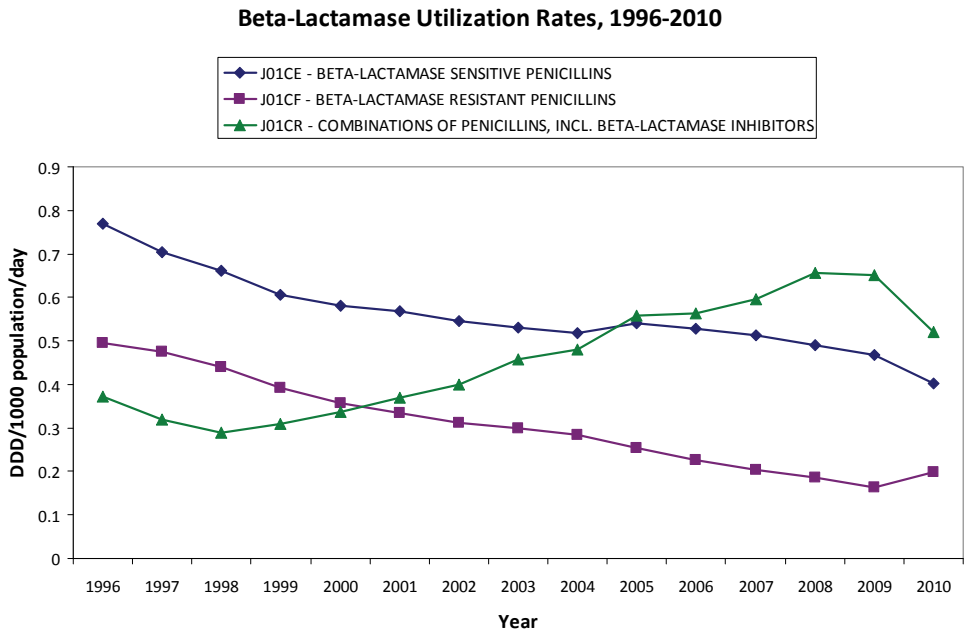


Figure 27 Defined daily rate of penicillin utilization: focus on penicillins with utilization rate of less than 1.0 DDD/1000 inhabitant/day

Source: PharmaNet

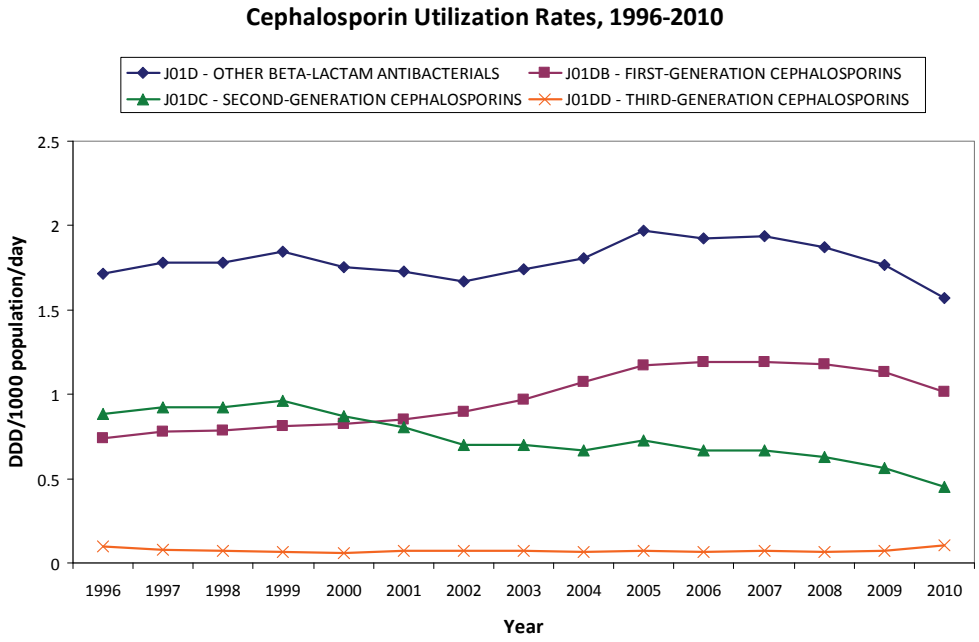


Figure 28 Defined daily rate of cephalosporin utilization
Source: PharmaNet

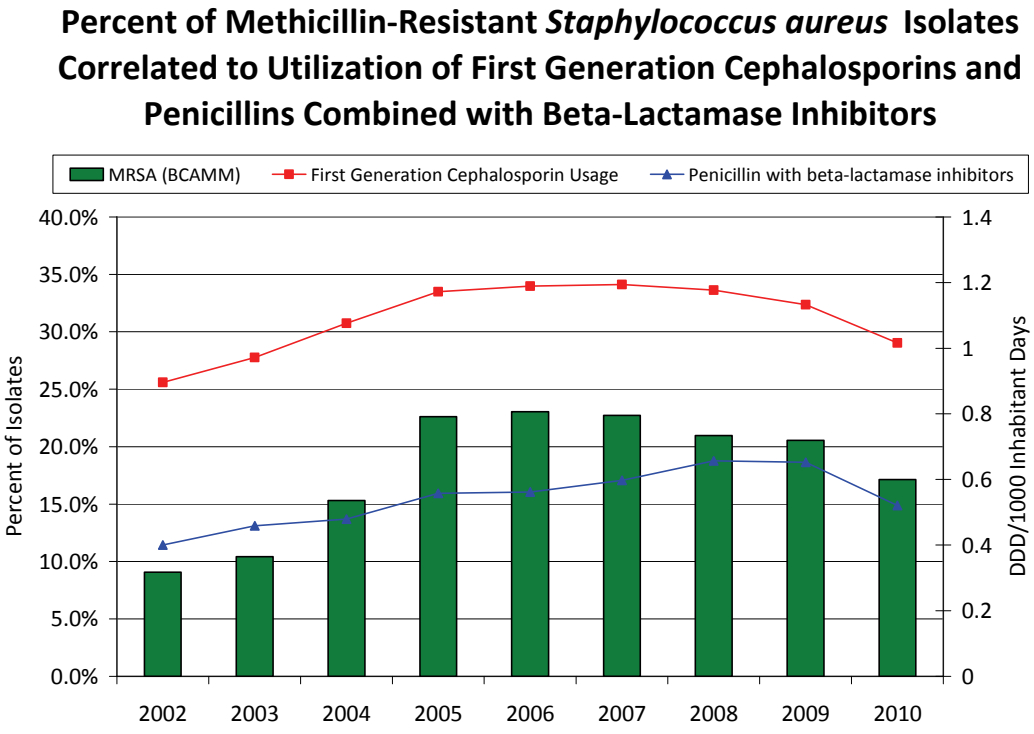


Figure 29 Percent of methicillin-resistant *Staphylococcus aureus* isolates (BCAMM) correlated with the utilization of first generation cephalosporins and penicillins combined with beta-lactamase inhibitors
Source: BCAMM (3); PharmaNet

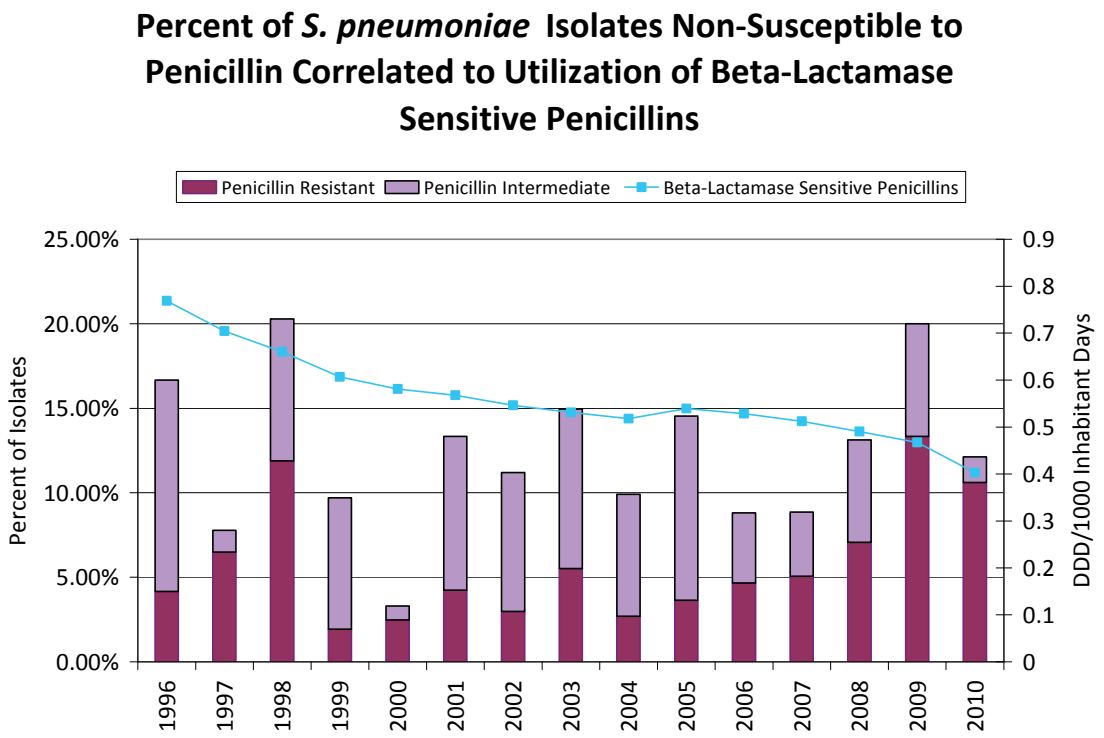


Figure 30 Percent of *Streptococcus pneumoniae* isolates (CBSN) non-susceptible to penicillin correlated with the utilization of β-lactamase sensitive penicillins

Source: CBSN; PharmaNet

3. Macrolides and Lincosamides

Examples

Macrolides – Erythromycin, Clarithromycin

Lincosamides – Clindamycin, Lincomycin

Background

Macrolide antimicrobials (e.g. erythromycin, clarithromycin, and azithromycin) are typically used to treat Gram-positive bacteria that infect the respiratory tract such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* (16). The increased use of macrolides over β-lactams has lead to an increase in macrolide resistance in recent years, especially in *S. pneumoniae* isolates (59). In addition, the longer half-life of newer macrolides (e.g. clarithromycin, azithromycin, spiramycin and telithromycin) results in the exposure of pathogens to suboptimal treatment concentrations for longer durations, which further propagates the resistance trends.

Macrolide and lincosamide (e.g. clindamycin) antimicrobials bind to the 50S ribosomal subunit and prevent elongation of peptides during bacterial RNA-dependent protein synthesis (21). Resistance to these antimicrobials occurs through two mechanisms: increased antimicrobial efflux due to expression of an efflux pump or ribosomal modification due to expression of a ribosomal methylase (21;22). These resistance mechanisms are respectively associated with the M phenotype and MLS_B phenotype, which confers multidrug resistance to macrolides, lincosamides, and streptogramin B (21;22).

Results

As the utilization of erythromycin, an older macrolide, decreased during the available time period, 1996 to 2010, the utilization of new macrolides (clarithromycin and azithromycin) increased (*Figure 31*). The most consistent increase of new macrolides was from 1997 to 2005. Clarithromycin was the most frequently prescribed macrolide with a defined daily rate of 2.50 DDD/1000 inhabitant/day in 2010 (*Figure 31*). Although use of new macrolides had been increasing in past years, the utilization of azithromycin has been decreasing since 2007, and use of clarithromycin has remained relatively stable since 2005; this has caused new macrolide utilization to reach 2.90 DDD/1000 inhabitant/day, its lowest point since 2004 (*Figure 31*). Utilization of lincosamides (e.g. clindamycin) saw a similar increase from 1996 to 2010 attributable to the increase in skin/soft tissue infections, but the utilization rate was much lower than that of macrolides, with a defined daily rate of 0.38 DDD/1000 inhabitant/day (data not shown).

As indicated by CBSN data, the percent of *S. pneumoniae* isolates non-susceptible to erythromycin increased between years 2001 to 2010 (*Figure 32Figure 32*). This data is generally associated to the utilization observed for macrolide utilization from years 2001 to 2010 (*Figure 32*). The percent of invasive Group A Streptococcus (iGAS) isolates non-susceptible to erythromycin, according to NCS-iPHIS linked data, increased until 2005 and decreased after; this is associated with the utilization of macrolides which underwent a similar, albeit less dramatic trend over the same years (*Figure 33*).

Using susceptibility data from BC Biomedical Laboratories decreases were observed in the percent of *S. pyogenes* and MRSA isolates non-susceptible to erythromycin from 2005 to 2010, (*Figure 34*). During the same period, utilization of macrolides stayed relatively steady, but did correlate well with MRSA resistance. On the other hand, data from BC Biomedical Laboratories (for MSSA) showed that the percentage of MSSA non-susceptible to clindamycin during 2002 to 2010 were correlated (non-significantly) to the increase observed in the utilization of clindamycin (*Figure 35*).

Discussion

The parallel trends in all macrolide and new macrolide utilization along with the steady decline in erythromycin utilization suggest a transition from older to newer macrolide prescription. This trend is of concern due to the long duration of suboptimal antimicrobial concentrations that are associated with newer macrolides. As well, due to the prevalent MLS_B phenotype, resistance to macrolides often indicates multidrug resistance to lincosamides and streptogramin B in addition to macrolides.

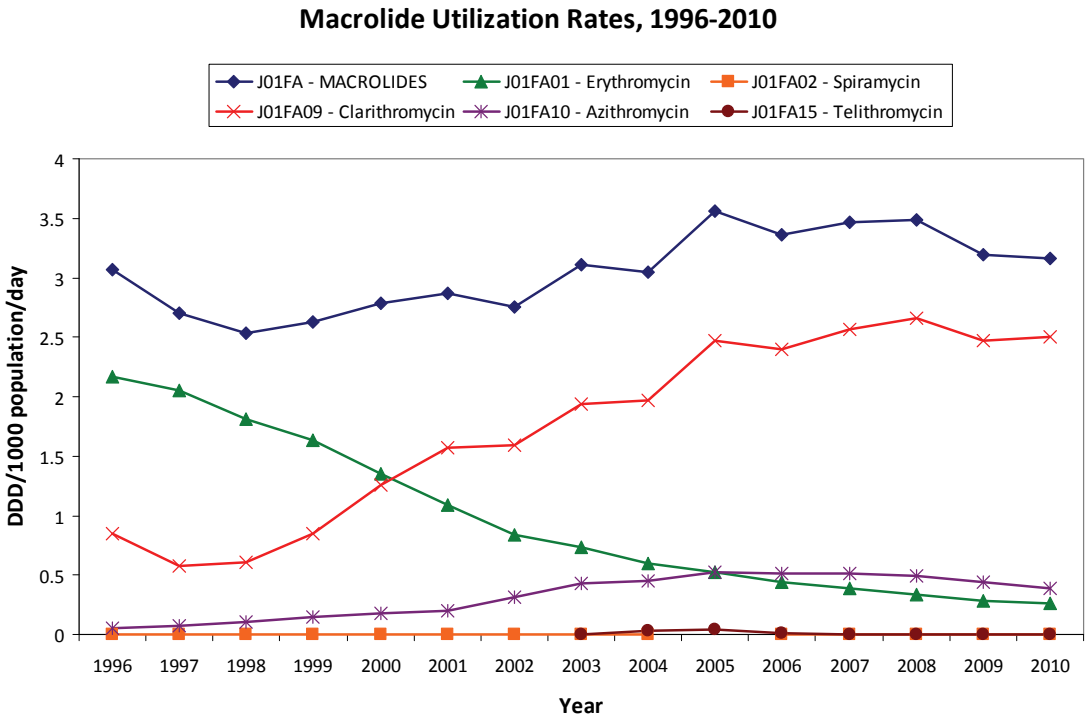


Figure 31 Defined daily rate of macrolide utilization
Source: PharmaNet

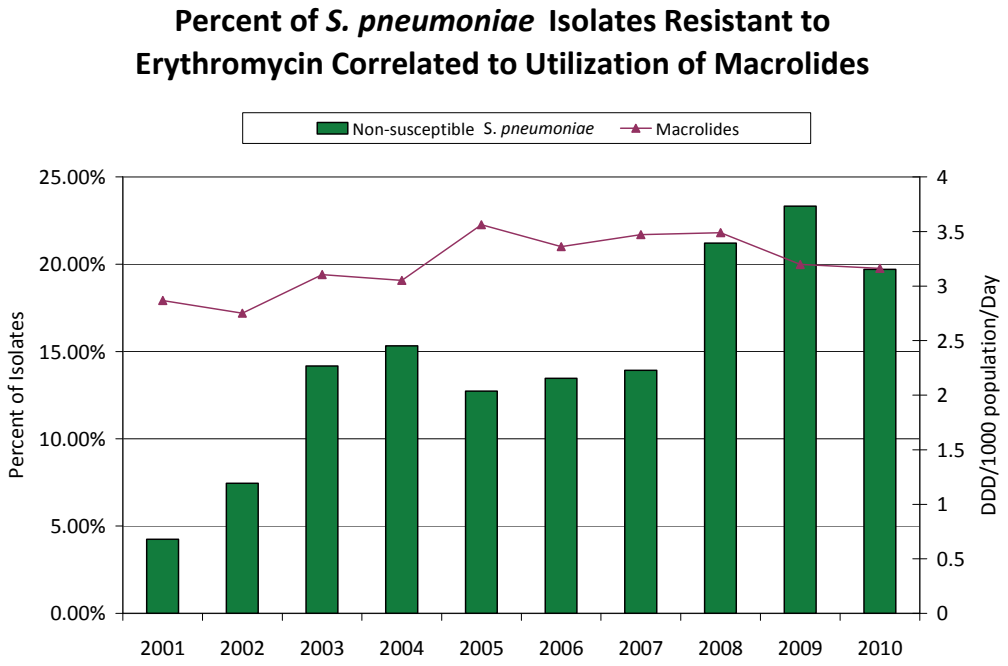


Figure 32 Percent of *Streptococcus pneumoniae* isolates (CBSN) non-susceptible to erythromycin correlated with the utilization of macrolides

Source: CBSN; PharmaNet

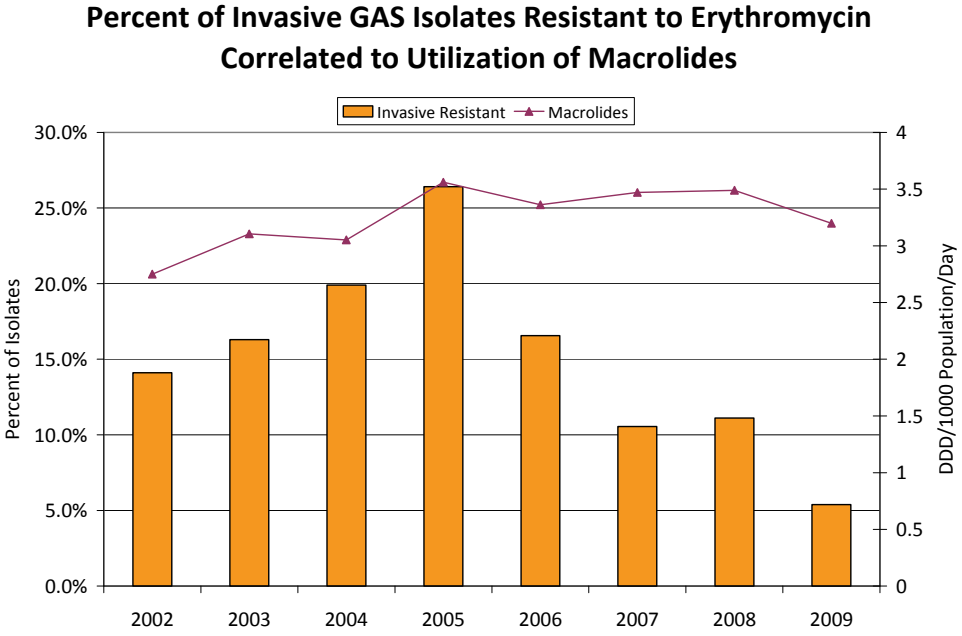


Figure 33 Percent of invasive Group A *Streptococcus* isolates resistant to erythromycin correlated with the utilization of macrolides

Source: NCS-iPHIS linked dataset; PharmaNet

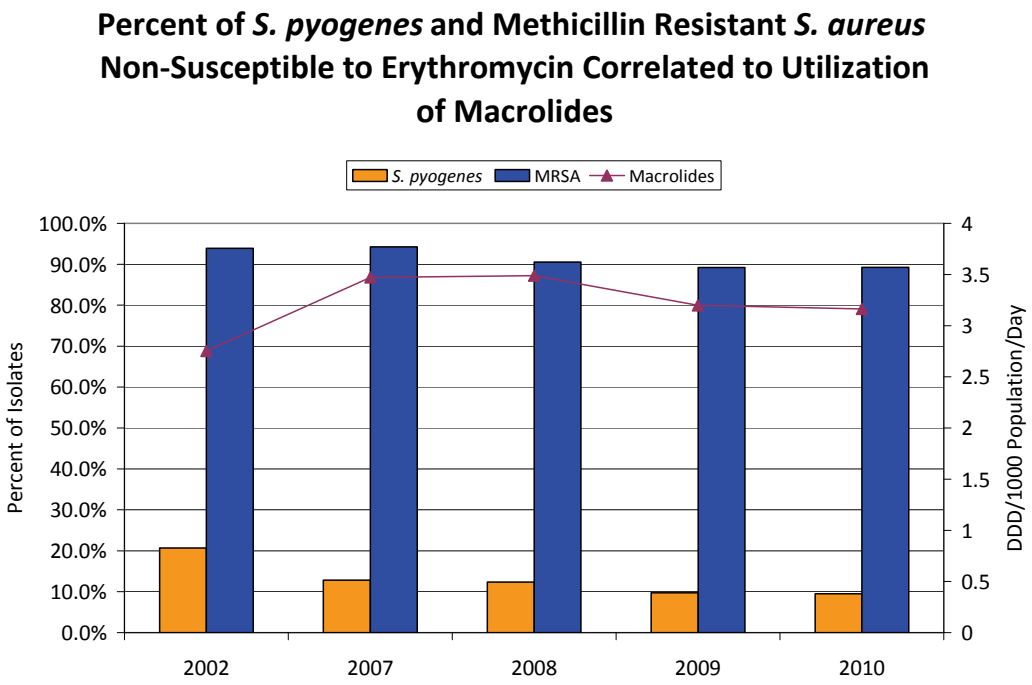


Figure 34 Percent of MRSA and *S. pyogenes* isolates resistant to erythromycin correlated with utilization of macrolides

Source: BC Biomedical Laboratories; PharmaNet

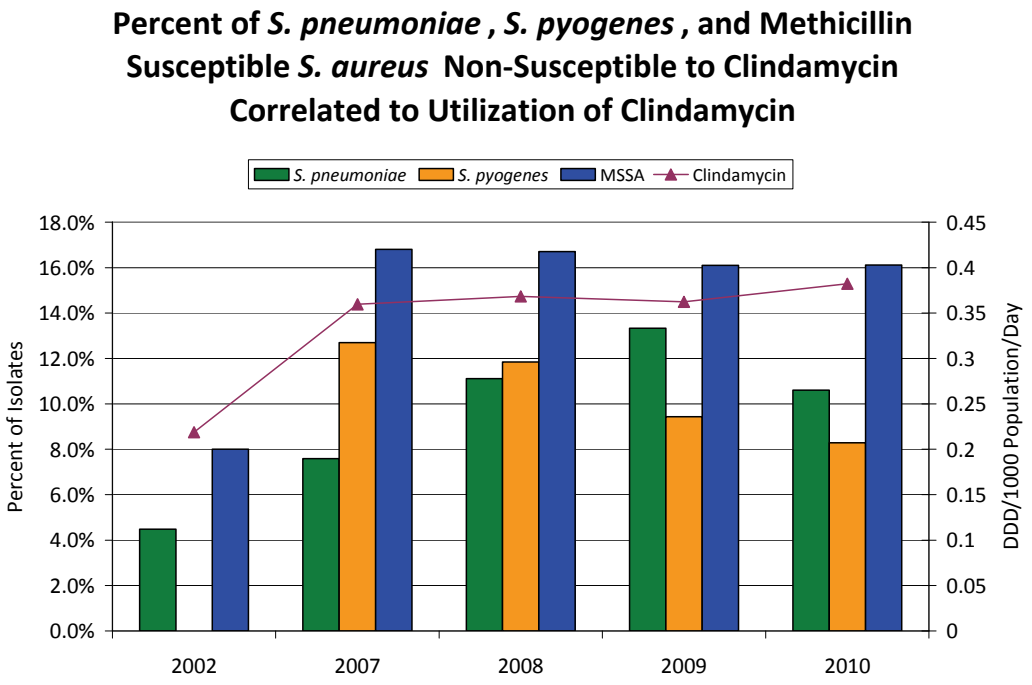


Figure 35 Percent of isolates (BC Biomedical Laboratories for MSSA and *S. pyogenes*, CBSN for *S. pneumoniae*) non-susceptible to clindamycin correlated with utilization of clindamycin

Source: BC Biomedical Laboratories; CBSN; PharmaNet

4. Tetracyclines

Examples

Tetracycline

Doxycycline

Minocycline

Background

Tetracyclines are active against a broad-spectrum of Gram-negative and Gram-positive bacteria; however, widespread resistance has limited their use (21). These antimicrobials are classified as short-acting (e.g. tetracycline) or long-acting (e.g. doxycycline and minocycline) depending on the duration of their therapeutic concentration in the body. Tetracyclines bind to the 30S ribosomal subunit and prevent the attachment of the incoming aminoacyl-tRNA during protein synthesis (21). Resistance to tetracyclines can be either chromosomally or plasmid-mediated through the expression of *tet* genes (21). These genes encode an efflux pump for increased export of tetracyclines or ribosome binding proteins that alter the confirmation of the ribosome such that tetracyclines can no longer bind (21).

Results

From 1996 to 2010, the utilization rate for the overall tetracyclines drug class decreased including the drug tetracycline which experienced a 50% drop in 2010 alone (*Figure 36*). However, due to the substantial increase in doxycycline and minocycline utilization, the tetracycline class reached its highest utilization rate since 2003, and saw a larger increase in 2010 than any other year recorded (*Figure 36*). Doxycycline has seen an increase in utilization from 1.05 DDD/1000 inhabitant/day in 2002 to 1.61 DDD/1000 inhabitant/day in 2010, up from 1.31 DDD/1000 inhabitant/day in 2009 (*Figure 36*). The utilization rate of minocycline also increased slightly over the available time period; although it remains under 1.0 DDD/1000 inhabitant/day, in 2010 minocycline experienced its greatest increase since 1998 (*Figure 36*).

According to CBSN, there was no significant correlation between *S. pneumoniae* resistance to tetracycline and utilization of tetracyclines.

Conclusion

Overall, the utilization of tetracyclines decreased from 1996 to 2010, although 2010 saw a jump in tetracycline utilization from the large sudden increases in minocycline and doxycycline utilization. The tetracycline drug has seen a decline in utilization, while doxycycline and minocycline have seen general increases during the same time period. BC Biomedical Laboratories data were not available at time of writing because tetracycline resistance data were not provided for years before 2007.

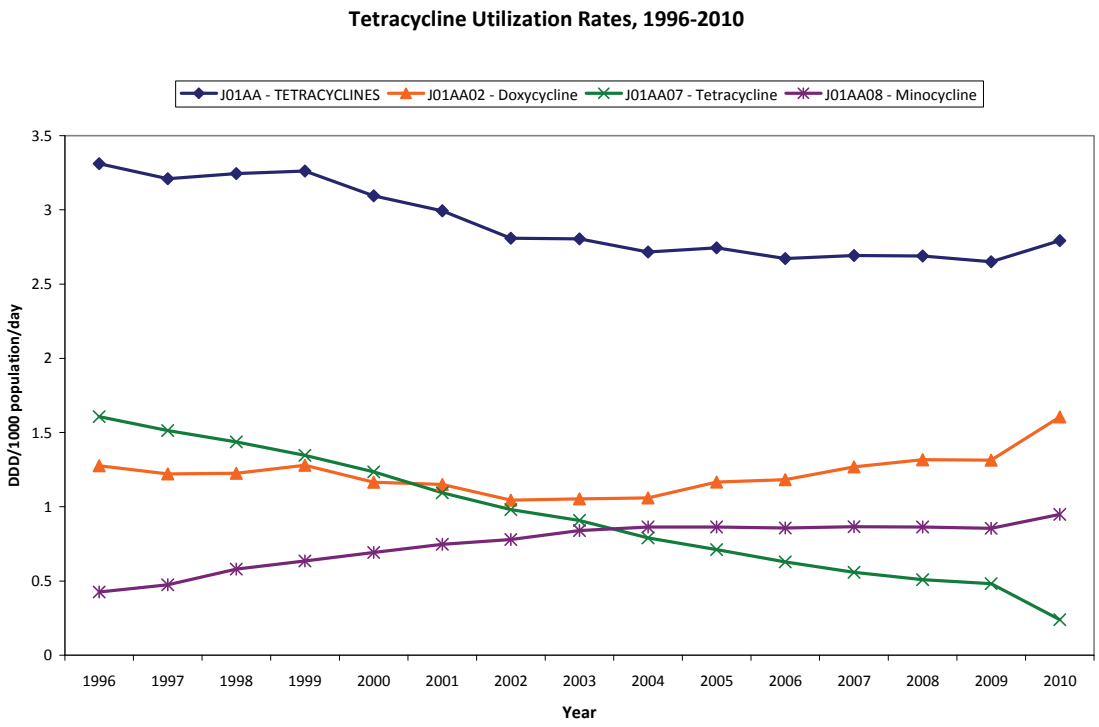


Figure 36 Defined daily rates of tetracycline utilization
Source: PharmaNet

5. Quinolones

Examples

Ciprofloxacin

Levofloxacin

Norfloxacin

Moxifloxacin

Background

Quinolone antimicrobials are active against a broad-spectrum of both Gram-positive and Gram-negative bacteria. As such, this class has been used extensively in the past decade, with utilization rates almost reaching that of cephalosporins. Most clinically used quinolones belong to the fluoroquinolones subclass, named for the presence of a fluoro group attached to the parent molecule, nalidixic acid. Due to its broad spectrum coverage, this class of antimicrobials is used to treat urinary tract infections (UTI), gastroenteritidis and respiratory infections such as pneumonia (60). However, in the past decade many organisms have developed resistance towards fluoroquinolones, especially moxifloxacin. These organisms include but are not limited to *Staphylococcus aureus*, enterococci and *Streptococcus pyogenes* (60). Misuse and overuse of fluoroquinolone antimicrobials for non-severe or non-life-threatening infections is now a serious problem around the world (61).

Quinolone antimicrobials bind to DNA gyrase and topoisomerase IV enzymes, inhibit DNA synthesis, and consequently prevent bacterial replication (21). Resistance to quinolones occurs via mutations in the genes encoding DNA gyrase (*gyrA* and *gyrB*) and topoisomerase IV (*parC* and *parE*) or via increased efflux of the antimicrobial (21). The specificity and magnitude of the resistance is related to the number of mutations present in the DNA supercoiling genes (21).

Results

Ciprofloxacin constitutes the majority of fluoroquinolone prescriptions in BC. Increased use of ciprofloxacin between 1996 and 2007 (*Figure 37*) had driven the overall increase of fluoroquinolone usage in this period. Although the ciprofloxacin utilization rate has decreased since 2008, the utilization rate remains high, with 2010 figures showing rates of 1.15 DDD/1000 inhabitants/day, an increase of 80% since 1996 (*Figure 37*). Utilization of newer quinolones (levofloxacin ofloxacin) increased until a peak of 0.22 DDD/1000 inhabitants/day in 2004 before decreasing to 0.07 DDD/1000 inhabitants/day in 2010 (*Figure 37*). The utilization of the older fluoroquinolone, norfloxacin, showed a decreasing pattern for all available years (*Figure 37*). Moxifloxacin rates significantly increased since its introduction in 2000 (*Figure 38*). It was the second most prescribed quinolone after ciprofloxacin, at 0.37 DDD/1000 inhabitant/day in 2010 (*Figure 38*).

The percent of urinary tract infection (UTI) pathogens such as *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae* non-susceptible to ciprofloxacin all demonstrated increases between years 1998 to 2010 according to data from BC Biomedical Laboratories (*Figure 39*). *P. mirabilis* and *K. pneumoniae* had significant correlations between 1999 and 2008 and 1999 and 2010, respectively. The increase in fluoroquinolone resistance by UTI

pathogens corresponds to the increase in ciprofloxacin utilization which occurred during the same time period (*Figure 39*). A significant correlation was found between the percent of *P. mirabilis* isolates non-susceptible to ciprofloxacin and ciprofloxacin utilization from 1999 to 2010. Although *Enterococcus* spp. isolates more frequently demonstrated resistance against ciprofloxacin, the percent of *Enterococcus* spp. isolates non-susceptible to ciprofloxacin did decrease significantly between years 2002 and 2011, while the other presented UTI pathogens continued to increase (*Figure 39*).

Data regarding fluoroquinolone non-susceptibility in the staphylococci are no longer available due to changes in testing procedures at BC Biomedical Laboratories.

Discussion

Ciprofloxacin non-susceptibility continues to increase amongst UTI pathogens. This trend should be monitored in subsequent years as ciprofloxacin has been a recommended therapy for treating UTIs although current guidelines (62) recommend nitrofurantoin and TMP-SMX.

Increases in the percent of isolates non-susceptible to fluoroquinolones correlate with overall increases in utilization, driven in recent years by addition of newer agents. Despite the observable increases, the majority of *S. pneumoniae* isolates remain susceptible to fluoroquinolone antimicrobials.

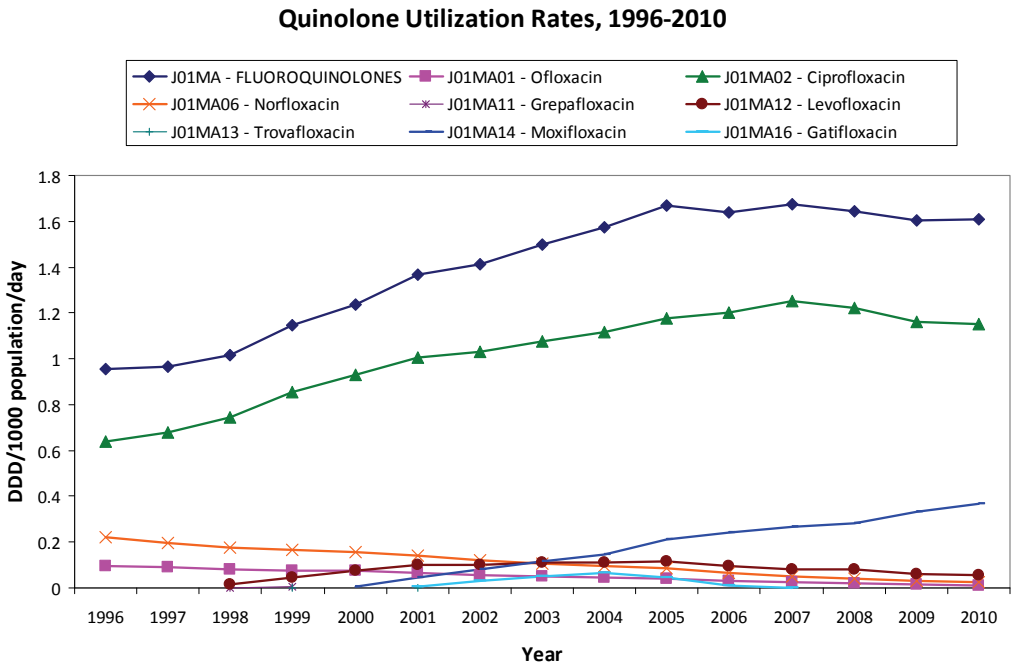


Figure 37 Defined daily rate of fluoroquinolone utilization
Source: PharmaNet

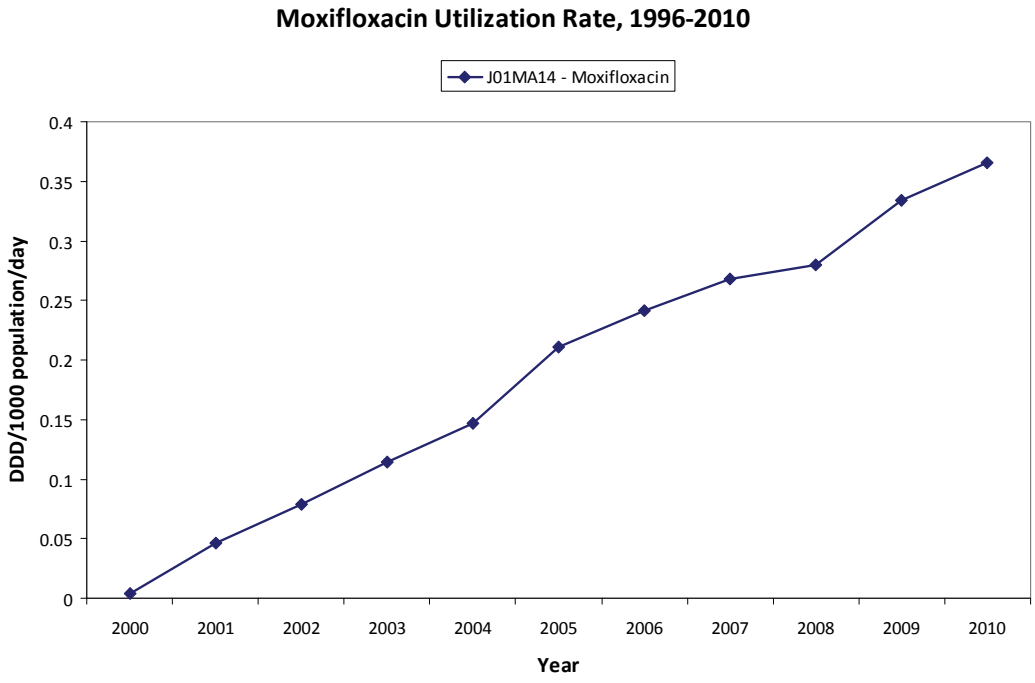


Figure 38 Defined daily rate of moxifloxacin utilization
Source: PharmaNet

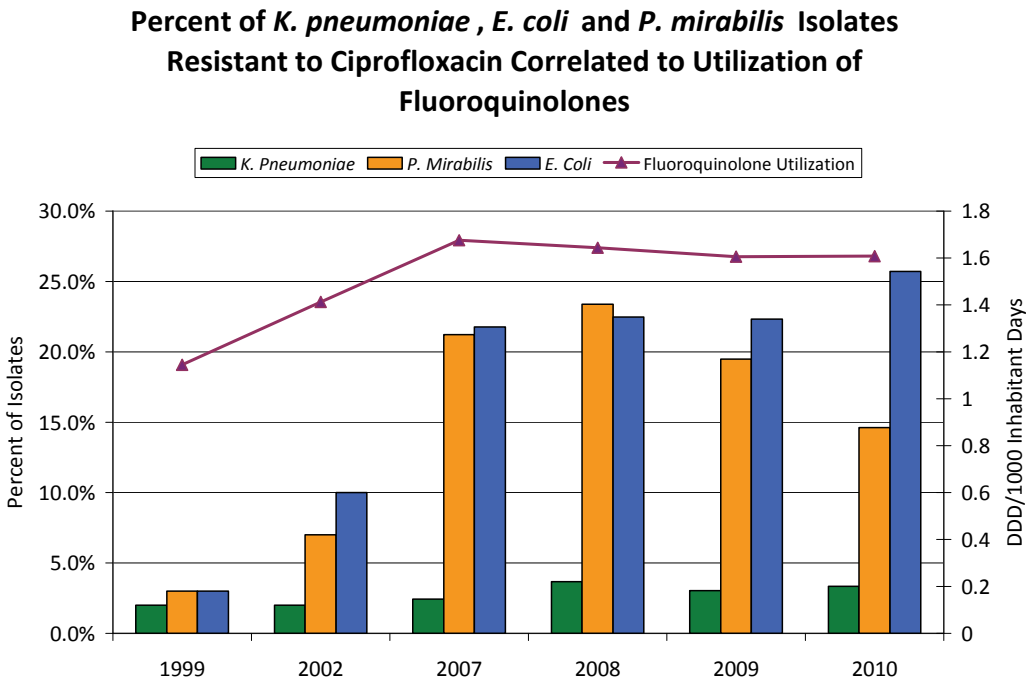


Figure 39 Percent of urinary tract infection pathogens (BC Biomedical Laboratories) non-susceptible to ciprofloxacin correlated with utilization of fluoroquinolones
Source: BC Biomedical Laboratories; PharmaNet

6. Sulfonamides and Trimethoprim

Examples

Trimethoprim-sulfamethoxazole (TMP-SMX)

Background

First synthesized prior to World War II, sulfonamides, also known as Sulfa drugs, are amongst the oldest agents shown to have antimicrobial properties, active also against certain protozoa. When combined with trimethoprim, sulfonamides are primarily used to treat urinary tract infections (UTIs) (16). These agents inhibit folic acid synthesis and, consequently, impede bacterial growth. Sulfonamides compete with *p*-amino-benzoic acid (PABA) for binding dihydropteroate synthase (DHPS), a critical enzyme in the folic acid synthesis pathway (21). Trimethoprim binds to dihydrofolate reductase (DHFR), another critical enzyme in the folic acid synthesis pathway and inhibits its function (21). Resistance mechanisms include the overproduction of PABA and DHFR, and modification of DHPS and DHFR (21).

Results

Trimethoprim-sulfamethoxazole (TMP-SMX), constitute the vast majority of sulfonamide and trimethoprim prescriptions. Utilization rates for trimethoprim and its derivatives, short-acting sulfonamides, and intermediate-acting sulfonamides not prescribed in combinations were less than 0.05 DDD/1000 inhabitant days for all available years (data not shown). Utilization of TMP-SMX shows a decreasing trend from 1996 to 2010, dropping 59% in that time period (*Figure 40*)

Despite the decrease in TMP-SMX utilization, the percent of UTI pathogens (*Escherichia coli, Proteus mirabilis*) non-susceptible to TMP-SMX showed an increasing trend between years 1998 to 2009 (*Figure 42*). Although a large decrease in resistance was observed in 2010, the percent of *P. mirabilis* isolates non-susceptible to TMP-SMX was significantly negatively correlated with the utilization of TMP-SMX from 1998 to 2009 (*Figure 42*). However, the percent of *Klebsiella pneumoniae* isolates non-susceptible to TMP-SMX has fluctuated at around 10% during the same time period (*Figure 42*). The percent of *Staphylococcus aureus* non-susceptible to TMP-SMX dramatically decreased from 2005 to 2011, matching the decrease in TMP-SMX utilization (*Figure 2*;*Figure 40*). The percent of CBSN *Streptococcus pneumoniae* isolates and BC Biomedical Laboratories *Streptococcus pneumoniae* isolates non-susceptible to TMP-SMX, on the other hand, have fluctuated in values since the late 1990s to 2010. As a result, the percent of CBSN *S. pneumoniae* isolates non-susceptible to TMP-SMX is not correlated to the utilization of TMP-SMX (*Figure 41*).

Discussion

Trimethoprim-sulfamethoxazole (TMP-SMX), which shows a decreasing trend in recent years, continues to be the major drug used in the sulfonamides and trimethoprim class. There is a significant decrease in the percent of *S. aureus* non-susceptible to TMP-SMX, which matches the decreasing trend seen in TMP-SMX utilization. *E. coli* and *P. mirabilis*

show increasing trends in non-susceptibility despite recent fluctuations, while *K. pneumoniae* non-susceptibility remains stable at approximately 10% non-susceptibility.

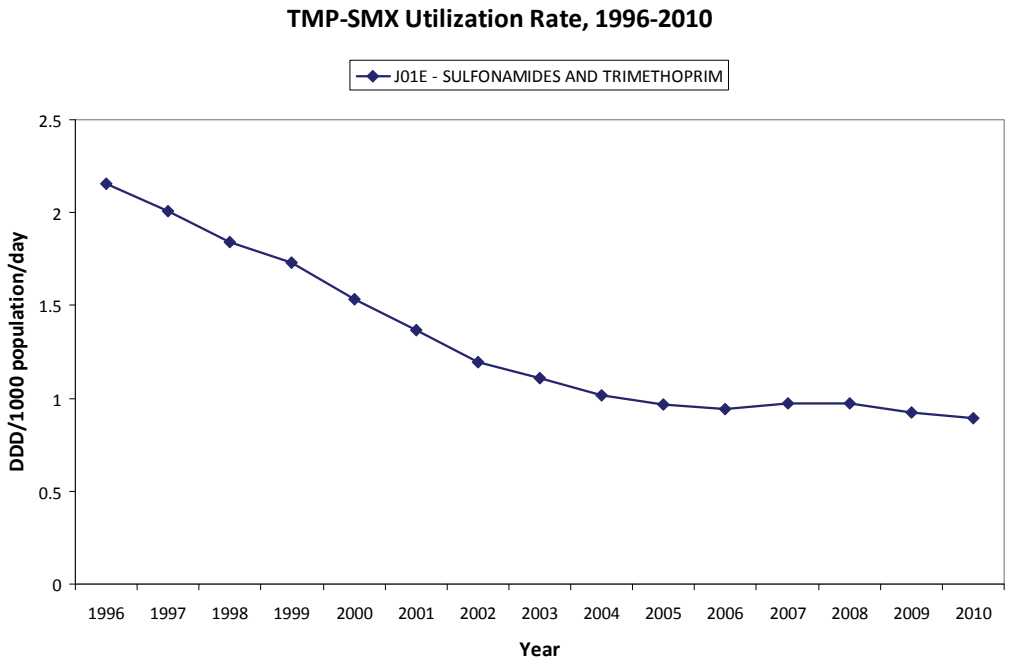


Figure 40 Defined daily rate of TMP-SMX utilization
Source: PharmaNet

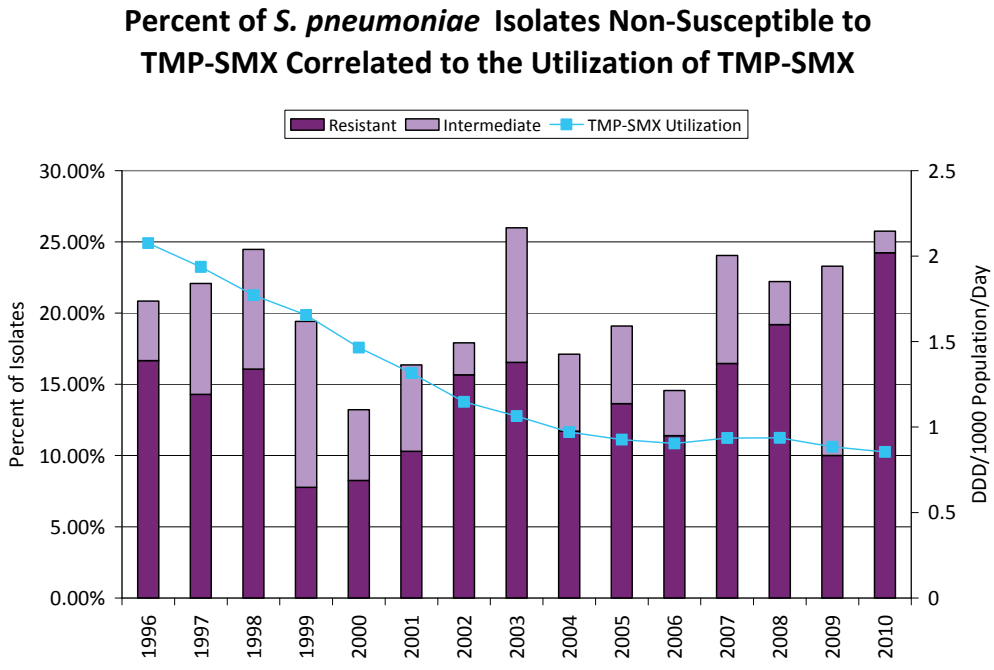


Figure 41 Percent of *Streptococcus pneumoniae* isolates (CBSN) non-susceptible to TMP-SMX correlated with utilization of TMP-SMX
Source: CBSN; PharmaNet

Percent of *K .pneumoniae* , *E. coli* and *P. mirabilis* isolates Resistant to TMP-SMX correlated to Utilization of TMP-SMX

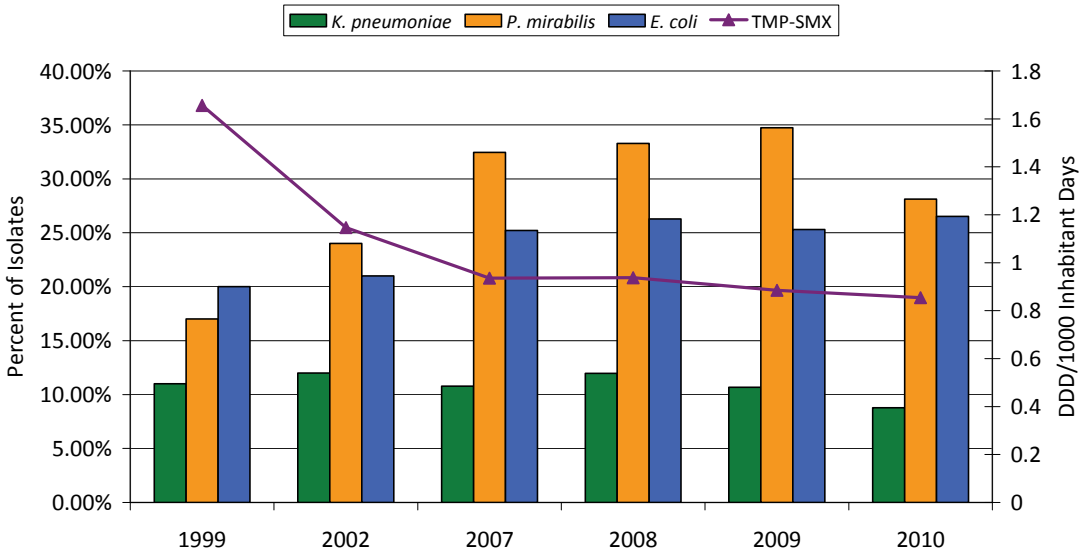


Figure 42 Percent of urinary tract infection pathogenic isolates (BC Biomedical Laboratories) non-susceptible to TMP-SMX correlated with utilization of TMP-SMX

Source: BC Biomedical Laboratories; PharmaNet

7. Other Antimicrobials

Examples

Vancomycin

Metronidazole

Nitrofurantoin

Fusidic acid

Methenamine

Fosfomycin

Linezolid

Background

Other antimicrobials not discussed in the previous sections include the glycopeptides (e.g. vancomycin) and nitrofuran derivatives (e.g. nitrofurantoin). Vancomycin is known for its activity against Gram-positive pathogens, especially pathogens that are resistant to β-lactam antimicrobials such as methicillin-resistant *Staphylococcus aureus* (MRSA) (16). Similar to β-lactam antimicrobials, vancomycin interferes with cell wall synthesis by binding to peptidoglycan precursors, D-Ala-D-Ala (21). Resistance to vancomycin occurs via acquisition of the *van* gene cassette that encodes an altered peptidoglycan precursor, D-Ala-D-Lac, with reduced affinity for glycopeptides (21). Vancomycin-resistant strains, especially *Enterococcus* spp. (VRE), are of concern due to fewer effective therapeutic agents and the frequency of gene transfer to other bacterial stains such as MRSA. Nitrofurantoin is used exclusively to treat urinary tract infections (UTIs) (16). Its mechanism of action is not well known, but evidence suggests that bacterial nitroreductase converts nitrofurantoin into a highly reactive electrophilic intermediate which then attacks ribosomal proteins and therefore disrupts protein synthesis (21). Resistance to nitrofurantoin is largely attributed to diminished nitroreductase activity (21). Metronidazole accepts an electron from ferredoxins, yielding a radical anion which results in DNA damage and cell death (21). Resistance to metronidazole is due to decreased uptake and a reduced rate of reduction (21).

Results

Nitrofurantoin and metronidazole are the two most commonly used antimicrobial classified under this class. Nitrofurantoin and metronidazole utilization rates have remained below 0.1 DDD/1000 inhabitant/day from 1996 to 2010 (*Figure 43*). However, within this time period, the utilization of nitrofurantoin has increased by over 200% since 2002 with its greatest single year of increase being 2010 (*Figure 43*). Although metronidazole has also seen an upward trend since 2002, it has been slight and usage has remained relatively constant from 2007 to 2010 (*Figure 43*).

The percent of *Enterococcus* spp. isolates non-susceptible to vancomycin remains low in BC. Vancomycin utilization rate remains below 0.005 DDD/1000 population/day; although within this range the rate has been steadily increasing since 2003 (*Figure 44*). According to

the BC Biomedical Laboratories data, approximately 1% of Enterococcus isolates demonstrated vancomycin resistance between 1999 and 2011, although lower rates were seen from 2005 to 2009 (Figure 8). BCAMM reports low vancomycin resistance in Enterococci from 2002 to 2010 (data not shown). The percent of isolates non-susceptible to nitrofurantoin varies between UTI pathogens. 1.7% of *Enterococcus* spp. and 3.8% of *Escherichia coli* isolates demonstrated resistance to nitrofurantoin in 2011. In contrast, 50.1% of *Klebsiella pneumoniae* isolates demonstrated resistance to nitrofurantoin in 2011. *Proteus mirabilis* isolates are considered always resistant to nitrofurantoin. Nitrofurantoin non-susceptibility rate in *K. pneumoniae* has decreased from 71.0% in 2002 to 50.1% in 2011 (*Figure 12*). This is the only observable decrease in UTI pathogens. All other UTI pathogens show increasing trends for nitrofurantoin non-susceptibility.

Discussion

The percent of vancomycin-resistant *Enterococcus* (VRE) isolates remained close to 1% over the available time period, 2002 to 2011. This trend should be observed closely in subsequent years as vancomycin resistance genes are readily transmitted to other bacterial species, especially methicillin-resistant *Staphylococcus aureus* (MRSA) as vancomycin is one of the few remaining treatment options for MRSA. Even though the usage rate for vancomycin remains low in BC, there is still a significant increase in usage since 2003.

The percent of UTI isolates non-susceptible to nitrofurantoin widely varies between bacterial species. Nitrofurantoin non-susceptibility rate decreased only in *K. pneumoniae* while increased in other UTI pathogens. As the predominant pathogen causing UTIs, empiric treatment strategies generally target *E. coli* (27). When another uropathogen is suspected, cultures should be taken to confirm appropriate therapy.

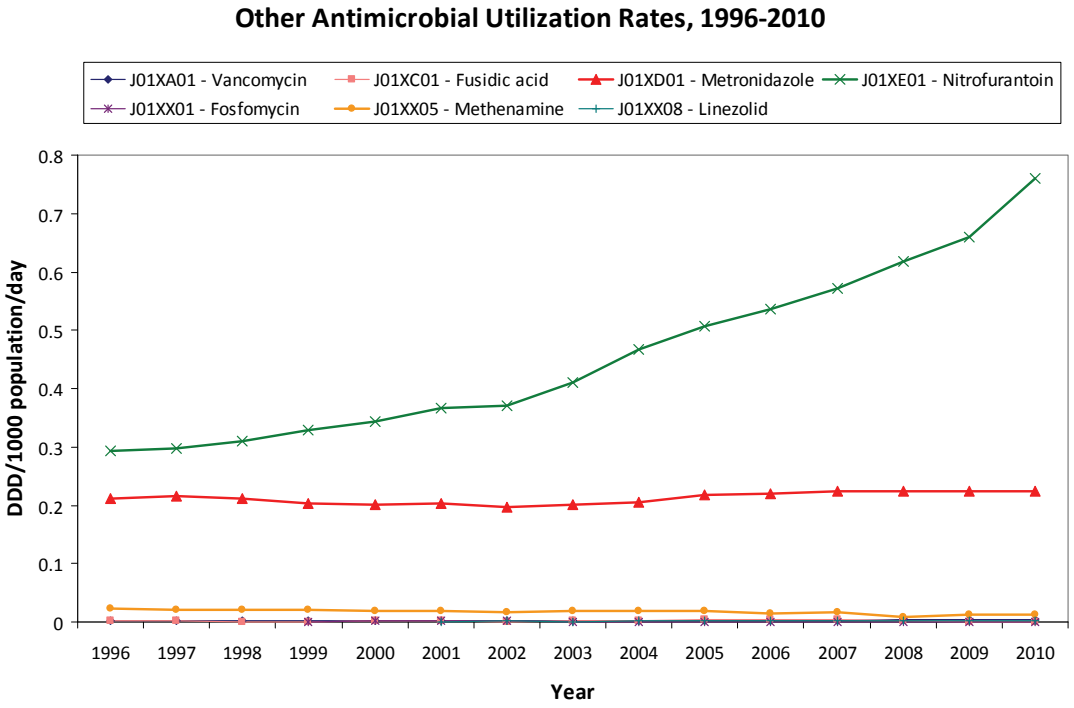


Figure 43 Defined daily rate of other antimicrobials (nitrofurantoin, metronidazole, methenamine, fusidic acid, fosfomycin, vancomycin, and linezolid) utilization

Source: PharmaNet

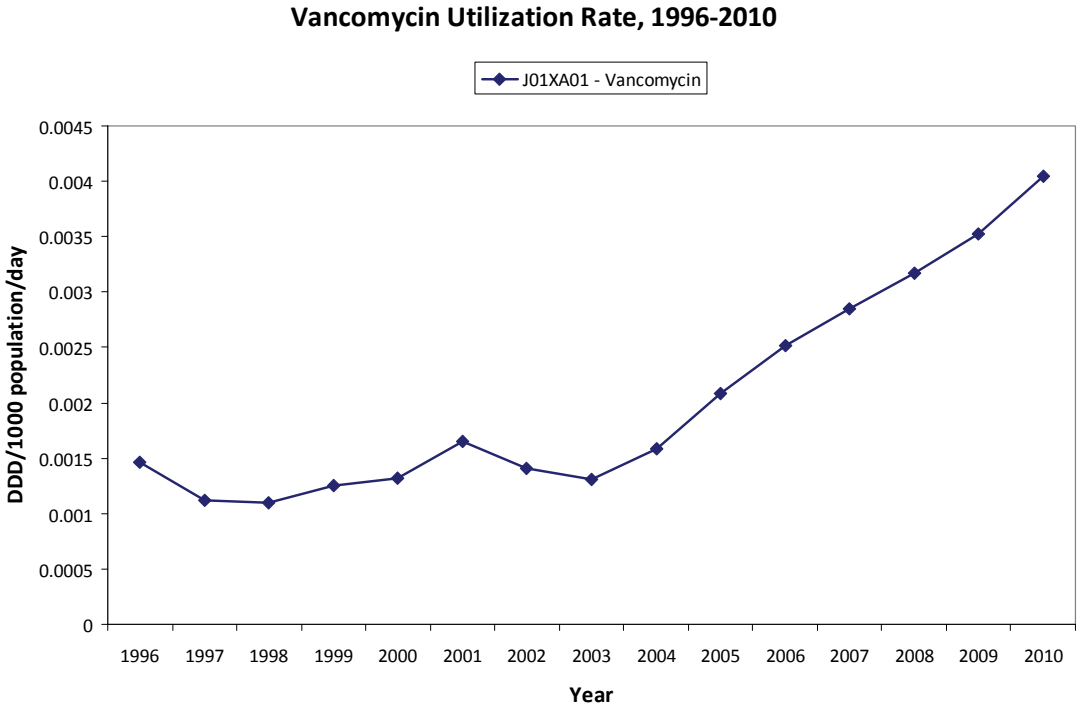


Figure 44 Defined daily rate of vancomycin utilization

Source: PharmaNet

Discussion

Three major antimicrobial resistance trends are apparent in BC and should be monitored closely in subsequent years: proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) especially in community-associated infections, macrolide resistance in *Streptococcus pneumoniae*, and fluoroquinolone resistance in urinary tract infection (UTI) pathogens.

Both BC Biomedical Laboratories and BCAMM report an increasing percentage of *S. aureus* isolates demonstrating methicillin resistance since 2002, but a decreasing percentage since 2007. BC Biomedical Laboratories reports more variable and slightly higher proportions than BCAMM. As MRSA isolates originating from community sources show higher susceptibility to antimicrobials, a steady decline in MRSA resistance to erythromycin, clindamycin, and TMP-SMX demonstrate the increasing prevalence of CA-MRSA strains over HA-MRSA strains. The CA-MRSA antibiotic resistance profile and limited reference testing at BCCDC PHRML supports the conjecture that these isolates are genetically related to community-associated strains worldwide.

While overall antimicrobial utilization has decreased since 2005, the increase in utilization of new long half-life macrolides such as clarithromycin and azithromycin may drive an increase in macrolide resistance, especially in *S. pneumoniae*. The longer half-life may foster resistance more than older macrolides such as erythromycin, whose utilization has decreased substantially since 1996.

Ciprofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole (TMP-SMX) are often recommended as treatment for urinary tract infections (UTIs). Uropathogen susceptibility patterns to these antimicrobials vary. Most UTI pathogens (*E. coli* and *K. pneumoniae*) have displayed increasing resistance towards ciprofloxacin since 1999. Interestingly, *P. mirabilis* isolates demonstrated a varying non-susceptibility to ciprofloxacin since the non-susceptibility percentage peaked in 2008. Ciprofloxacin non-susceptibility should be monitored closely as fluoroquinolone antimicrobials are active against a broad-spectrum of bacterial pathogens and resistance genes are easily transferred between bacterial species. Of concern is also the TMP-SMX resistance in *E. coli* and *P. mirabilis* isolates. Although TMP-SMX utilization decreased progressively for all years available, resistance to TMP-SMX increased since 1998 in both of these organisms. As of 2011, 26.0% of *E. coli* isolates and 30.5% of *P. mirabilis* isolates are resistant to TMP-SMX. Although 50.1% of all *K. pneumoniae* isolates are non-susceptible to nitrofurantoin, *E. coli* isolates remain highly susceptible to nitrofurantoin (>96%). This is reassuring as 85% to 90% of all uncomplicated UTI infections are caused by *E. coli*.

Antimicrobial utilization rates have decreased from 2005 to 2010. Although the β-lactams class continues to have the highest utilization in BC, utilization rates along with those of TMP-SMX have seen noticeable decreases since 1996. Macrolides and lincosamides have seen a dramatic increase in utilization since 1998 and are now the second highest prescription drug class. Tetracyclines, eclipsed by macrolides and lincosamides in 2001, comprise the third most prescribed antibacterial class and despite a stable recent past, tetracyclines' utilization rate increased quite substantially in 2010. Quinolones and other

antibacterials are the next highest classes of antimicrobials with a similar increasing trend since 1996, although the quinolones rate has begun to decline in recent years while the other antibacterials rate has increased. Sulfonamides and trimethoprim are the sixth highest prescribed class of antibacterials (not counting other antibacterials) despite being the fourth highest in 1996.

Antimicrobial resistance (AMR) data for the organisms of interest were obtained from various provincial and national sources which are described in detail in the methods section. Most of these sources test bacterial isolates that are submitted on a voluntary basis from BC hospitals or through physician referrals. As such, the data presented in this report are an approximation of the current status of AMR trends in BC. As well, most data were provided in aggregated form for years where data were available. At this level of surveillance, certain trends may not be apparent while other trends may be exaggerated. Caution should be exercised when interpreting correlations between AMR trends and antimicrobial utilization. A positive correlation between an AMR trend and utilization of a certain class of antimicrobial may be the result of coincidental increase in each variable resulting from other unexplored factors or ecological fallacy rather than a causative relationship.

This report does not take antimicrobial utilization in food-producing animals into consideration, nor does it consider the impact of antibacterial hygiene products on selecting for antimicrobial resistant strains. Both of these areas require further investigation to establish their individual and combined impacts on AMR trends. The trends presented in this report are based on a retrospective analysis of ecological data. For this reason, the trends represent generalizations regarding AMR in BC. A more detailed time-series analysis of AMR data is required to determine the prevalence of AMR pathogens in BC and to access the impact of public health interventions aimed to reduce AMR proliferation such as the “Do Bugs Need Drugs?” program. Continued surveillance and reporting of resistant organisms is necessary to accurately ascertain the status of AMR trends in BC and to monitor the impacts of public health interventions.

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Appendix A

Table 6 List of Abbreviations

Abbreviation	Definition
AMR	Antimicrobial Resistance
ATC	Anatomical Therapeutic Classification
BC	British Columbia
BCAMM	British Columbia Association of Medical Microbiologists
BCCDC	British Columbia Centre for Disease Control
CA-MRSA	Community-Associated Methicillin-Resistant *Staphylococcus aureus*
CANWARD	Canadian Ward Surveillance Study
CBSN	Canadian Bacterial Surveillance Network
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CLSI	Clinical and Laboratory Standards Institute
CNISP	Canadian Nosocomial Infection Surveillance Program
DDD	Defined Daily Dose
DNA	Deoxyribonucleic acid
D-test	Double Disk Diffusion Test
ESBL	Extended-Spectrum β-lactamase
E-test	Epsilometer Test
GAS	Group A Streptococcus
GES	Generalized Estimation System
HA-MRSA	Hospital-Associated Methicillin-Resistant *Staphylococcus aureus*
iPHIS	Integrated Public Health Information System
MIC	Minimum Inhibitory Concentration
MLS_B	Macrolide, Lincosamide, Streptogramin B Resistance
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
NAUTICA	North American Urinary Tract Infection Collaborative Alliance
NCS	National Centre for Streptococcus
NML	National Microbiology Laboratory
PABA	*p*-Amino-Benzoic Acid
PBP	Penicillin-Binding Protein
PEOPLE 35	Population Extrapolation for Organizational Planning with Less Error Projection 35
PFGE	Pulse Field Gel Electrophoresis
PPNG	Penicillinase-Producing *Neisseria gonorrhoeae*
SCC	Staphylococcal Cassette Chromosome
TMP-SMX	Trimethoprim-Sulfamethoxazole
UTI	Urinary Tract Infection
VRE	Vancomycin-Resistant *Enterococcus*
VRSA	Vancomycin-Resistant *Staphylococcus aureus*
WHO	World Health Organization

Appendix B

Table 7 Summary of antimicrobial modes of action and bacterial mechanisms of resistance. Adapted from (20).

Antimicrobial Class Example(s)	Action	Antimicrobial Mechanism	Resistance Mechanism	Common bacteria exhibiting resistance mechanism
B-lactams Ampicillin Amoxicillin Penicillin Cephalosporins	Bactericidal	*Inhibit cell wall synthesis*; Bind to penicillin-binding proteins (PBPs) and prevent transpeptidation of bacterial cell wall	1. Alter composition of PBPs and prevent β-lactam binding 2. Production of β-lactamases	1. *S. aureus* (MRSA), *S. pneumoniae* 2. *Enterococcus* spp., *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *H. influenzae*, *N. gonorrhoeae*
Glycopeptides Vancomycin	Bactericidal	*Inhibit cell wall synthesis*; Bind to D-Ala-D-Ala dipeptide precursor and prevent peptidoglycan synthesis	1. Acquisition of *van* gene cassette, which encodes an alternate dipeptide precursor, D-Ala-D-Lac, with reduced affinity for glycopeptides	1. *Enterococcus* spp. (VRE), *S. aureus* (VRSA)
Aminoglycosides Streptomycin GentamicinAmikacin	Bactericidal	*Inhibit protein synthesis*; Bind to the 30S ribosomal subunit and prevent peptide elongation	1. Mutation in the ribosome binding site 2. Increased efflux or decreased uptake 3. Enzymatic modification via phosphorylation, adenylation, or acetylation	1. *Enterococcus* spp., *Salmonella* 2. *P. aeruginosa* 3. Gram-negative bacteria
Macrolides Erythromycin Clarithromycin Azithromycin	Bacteriostatic	*Inhibit protein synthesis*; Bind to 23S rRNA in the 50S ribosomal subunit and prevent peptide elongation	1. Increased efflux due to acquisition of *mef* gene, which encodes the efflux system (M phenotype) 2. Methylation of the 23S rRNA due to acquisition of the *erm* gene, which encodes a ribosomal methylase (MLS_B phenotype)	1. *S. pneumoniae*, *S. pyogenes* 2. *S. aureus*, *S. pneumoniae*, *S. pyogenes*
Lincosamides Clindamycin	Bacteriostatic	*Inhibit protein synthesis*; Bind to 23S rRNA in the 50S ribosomal subunit and prevent peptide elongation	1. Methylation of the 23S rRNA (MLS_B phenotype)	1. *S. aureus*, *S. pneumoniae*, *S. pyogenes*
Tetracyclines Tetracycline Doxycycline Minocycline	Bacteriostatic	*Inhibits protein synthesis*; Bind to 30S ribosomal subunit and prevent binding of incoming aminoacyl-tRNA	1. Mutation in the 30S ribosomal subunit 2. Increased efflux	1. Gram-negative and Gram-positive bacteria 2. Gram-negative and Gram-positive bacteria
Quinolones Ciprofloxacin Levofloxacin Moxifloxacin	Bactericidal	*Inhibit DNA and RNA synthesis*; Inhibit supercoiling enzymes, DNA gyrase A and topoisomerase IV	1. Mutation in supercoiling enzymes causing reduced affinity for quinolones 2. Increased efflux	1. *S. aureus*, *S. pneumoniae*, Gram-negative bacteria 2. *S. aureus*
Sulfonamides and Trimethoprim TMP-SMX	Bactericidal	*Prevent synthesis of folic acid*; Sulfonamides - compete with *p*-amino-benzoic acid by binding dihydropteroate synthase Trimethoprim – bind dihydrofolate reductase and prevent production of folic acid	1. Mutations in folic acid synthesis enzymes causing reduced affinity for sulfonamides and trimethoprim 2. Overproduction of enzymes	1. *S. aureus*, *S. pneumoniae*, Gram-negative bacteria 2. *E. coli*
Nitrofurans Nitrofurantoin	Bactericidal	Thought to prevent protein synthesis by damaging ribosomal proteins	1. Diminished nitroreductase activity causing less electrophilic conversion of nitrofurantoin	1. Urinary tract infection pathogens