Antimicrobial Resistance Trends in the Province of British Columbia

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Epidemiology Services
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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 AMR trends with antibiotic utilization.

Methods
Data were obtained from various provincial and national sources for a broad-spectrum view of clinically relevant gram-positive and gram-negative bacteria. Rates of antimicrobial utilization were available from the Pharmanet database. Data were analyzed in Microsoft Excel and SPSS using a two-sided Spearman Rank test.

Results
- The percent of *Staphylococcus aureus* isolates that were methicillin-resistant (MRSA) has significantly increased between the years 1998 to 2007, with the rates stabilizing in 2008. This increase is primarily due to the prevalence of community-associated (CA) isolates. The percent of *Enterococcus spp.* isolates demonstrating resistance against vancomycin has remained under 1% in BC for years 1999 to 2008.
- Gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* have demonstrated an increasing resistance against erythromycin. These trends are correlated with utilization of new macrolides such as azithromycin and clarithromycin.
- Urinary tract pathogens such as *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*, have demonstrated an increasing resistance against both ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMX) as well as variable resistance against nitrofurantoin. These trends are concerning as all three of these drugs are currently considered first line agents for urinary tract infections.
- Overall antimicrobial utilization decreased over the available time period, 1996 to 2007 but an upward rebound was observed from 2003 to 2005 which appears to have ended. β-lactam antimicrobials constitute the majority of antimicrobial prescriptions with a rate of 5.2 DDD/1000 inhabitant days in 2007. β-lactams are followed by macrolides, tetracyclines, quinolones and trimethoprim/sulfa combinations.
- Macrolide and quinolone utilization rates significantly increased between years 1996 to 2007, while β-lactam, tetracycline, and trimethoprim/sulfa utilization significantly decreased.

Conclusion
Continued reporting and surveillance of AMR trends is necessary to ascertain the prevalence of AMR pathogens in BC and to guide control efforts. The compilation of this report would not be possible without the provision of data from both provincial and national sources. Continued collaboration with these and additional data sources will be necessary to monitor changes in AMR trends in subsequent years.
**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.

**Introduction**

Bacterial strains that acquire resistance to one or more front-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 inappropriate antimicrobial use that selects for resistant organisms. 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;2). This report aims to provide a comprehensive overview of AMR prevalence in BC and attempts to correlate this surveillance with antimicrobial utilization rates. It is an update of the report “Antimicrobial Resistance Trends in the Province of British Columbia” prepared at the BC Centre for Disease Control by Catherine Chambers in 2006 and Amanda Chau in 2007.

**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, all data sources used the microbroth dilution method in accordance with the Clinical Laboratory Standards Institute (CLSI) guidelines in order to classify resistant isolates. BC Biomedical Laboratories used a combination of agar dilution, Kirby-Bauer, E-test, and D-test methods in accordance with current CLSI guidelines. BCCDC uses the E-test method in accordance with current CLSI guidelines.

Wherever possible, data are presented for both resistant and intermediately-resistant isolates. Unless otherwise indicated, all other presented data include both resistant and intermediate-resistant 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 \( \alpha=0.05 \). Antimicrobial utilization typically precedes the selection of antimicrobial resistant phenotypes by approximately eight to twelve months. Unless otherwise indicated, all presented correlation coefficients and p-values reflect correlation results using utilization data with a twelve month time lag as these values most accurately reflect the biological mechanisms associated with AMR phenotype selection.
Data Sources

BC Biomedical Laboratories

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 treatment guidelines for physicians in the form of empiric therapy antibiograms from which data for this report were obtained. For each organism, the percent of isolates 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 1998, 1999, 2002, 2005, 2007 and 2008. For 2008, isolates from January and February were analyzed as the 2008 antibiogram was not yet available as of writing. For *S. aureus*, data were available up to July 2008.

BC Association of Medical Microbiologists (BCAMM)
*Methicillin-resistant Staphylococcus aureus, Vancomycin-resistant Enterococcus (VRE)*

The BC Association of Medical Microbiologists (BCAMM) collects data from a representative sample of community-based (n=2) and hospital-based (n~30) laboratories in BC. Refer to the BCAMM 2007 Report for a complete list of all participating laboratories (3). Note that the participating community-based laboratories include BC Biomedical Laboratories and MDS Metro Laboratories. Limitations of the BCAMM data include multiple samples from the same patient being collected at different participating sites, re-testing of isolates at certain sites, the frequent presence of enterococci in the normal flora, and the inability to differentiate community-acquired and hospital-acquired infections. Aggregated data were available for years 2002 to 2006.

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

The Canadian Bacterial Surveillance Network (CBSN) received isolates from the following BC hospitals: Royal Jubilee Hospital (Victoria), Royal Inland Hospital (Kamloops), Richmond Hospital, Nanaimo Regional General Hospital, Kelowna General Hospital, Vernon Jubilee Hospital, Burnaby General Hospital, Metro McNair Clinical Laboratory (Burnaby), and Lion’s Gate Hospital (North Vancouver). Isolates obtained from both invasive and non-invasive bacterial disease were submitted on a voluntary basis from the above listed hospitals to the Mount Sinai Hospital Laboratory in Toronto, Ontario for susceptibility testing. For this reason, a bias may exist in antimicrobial resistance trends as isolates suspected of displaying resistance may be submitted on a more frequent basis. As well, only the first four listed hospitals submitted isolates to the CBSN on a regular basis. Aggregated data were available for years 1994 to 2007.

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

*Salmonella* isolates from the BC Centre for Disease Control (BCCDC) 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 2007.

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

*Streptococcus pneumoniae, Streptococcus pyogenes* (Group A Streptococcus)

In BC, all reported cases of invasive streptococci disease were documented in the Integrated Public Health Information System (iPHIS) at the BCCDC. 2008 NCS susceptibility data for both *Streptococcus* species were linked to cases documented in iPHIS and analyzed by Nabeela Rasool. *S. pyogenes* isolates were classified as invasive or non-invasive based on assigned disease code from the iPHIS database.

**STI Clinic and Laboratory Services, BC Centre for Disease Control (BCCDC)**

*Neisseria meningitides, Neisseria gonorrhoeae, methicillin-resistant Staphylococcus aureus*

Invasive meningococcal disease and venereal gonorrhoea infection are both reportable to the BCCDC (6). Due to the increased use of molecular typing methods to identify *Neisseria* spp. infections, not all reported cases of meningococcal disease or gonorrhoea infection are cultured and tested for susceptibility. As such, this dataset may exaggerate *Neisseria* spp. AMR trends as isolates suspected of displaying resistance may be cultured more frequently. An extract of all tested *N. meningitides* isolates from 1992 to 2008 (n=70) were provided by Laboratory Services at the BCCDC. Aggregated data from 2006 were available for the number of *N. gonorrhoeae* cases resistant to tested antibiotics from the STI Clinic at the BCCDC. Presumptive gonorrhreal cases (n=98) were excluded from the total number of cases (n=8286). Minimum inhibitory concentration (MIC) values were classified according to current CLSI guidelines (7). Laboratory Services routinely test *Staphylococcus aureus* isolates that are suspected of demonstrating methicillin-resistance for the presence of the staphylococcal *mecA* gene and the Panton-Valentine leukocidin-coding genes as well as determining the subtype of the SCC*mec* cassette.

**PharmaNet**

**Antimicrobial Utilization Data**

PharmaNet collects all the individual prescription medications dispensed to BC residents by retail pharmacies. This provides the ability to analyze the utilization at population level. Antimicrobial utilization data were analyzed by Mei Chong at the BCCDC. Antimicrobial utilization was measured as the defined daily dose (DDD) per 1000 inhabitant days in accordance with World Health Organization (WHO) guidelines using the Anatomical Therapeutic Classification (ATC) 2006 Index. BC population estimates and projections were obtained from 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 31 (PEOPLE 31). Data were available from January 1996 to December 2007 and were aggregated by year.
Antimicrobial Resistance (AMR) Trends

1. Gram-positive Organisms

1.1. *Staphylococcus aureus*

**Data Source(s)**
- BC Biomedical Laboratories
- BC Association of Medical Microbiologists (BCAMM)
- Laboratory Services, BC Centre for Disease Control (BCCDC)

**Background**

Methicillin-resistant *Staphylococcus aureus* strains are the most prevalent and most clinically important form of antimicrobial resistance among the staphylococci. A prominent nosocomial pathogen, MRSA infections were traditionally only acquired in the hospital setting, however community-acquired MRSA (CA-MRSA) strains have grown to become prevalent in recent years. Hospital-acquired MRSA (HA-MRSA) infections are typically resistant to multiple classes of antimicrobials in addition to β-lactam antimicrobials due to the presence of multiple AMR genes in their SCCmec gene cassette (9-11).

In Canada, the Canadian Nosocomial Infection Control System (CNISP) has monitored the prevalence of HA-MRSA since 1995. CNISP reports an increase in HA-MRSA colonization and infection rates from 0.95 per 100 *S. aureus* isolates in 1995 to 8.04 per 100 *S. aureus* isolates in 2006 (10). This increase was observed nationwide; however, MRSA rates for the western provinces were considerably lower than rates for central Canada (12;13). Treatment options for MRSA strains are both clinically and economically challenging and Kim et al. predict that the economic burden of controlling MRSA infections would range from $42 million to $59 million annually based on the current resistance rates in Canada (14).

![Figure 1](image)

*Source: BC Biomedical Laboratories; BCAMM
*Only isolates from January to July were included for 2008
Results

Data from BC Biomedical Laboratories indicate that the number of MRSA isolates as a percent of all \textit{S. aureus} isolates increased between 1998 and 2007, a trend that appears to be stabilizing in 2008 (Figure 1). According to BC Biomedical data, the proportion of all \textit{S. aureus} isolates resistant to methicillin steadily increased from 3.4% in 1999 to 30.5% in 2007, and has decreased to 20.3% in 2008 (Figure 1).

The proportion of isolates resistant to clindamycin, erythromycin, and trimethoprim-sulfamethoxazole (TMP-SMX) was considerably higher for MRSA isolates in comparison to methicillin-susceptible \textit{S. aureus} (MSSA) isolates (Figure 2). Among MRSA, resistance to clindamycin and to TMP-SMX declined from 2002 to 2008 ($r=0.800$), in keeping with the increasing role of CA-MRSA. Resistance to erythromycin has also shown a decline in 2008. All strains of MRSA continued to remain susceptible to vancomycin in 2008 (data not shown) while 96% of isolates remained susceptible to fusidic acid and 95.8% to mupirocin. As expected, MRSA isolates continued to show 100% resistance towards cephalothin, and cephalozin and MSSA isolates continued to remain fully susceptible to both cephalosporins.

Laboratory Services at BCCDC routinely test \textit{Staphylococcus aureus} isolates that are suspected of demonstrating methicillin-resistance for the presence of the staphylococcal \textit{mecA} gene and the Panton-Valentine leukocidin-coding genes, Luk-S and Luk-F, as well as determining the subtype of the SCC\textsubscript{mec} cassette. BCCDC reports an increase in the number of MRSA isolates that are community-associated. The CA-MRSA isolates all contain the SCC\textsubscript{mec} type IVa and are all positive for the Panton-Valentine leukocidin-coding genes suggesting that these isolates are more virulent than their hospital-acquired counterparts (9). The majority of 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. Also noted, CA-MRSA strains are now seen causing nosocomial outbreaks in hospitals.

\textit{Cellulitis and Abscess}

The absolute rate of physician visits for skin infections, cellulitis and abscess, has increased nearly 50% from 28 to 43 per 1000 population per year, between 1990 and 2007. Much of this increase has occurred since 2001. The most likely explanations for such an increase include the increase in injection cocaine use during the mid-1990’s and the spread of CA-MRSA during this decade. These data are provided by BC MoHS and are derived from MSP billings coded for 682 – cellulitis and abscess.

Conclusions

MRSA now makes up approximately 1 in 5 \textit{S. aureus} isolates processed in BC labs. The decrease in non-susceptibility rates for most of the tested antimicrobials between 2002 to 2008 reflects an increased proportion of CA-MRSA strains, which are typically more susceptible to antimicrobials than their hospital-acquired counterparts (9-11;15).

\(\beta\)-lactamase resistant penicillins (e.g. cloxacillin) remain a sound treatment option for MSSA infections. While the majority of MSSA isolates remain susceptible to TMP-SMX, they have been showing an increasing resistance towards both erythromycin and clindamycin. 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 if antibiotic treatment is required.

By only looking at the increase which has occurred since the emergence of CA-MRSA in 2000, it is plausible that an excess of up to 40,000 physician visits per year has resulted due to the circulation of CA-MRSA in the province.
Figure 2  Percent of MRSA and MSSA isolates resistant to clindamycin, erythromycin, TMP-SMX, and doxycycline.

Source:  BC Biomedical Laboratories

*Only isolates from January to July were included for 2008

Figure 3  Rates of physician visits and unique patients presenting with cellulitis or abscess

Source: BC Ministry of Health Services, MSP Claims Data
1.2. Streptococcus pneumoniae

**Data Source(s)**
- Canadian Bacterial Surveillance Network (CBSN)
- National Centre for Streptococcus (NCS) and Integrated Public Health Information System (iPHIS) linked dataset

**Background**

*Streptococcus pneumoniae* (pneumococcus) is the leading cause of community acquired pneumonia, but also commonly presents as acute otitis media, bacteremia, and meningitis. Treatment for pneumococcal infections typically includes β-lactams, macrolides, and fluoroquinolones or a combination of these drugs with or without the inclusion of β-lactamases (16;17). Resistance to all three of these drug classes is prevalent in Canada, particularly in children under the age of five and adults over the age of sixty-five (5;16;18;19).

Resistance to penicillin first began to emerge in the mid-1960s with the first penicillin-resistant isolate in BC being reported in 1993 (20). Although the proportion of penicillin susceptible pneumococcal isolates has increased in the greater Vancouver area since 1998, 22% of pneumococcal isolates were resistant or intermediately-resistant to penicillin in 2003 (21).

**Results**

According to NCS-iPHIS data, the largest proportions of isolates were non-susceptible to clindamycin (4.5%), penicillin (6.2%), erythromycin (7.6%), and TMP-SMX (44.1%) (Figure 4). The large increase in the percent of isolates intermediately resistant to TMP-SMX observed between 2005 (4.5%) and 2006 (35.3%) was due to the serotype 5 outbreak. Few isolates demonstrated resistance against levofloxacin (<1%), cefotaxime (<1%), chloramphenicol (1%), and vancomycin (no resistance detected). No significant AMR trends were observed for penicillin, TMP-SMX, clindamycin, or erythromycin non-susceptibility for invasive pneumococcal disease.

Data from the CBSN indicate a significant increase in the number of isolates non-susceptible to ceftriaxone, tetracycline, and erythromycin between the years 1994 to 2007 (p≤0.05, Figure 5). In 2007, non-susceptibility rates for, ciprofloxacin, were low (<3%), while susceptibility for levofloxacin and moxifloxacin rose to 100%. From 2005 to 2007, a decrease in the percent of isolates non-susceptible to penicillin was observed, however TMP-SMX non-susceptibility continued to remain high, while erythromycin resistance began to stabilize at approximately 8%. Clindamycin and ciprofloxacin updates for 2007-08 were unavailable by the CBSN at the time of writing.

**Conclusions**

Both data sources indicate similar non-susceptibility rates for the tested antimicrobials. *S. pneumoniae* isolates demonstrate resistance against penicillin, erythromycin, and TMP-SMX more frequently than the other tested antimicrobials. An overall increasing trend was observed for resistance against ceftriaxone, tetracycline, and erythromycin using data obtained from CBSN for years 1994-2007. However, as of 2006 the percent of isolates non-susceptible to erythromycin and clindamycin have remained relatively stable. This was validated using the NCS-iPHIS dataset, resistance to erythromycin and clindamycin were neither increasing nor decreasing between 2002 and 2006. Penicillin and TMP-SMX non-susceptibility rates remain relatively constant over the years for which data were available.
Non-susceptibility percentages derived from CBSN data are slightly higher than those percentages derived from the NCS-iPHIS data. This observation is likely due to the inclusion of non-invasive isolates (22). Also note that a bias may exist in antimicrobial resistance trends as isolates suspected of displaying resistance may be submitted on a more frequent basis to the two data sources.

An increase in the identification of intermediate-resistance to TMP/SX during 2006 has been associated with an outbreak of serotype 5 pneumococcal disease in western Canada that year.

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

Source: NCS-iPHIS linked dataset
Figure 5  Percent of Streptococcus pneumoniae isolates non-susceptible to penicillin, ceftriaxone, ciprofloxacin, levofloxacin, TMP-SMX, erythromycin, clindamycin, moxifloxacin and tetracycline

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* is the dominant member of the Group A Streptococci (GAS) organisms. *S. pyogenes* 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 (17). Erythromycin-resistant isolates of *S. pyogenes* were first documented in the United Kingdom during the 1950s (23).

Two *S. pyogenes* phenotypes are typically associated with resistance against macrolide (e.g. erythromycin) antimicrobials. MLSB strains encode a ribosomal modification gene (*erm*) that confers decreased susceptibility to macrolides, lincosamides, and streptogramin B (24;25). A second resistance mechanism against macrolides is associated with the M phenotype, which encodes an efflux system (*mef*) for macrolide antimicrobials (24;25). 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**

The proportion of BC Biomedical isolates resistant to erythromycin and penicillin was similar to NCS-iPHIS linked data. While 100% of isolates remained susceptible to penicillin and vancomycin as of 2008, the percent of isolates resistant to erythromycin peaked at 23.8% in 2005 then decreased dramatically to 7.0% in 2008 (Figure 6). Similarly, inducible clindamycin non-susceptibility peaked in 2005 (18.1%) and declined to 7.0% in 2008 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.

According to NCS-iPHIS linked data, while 100% of isolates remain susceptible to vancomycin and penicillin, the proportion of *S. pyogenes* isolates resistant chloramphenicol also remained low at 1.4%. Resistance towards erythromycin however peaked in 2005 at 26.4%, before decreasing to 11.6% as of 2008. (Figure 7). Resistance to clindamycin (2.1%) was considerably less than to erythromycin, however both have appeared to decrease as of 2008 (Figure 7). Although the NCS implements the D-test for inducible clindamycin resistance, the results were not included within the provided dataset.

**Conclusions**

According to data from BC Biomedical Laboratories, erythromycin-inducible clindamycin non-susceptibility rates are increasing among *S. pyogenes* isolates, which may suggest an increased prevalence of the MLSB phenotype. Regardless of the decreasing number of isolates non-susceptible to erythromycin and clindamycin, most isolates continue to remain susceptible to penicillin, and vancomycin.

According to the BC Biomed data, no differences were found between erythromycin and clindamycin non-susceptibility rates, however, literature frequently reports higher resistance among non-invasive
streptococci (22). The lack of observable difference may be due to the small number of non-invasive isolates provided in the dataset.

**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)

Source: BC Biomedical Laboratories

**Figure 7** Percent of invasive, non-invasive, and all Streptococcus pyogenes isolates non-susceptible to erythromycin and clindamycin

Source: NCS and iPHIS linked dataset

* Only isolates from January and February were included for 2008
1.4. Enterococcus

**Data Source(s)**
- BC Biomedical Laboratories
- BC Association of Medical Microbiologists (BCAMM)

**Background**

A prominent nosocomial pathogen, enterococci, more specifically *Enterococcus faecalis* and *E. faecium*, are normal flora bacteria that commonly 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. Vancomycin and gentamicin are amongst the few antimicrobials that are used to treat enterococcal infections (17).

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 (26). Within Canada, VRE strains remain rare, with fewer than 1% of *Enterococcus* spp. isolates demonstrating resistance to vancomycin in 2002 (27). The Canadian Nosocomial Infection Control System (CNISP) also reports that the incidence of VRE in Canada is low as most individuals are colonized rather than infected with VRE strains (28). Of concern, however, 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 data, the proportion of *Enterococcus* spp isolates resistant to vancomycin rose to 1.0% in 1999 and in 2002, before falling down to 0.2% as of 2007 where it has remained for the past two years (r=-0.40). Similarly *Enterococcus* resistance towards ampicillin has also decreased as of 2002 (2.0%), with the exception of a spike in 2007 (1.3%, Figure 8). Resistance to ciprofloxacin continued to remain high at approximately 30% however decreasing since its peak in 2002, while nitrofurantoin continued to remain low with less than 1% of isolates demonstrating resistance for the past three available years. As of 2008, almost all isolates tested demonstrated resistance towards TMP-SMX (99.2%, p≤0.01) and penicillin (99.4%; data not shown).

Between the years 2002 and 2006 the BCAMM data estimates that the proportion of vancomycin-resistant *Enterococcus* in BC remains less than 1% (data not shown).

**Conclusions**

The majority of *Enterococcus* spp. isolates remain susceptible to vancomycin, ampicillin, and nitrofurantoin. However, approximately a third of *Enterococcus* spp. isolates demonstrate ciprofloxacin non-susceptibility. The prevalence of VRE infections in BC is low.
Figure 8  Percent of Enterococcus spp. isolates resistant to ampicillin, nitrofurantoin, and vancomycin, and non-susceptible ciprofloxacin.

Source: BC Biomedical Laboratories

* Only isolates from January and February were included for 2008
2. Gram-negative Organisms

2.1 Escherichia coli

Data Source(s)
BC Biomedical Laboratories

Background
Escherichia coli is an opportunistic pathogen that causes gastrointestinal and urinary tract infections (UTIs). Treatment for E. coli infections usually consists of TMP-SMX or nitrofurantoin, an antimicrobial used only to UTIs, as primary treatment regimes (17;29). Additional antimicrobial treatment may include fluoroquinolones, such as ciprofloxacin, and aminoglycosides, such as gentamicin (17;29). Most E. coli strains that are resistant to multiple antimicrobials produce extended spectrum β-lactamases (ESBLs), which confer resistance to β-lactam antimicrobials. In Canada, the first reported outbreak of multidrug-resistant ESBL-producing E. coli strains occurred in Ontario in 2000 (30). The North American Urinary Tract Infection Collaborative Alliance (NAUTICA) report resistance against β-lactam antimicrobials, fluoroquinolones, and TMP-SMX, suggesting that alternate treatment regimes may be necessary (29;31).

Results
The number of E. coli isolates resistant to ciprofloxacin, TMP-SMX, and gentamicin significantly increased across years 1998 to 2008 (p≤0.01; Figure 9). The proportion of isolates resistant to nitrofurantoin remained relatively stable with only ≤4% of isolates demonstrating resistance (Figure 9). The most noticeable increase occurred in E. coli isolates resistant to ciprofloxacin (Figure 9) in which a 10-fold increase in resistance occurred between 1998 (2.2%) and 2008 (22.5%). The highest proportion of non-susceptible isolates occurred for TMP-SMX (25.3%) and ciprofloxacin (22.5%) in 2008. There was an increase in non-susceptibility against amikacin from 0.6% in 2005 to 5.0% in 2008 (p≤0.01; data not shown).

Conclusions
The increasing proportion of isolates resistant to fluoroquinolone antimicrobials and TMP-SMX is a rapidly growing concern. The percent of isolates resistant to nitrofurantoin however, continues to remain stable and low.
Figure 9  Percent of Escherichia coli isolates resistant to, ciprofloxacin, gentamicin, nitrofurantoin, and trimethoprim-sulfamethoxazole (TMP-SMX), and non-susceptible to ampicillin

Source: BC Biomedical Laboratories

* Only isolates from January and February were included for 2008
2.2 Proteus mirabilis

Data Source(s)

BC Biomedical Laboratories

Background

Proteus mirabilis is an enteric bacterium that commonly causes UTIs. Treatment for UTIs typically consists of trimethoprim-sulfamethoxazole (TMP-SMX); however, prescription of fluoroquinolones (e.g. ciprofloxacin) and aminoglycosides (e.g. gentamicin) has become more common (17;29). P. mirabilis isolates commonly produce extended spectrum β-lactamases (ESBLs), which confer resistance to β-lactam antimicrobials. In Canada, the percent of isolates producing ESBLs is considerably less than other countries (32). The resistance profile of P. mirabilis isolates are similar to other UTI pathogens such as Escherichia coli and include resistance against β-lactams, ciprofloxacin, TMP-SMX, and nitrofurantoin (33;34).

Results

The number of P. mirabilis isolates non-susceptible to ciprofloxacin and TMP-SMX increased from years 1998 to 2008 (p≤0.01; Figure 10). The percentage of isolates non-susceptible towards ciprofloxacin has increased considerably from 0.8% in 1998 to 29.1% in 2008. The percent of isolates resistant towards TMP-SMX has more than doubled between 1998 (15.0%) and 2008 (35.7%). In addition to the antimicrobials primarily used for UTIs (such as ciprofloxacin and TMP-SMX), the percent of isolates resistant towards ampicillin has more than tripled from 10.0% 1998 to 36.2% in 2008 (p≤0.01, Figure 10). The percent of isolates resistant to gentamicin dramatically decreased in 2005 to 5.8% and has continued to remain low through to 2008 (4.2%).

In 2008, approximately one out of three P. mirabilis isolates demonstrated resistance against ampicillin, TMP-SMX or both. As expected, almost all isolates were resistant to nitrofurantoin (data not shown).

Conclusions

P. mirabilis isolates demonstrated non-susceptibility against ciprofloxacin, TMP-SMX, and nitrofurantoin. Of concern is the high and increasing percent of isolates non-susceptible to ciprofloxacin and TMP-SMX.
Figure 10 Percent of Proteus mirabilis isolates non-susceptible to ciprofloxacin and resistant to TMP-SMX, gentamicin, and ampicillin.

Source: BC Biomedical Laboratories

* Only isolates from January and February were included for 2008
2.3 *Klebsiella pneumoniae*

**Data Source(s)**
BC Biomedical Laboratories

**Background**
*Klebsiella pneumoniae*, the second leading cause of UTIs after *Escherichia coli*, can also lead to pneumonia, bacteremia, and skin and soft tissue infections (34). The majority of *K. pneumoniae* isolates which result in pneumonia remain susceptible to β-lactams (e.g. penicillins and cephalosporins), carbapenems (e.g. meropenem and imipenem), aminoglycosides (e.g. gentamicin), and to a lesser extent fluoroquinolones (e.g. ciprofloxacin) (35). As of 2002, approximately 5% of *K. pneumoniae* isolates produced extended spectrum β-lactamases, which cleave β-lactam antimicrobials (32;35). *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 (34;36).

**Results**
The number of isolates resistant to ciprofloxacin has significantly increased over the last six available years from 0.5% in 1998 to 3.3% in 2008 (p≤0.01; Figure 11). The percent of isolates resistant to gentamicin remains steady and low, within the past three recordable years, with only 0.9% of isolates showing signs of resistance in 2008 (Figure 11). Nitrofurantoin and TMP-SMX resistance continues to stay high with 67.2% of isolates demonstrating resistance towards nitrofurantoin in 2008, and 13.1% of isolates showing signs of resistance towards TMP-SMX in the same year (Figure 11).

While all tested isolates were resistant to ampicillin between 2005 and 2008, meropenem susceptibility continued to increase until 2007 when isolates stopped showing signs of resistance (data not shown).

**Conclusions**
The majority of *Klebsiella pneumoniae* isolates tested are resistant to nitrofurantoin while ciprofloxacin and gentamicin resistance remains low.
Percent of *Klebsiella Pneumoniae* Isolates Resistant to Ciprofloxacin

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2002</th>
<th>2005</th>
<th>2007</th>
<th>2008*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>0.5%</td>
<td>2.0%</td>
<td>2.0%</td>
<td>2.8%</td>
<td>2.4%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Percent of *Klebsiella Pneumoniae* Isolates Resistant to Gentamicin

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2002</th>
<th>2005</th>
<th>2007</th>
<th>2008*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>0.0%</td>
<td>1.0%</td>
<td>2.0%</td>
<td>1.1%</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

Percent of *Klebsiella Pneumoniae* Isolates Resistant to Nitrofurantoin

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2002</th>
<th>2005</th>
<th>2007</th>
<th>2008*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>44.7%</td>
<td>68.0%</td>
<td>71.0%</td>
<td>67.6%</td>
<td>67.6%</td>
<td>67.2%</td>
</tr>
</tbody>
</table>

Percent of *Klebsiella Pneumoniae* Isolates Resistant to TMP-SMX

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2002</th>
<th>2005</th>
<th>2007</th>
<th>2008*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>10.5%</td>
<td>11.0%</td>
<td>12.0%</td>
<td>9.0%</td>
<td>10.8%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

*Figure 11*  Percent of *Klebsiella pneumoniae* isolates resistant to ciprofloxacin, gentamicin, nitrofurantoin, and trimethoprim-sulfamethoxazole (TMP-SMX)

Source: BC Biomedical Laboratories

* Only isolates from January and February were included for 2008
2.4  

*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, and gastrointestinal tract. Treatment for *P. aeruginosa* infections typically includes piperacillin or tobramycin (17). Although the majority of infections remain susceptible to the antimicrobials listed above, *P. aeruginosa* isolates demonstrated resistance against β-lactams, aminoglycosides, and fluoroquinolones during the SENTRY Antimicrobial Surveillance Study (35). Of concern are the rates of resistance against ceftriaxone, which range from 38.0% to 86.4% depending on the source of isolation (35;36).

**Results**  
While the percent of *P. aeruginosa* isolates non-susceptible to aminoglycosides (tobramycin and gentamicin,) has decreased since the start of the testing period in 1998, the percentage of isolates demonstrating resistance towards ciprofloxacin increased during the same period (Figure 12). Over the testing period there are still few isolates (<3%) which have continued to remain non-susceptible towards piperacillin and ceftazidime.

**Conclusions**  
The percentage of isolates non-susceptible to aminoglycosides displays a decreasing trend compared to its peak in 1998. The number of isolates non-susceptible to ciprofloxacin, however, is increasing. 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0.0%</td>
<td>4.9%</td>
</tr>
<tr>
<td>1999</td>
<td>0.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>2002</td>
<td>0.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>2005</td>
<td>0.0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>2007</td>
<td>0.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>2008*</td>
<td>0.7%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0.0%</td>
<td>9.4%</td>
</tr>
<tr>
<td>1999</td>
<td>0.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>2002</td>
<td>0.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>2005</td>
<td>0.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>2007</td>
<td>0.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>2008*</td>
<td>0.7%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Percent of *P. Aeruginosa* Isolates Non-Susceptible to Ciprofloxacin

<table>
<thead>
<tr>
<th>Year</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0.0%</td>
<td>8.6%</td>
</tr>
<tr>
<td>1999</td>
<td>0.0%</td>
<td>12.0%</td>
</tr>
<tr>
<td>2002</td>
<td>0.0%</td>
<td>14.0%</td>
</tr>
<tr>
<td>2005</td>
<td>0.0%</td>
<td>13.1%</td>
</tr>
<tr>
<td>2007</td>
<td>3.1%</td>
<td>9.0%</td>
</tr>
<tr>
<td>2008*</td>
<td>3.6%</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

Percent of *P. Aeruginosa* Isolates Non-Susceptible to Piperacillin

<table>
<thead>
<tr>
<th>Year</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0.0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>1999</td>
<td>0.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>2002</td>
<td>0.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>2005</td>
<td>0.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>2007</td>
<td>3.1%</td>
<td>1.2%</td>
</tr>
<tr>
<td>2008*</td>
<td>0.0%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Percent of *P. Aeruginosa* Isolates Non-Susceptible to Ceftazidime

<table>
<thead>
<tr>
<th>Year</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0.0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>1999</td>
<td>0.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>2002</td>
<td>0.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>2005</td>
<td>0.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>2007</td>
<td>0.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>2008*</td>
<td>0.0%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

*Figure 12  Percent of *Pseudomonas aeruginosa* isolates non-susceptible to tobramycin, gentamicin, ciprofloxacin, piperacillin, and ceftazidime*

Source:  BC Biomedical Laboratories

* Only isolates from January and February were included for 2008
2.5  *Serratia, Providencia, Morganella, Citrobacter, Enterobacter*

**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. SPICE organisms are intrinsically resistant to cephalosporin antimicrobials.

**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 2002 testing period. (Figure 13). Resistance towards nitrofurantoin occurred most frequently, with 36.6% of isolates demonstrating resistance in 2005. All tested isolates were non-susceptible to β-lactams, ampicillin and cephalaxin, in 2005 (data not shown). Updates for 2007-08 were unavailable at the time of writing.

**Conclusions**

While susceptibility rates varied for the tested antimicrobials, resistance towards nitrofurantoin occurred most frequently. The observation that all SPICE isolates were non-susceptible to cephalaxin, however, is not surprising as these organisms have intrinsic cephalosporin resistance.
Figure 13  Percent of SPICE organisms (Serratia, Providencia, Morganella, Citrobacter, and Enterobacter) resistant to ciprofloxacin, tobramycin, gentamicin, nitrofurantoin, and TMP-SMX.

Source:  BC Biomedical Laboratories
2.6  *Salmonella Enteritidis*

**Data Source(s)**

Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)

**Background**

*Salmonella* is a common cause of gastroenteritis in Canada. *Salmonella* is usually a food-borne pathogen that is transmitted through contaminated or uncooked food products. It can also be transmitted through contaminated water or person-to-person contact. *Salmonella Enteritidis*, the most common form of *Salmonella* within Canada, can be transmitted to humans through egg born contamination or through intact and disinfected Grade A eggs. While most people do not require antibiotics, the elderly, infants and those with weak immune system are more likely to depend on antimicrobials for treatment.

**Results**

Of the tested antimicrobials, isolates demonstrated 100% susceptibility to ceftriaxone, ciprofloxacin, amikacin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole and cefotaxim as of 2007. Resistance towards ampicillin continues to decrease, remaining below 5% resistance as of 2005. Following an increase in susceptibility, tetracycline resistance continues to increase to 10.6% in 2007. *S. enteritidis* resistance towards streptomycin which continues to fluctuate, remained below 4.0% throughout the testing period. Nalidixic acid resistance towards *S. enteritidis* continues to remain high at 24.2% as of 2007, while resistance towards chloramphenicol remained below 2.0% since 2004 (Figure 14).

Table 1 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, sulfamethoxazole, streptomycin, 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. 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%), which are also common in multi-drug resistance patterns.

**Conclusions**

The percent of isolates resistant to nalidixic acid remained high, however, only a significantly increase trend was observed for nalidixic acid. Common antimicrobial resistance patterns include the ACSSuT, A2C, and A3C patterns as well as resistance against nalidixic acid alone and tetracycline alone.
Figure 14  Percent of Salmonella isolates resistant to ampicillin, tetracycline, streptomycin, nalidixic acid, and chloramphenicol

Source: CIPARS
Table 1  Frequently occurring multidrug resistance patterns in Salmonella isolates

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

\(^1\) AMC = amoxicillin-clavulanic acid; AMP = ampicillin; FOX = cefoxitin; NAL = nalidixic acid; SMX = sulfamethoxazole; STR = streptomycin; SXT = trimethoprim-sulfamethoxazole; TCY = tetracycline; TIO = ceftiofur; ACSSuT = ampicillin, chloramphenicol, sulfamethoxazole, streptomycin, tetracycline; ACKSSuT = ampicillin, chloramphenicol, kanamycin, sulfamethoxazole, streptomycin, tetracycline; A2C = amoxicillin-clavulanic acid, cefotaxin, ceftiofur; A3C = amoxicillin-clavulanic acid, cefotaxin, 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
2.7 *Haemophilus influenzae*

**Data Source(s)**

Canadian Bacterial Surveillance Network (CBSN)

**Background**

*Haemophilus influenzae* is a respiratory tract pathogen 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 (39;40). 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 (35;39;40). The majority of *H. influenzae* isolates remain fluoroquinolone (e.g. ciprofloxacin and levofloxacin) susceptible (39;40).

**Results**

Limited *H. influenzae* susceptibility data were available from the CBSN. Susceptibility data since 2005 are unavailable. The highest rate of β-lactam resistance which occurred during the testing period was in 2000 with 44% of isolates producing β-lactamases. Between years 2003 and 2004, however, the β-lactam non-susceptibility rates declined and remained relatively stable at approximately 17%.

**Conclusions**

The percentage of β-lactamase-producing *H. influenzae* isolates have shown a sharp decline during the testing period of 2000 and 2004. While this trend is comparable to the reported decline in β-lactam resistance across Canada, the results may be erroneous due to the small number of isolates (n=178) available to the CBSN. Erroneous results could also arise due to the voluntary nature of isolate referral to the CBSN (isolates suspected of demonstrating resistance may be submitted on a more frequent basis).

![Bar chart showing percent of β-lactamase producing Haemophilus influenzae isolates](chart)

*Figure 15 Percent of β-lactamase-producing Haemophilus influenzae isolates*

Source: CBSN
2.8 Neisseria meningitides

Data Source(s)
Laboratory Services, BC Centre for Disease Control (BCCDC)

Background

*Neisseria meningitides* 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 with fewer than 35 cases occurring annually from 2002 to 2004 (6). Third-generation cephalosporins, cefotaxime and ceftriaxone, are typically used to treat bacterial meningitis (17). Penicillin-resistant *N. meningitides* strains first appeared in Europe in the mid-1980s (2). In Canada, antimicrobial resistant *N. meningitides* strains are rare. However, an investigation of a *N. meningitides* outbreak in Saskatchewan in 1993 suggests that strains with reduced susceptibility to penicillin are prevalent in Canada (41).

Results

Between years 1996 and 2008, *N. meningitides* isolates were cultured and tested for susceptibility. Isolates were tested for resistance against the following antimicrobials: penicillin, rifampin, ciprofloxacin, and ceftriaxone. While isolates showed no resistance towards rifampin and ceftriaxone, non-susceptibility towards penicillin fell to 27.8%, though true resistance was seen in 6.3% of isolates in 2008. While isolates showed some resistance towards ciprofloxacin in 2006 (5.3%), no ciprofloxacin-resistant isolates were found in 2007 (data not shown).

Conclusion

Antimicrobial resistant *N. meningitides* isolates are rare in BC. This conclusion, however, is a generalization as not all reported cases of invasive *N. meningitides* infection are cultured and tested for susceptibility.

Figure 16 Percent of Neisseria Meningitides isolates non-susceptible to penicillin
2.9 Neisseria gonorrhoeae

Data Source(s)
Laboratory Services, BC Centre of Disease Control (BCCDC)

Background

*Neisseria gonorrhoeae* is the causative agent of gonorrhoea, a sexually transmitted infection of the urethra, cervix, or rectum. Due to the increasing prevalence of penicillin and tetracycline resistant *N. gonorrhoeae* strains, treatment of gonorrhoea typically includes third-generation cephalosporins, cefixime and ceftriaxone, or alternatively ciprofloxacin (a fluoroquinolone) or azithromycin (a macrolide) (17). 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 (42). The prevalence of chromosomally-mediated resistance genes, which potentially confer resistance against penicillin, tetracycline, erythromycin, and ciprofloxacin, has increased in Canada from 1994 to 1999 (42). No single antimicrobial resistant *N. gonorrhoeae* strains predominates in Canada suggesting that most gonorrhoea infections are imported from other countries (43;44).

Results

According to data obtained from the STI clinic at the BC Centre for Disease Control, the percent of isolates resistant to tetracycline and penicillin significantly decreased from 1996 to 2006 (Figure 17; p=0.01). Similar patterns in resistance were observed for tetracycline and penicillin.

The percent of isolates non-susceptible to ciprofloxacin increased from 1996 to 2006 with a dramatic increase in the proportion of non-susceptible isolates in 2002 and 2005 (Figure 17). In 2006, two (0.2%) isolates were resistant to azithromycin.

Conclusions

Parallel trends in decreasing resistance to penicillin and tetracycline were reported for the available years, 1996 to 2006. Penicillinase-producing *N. gonorrhoeae* (PPNG) and tetracycline-resistant *N. gonorrhoeae* (TRNG) plasmid-mediated strains are often associated with a common phenotype (PP/TRNG) (42).

Of concern is that an increasing number of isolates were non-susceptible to ciprofloxacin, especially in recent years. Few isolates demonstrated resistance against azithromycin. Consequently, the recommended treatment of gonorrhoea with third-generation cephalosporins or alternatively macrolides is still effective against *N. gonorrhoeae* isolates in BC.

Caution should be exercised when interpreting these AMR trends. The use of molecular typing methods such a polymerase chain reaction (PCR) to diagnose gonorrhoea infections is becoming increasingly common (43). As such, not all *N. gonorrhoeae* isolates are cultured and tested for antimicrobial resistance. These results likely represent a subset of all *N. gonorrhoeae* infections in BC. Those isolates suspected of displaying resistance may be cultured on a more frequently basis; consequently, resistant isolates may be overrepresented in this dataset.
Figure 17  Percent of Neisseria gonorrhoeae isolates resistant or non-susceptible to penicillin, tetracycline, and ciprofloxacin

Source: STI Clinic, BC Centre for Disease Control
Antimicrobial Utilization Rates and Correlations

Overall Utilization

Examples
- Beta-Lactamase
  - Macrolides and Lincosamides
  - Quinolones
  - Sulfonamides and Trimethoprim
- Other Antimicrobials

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 antibacterials for systemic use was steadily declining reaching its lowest level in 2002. Since then, the rate of utilization increased until 2005, and has since remained stable over the last two years (Figure 18).

The utilization trends of the main classes of antibiotics, as dictated by the Anatomical Therapeutic Chemical (ATC) classification system, are depicted (Figure 19). The class of penicillins was steadily declining but has remained steady since 2002. This class, which incorporates penicillins with extended spectrums, beta-lactamase sensitive and resistant penicillins, as well as combinations of penicillins including beta-lactamase inhibitors, continues to be the most frequently used class of antibiotics. Macrolides and lincosamides have been steadily increasing, most notably since 2002 (24.7%). This increase is primarily attributable to increased utilization of the new macrolides (azithromycin, clarithromycin and telithromycin) as erythromycin use has steadily declined since 1996 (Figure 27). Also apparent is the decline in tetracycline, sulfonamide and trimethoprim use and the increase in quinolone use. This latter trend is primarily driven by the elevated utilization of ciprofloxacin (Figure 34).

Conclusions

The rate of antibiotic utilization has remained stable over the last two years, arresting an upward trend seen between 2003 and 2005.

Although some classes are seeing dramatic decreases in utilization (i.e. penicillins), others are increasing in their rate of daily consumption. This increase is often attributable to the introduction of new drugs into the market rather than increases in utilization of previously existing pharmaceuticals.
Figure 18  Defined daily rate of all antimicrobials for systematic use

Figure 19 Defined daily rate antimicrobials by class
B-lactams

Examples
- Penicillins with extended spectrum – Amoxicillin, Amoxicillin
- B-lactamase sensitive penicillins – Penicillin V
- B-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 amongst 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 (24). 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;24). Methicillin-resistant *S. aureus* strains, for example, express the *meca* gene, which encodes an altered penicillin-binding protein, PBP2a.

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 (17). 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 are the most frequently prescribed class of antimicrobials in BC. The utilization rate of penicillin antimicrobials increased very slightly from 2001 to 2007 (Figure 20). 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. B-lactamase resistant (p≤0.01) and β-lactamase sensitive (p≤0.01) penicillins also demonstrate decreasing trends, while penicillins combined with β-lactamase inhibitors demonstrate an increasing trend between years 1996 to 2007 (p≤0.01; Figure 21).

First generation cephalosporins constitute the majority of cephalosporin prescriptions as the utilization rate of broad spectrum second and third-generation cephalosporins remains below 0.1 DDD/1000 inhabitant days (Figure 22). While third generation cephalosporins remained relatively constant, below 0.05 DDD/1000 inhabitant days, decreasing trends were observed for the utilization of second generation cephalosporins (p≤0.01) between 1996 and 2007. During this period, an increasing trend, was observed however, for the utilization of first-generation cephalosporins (p≤0.01).

A significant negative correlation exists between the percent of *S. aureus* isolates demonstrating methicillin resistance and the utilization of β-lactamase resistant penicillins (e.g. methicillin and cloxacillin) using data from the BCAMM (r=-1.0, p<0.01; Figure 23). Significant positive correlations
exist between the percent of MRSA isolates and the utilization of penicillins combined with β-lactamase inhibitors (e.g. amoxicillin-clavulanic acid; $r=1.0$, $p<0.01$) and first-generation cephalosporins (e.g. cephalexin; $r=1.0$, $p<0.01$; Figure 24).

In addition to the correlations between β-lactam resistance and β-lactam utilization, significant positive correlations also exist between the utilization of new macrolides (azithromycin, clarithromycin, spiramycin and telithromycin), lincosamides, and fluoroquinolones and the percent of *S. aureus* isolates demonstrating methicillin resistance using data from the BCAMM (data not shown). In contrast, a significant negative correlation exists between trimethoprim-sulfamethoxazole (TMP-SMX) utilization and proportion of MRSA isolates resistant (data not shown).

The percent of *N. gonorrhoeae* isolates resistant to penicillin are also significantly correlated to the utilization of penicillins (Figure 25). However, the proportion of *N. gonorrhoeae* isolates resistant to penicillin is not significantly associated with utilization of all cephalosporins (data not shown). No significant correlations existed between utilization rates and AMR trends using β-lactam data from the CBSN (e.g. *Streptococcus pneumoniae* isolates non-susceptible to penicillin; Figure 26).

**Conclusions**

The increasing utilization of penicillin antimicrobials is predominantly driven by the increasing utilization of pencillins with extended spectrum.

The negative correlation between utilization of and resistance to β-lactamase resistant penicillins is most likely because a proportion of *S. aureus* infections must now be treated with other classes of antibiotitic.

The penicillins are the most commonly prescribed antimicrobial class and utilization rates have been more or less stable in recent years.
Figure 20  Defined daily rate of all penicillins, penicillins with extended spectrum and amoxicillin utilization.

Source: PharmaNet

Figure 21  Defined daily rate of penicillin utilization: Focus on penicillins with utilization rate of less than 1.0 DDD/1000 inhabitant days

Source: PharmaNet
Figure 22  Defined daily rate of cephalosporin utilization

Source: PharmaNet

Figure 23  Percent of methicillin-resistant Staphylococcus aureus isolates (BC Biomedical Laboratories) correlated to the utilization of beta-lactamase resistance penicillins

Source: BC Biomedical Laboratories; PharmaNet
Figure 24  Percent of methicillin-resistant Staphylococcus aureus isolates (BCAMM) correlated to the utilization of first-generation cephalosporins

Source: BCAMM; PharmaNet

Figure 25  Percent of Neisseria gonorrhoeae isolates (Laboratory Services, BCCDC) non-susceptible to penicillin correlated to utilization of β-lactamase resistant penicillins

Source: STI Clinic, BCCDC; PharmaNet
Figure 26 Percent of Streptococcus pneumoniae isolates (CBSN) non-susceptible to penicillin correlated to utilization of β-lactamase sensitive penicillins

Source: CBSN; PharmaNet
Macrolides and Lincosamides

Examples

Macrolides – Erythromycin, Clarithromycin

Lincosamides – Clindamycin, Lincomycin

Background

Macrolide antimicrobials (e.g., erythromycin, spiramycin, clarithromycin, azithromycin, and telithromycin) are typically used to treat gram-positive bacteria that infect the respiratory tract such as Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes (17). Due to the broad spectrum of activity of macrolides and to the prevalence of β-lactam resistant pathogens, macrolide antimicrobials are sometimes preferred over their β-lactam counterparts. The increased use of macrolides over β-lactams has lead to an increase in macrolide resistance in recent years, especially in S. pneumoniae isolates (45). In addition, the longer half-life of newer macrolides (e.g., clarithromycin, azithromycin, 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 (24). 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, (24;25). These resistance mechanisms are respectively associated with the M phenotype and MLS\textsubscript{B} phenotype, which confers multidrug resistance to macrolides, lincosamides, and streptogramin B (24;25).

Results

As the utilization of erythromycin, an older macrolide, decreased during the available time period, the utilization of newer macrolides (clarithromycin, azithromycin and telithromycin) increased (p ≤ 0.01; Figure 27). Clarithromycin was the most frequently prescribed macrolide with a defined daily rate of 2.5 DDD/1000 inhabitant days. The utilization of lincosamides (e.g., clindamycin) saw a similar increase between 1996 to 2007 (p≤0.01; data not shown).

As indicated by CBSN data, the percent of S. pneumoniae isolates non-susceptible to erythromycin increased between years 2002 to 2007 (Figure 28). The percent of S. pyogenes isolates non-susceptible to erythromycin, according to NCS data, has been decreasing since 2006 (Figure 29). Using susceptibility data from BC Biomedical Laboratories, increases were observed in the percent of S. pneumoniae, S. pyogenes, and methicillin resistant S. aureus isolates non-susceptible to erythromycin between years 2002 to 2007 (Figure 30). These data are consistent with the increases observed for new macrolide (clarithromycin, and azithromycin) utilization.

Dramatic increases were observed in the percent of S. pneumoniae, S. pyogenes, and methicillin sensitive S. aureus isolates non-susceptible to clindamycin between years 2002 to 2007 according to BC Biomedical data (Figure 31).

Conclusions

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\textsubscript{B} phenotype, resistance to macrolides often indicates multidrug resistance to lincosamides and streptogramin B in addition to macrolides.
The percent of gram-positive isolates non-susceptible to erythromycin has increased in recent years. The significant correlations between erythromycin non-susceptibility and new macrolide utilization suggest that the increased selective pressure of newer macrolides, clarithromycin and azithromycin, is influencing these trends.

![Figure 27](image1.png) **Figure 27** Defined daily rate of macrolide utilization and new macrolides (clarithromycin, azithromycin and telithromycin)

Source: PharmaNet

![Figure 28](image2.png) **Figure 28** Percent of Streptococcus pneumoniae isolates (CBSN) non-susceptible to erythromycin correlated to utilization of new macrolides, clarithromycin, azithromycin and telithromycin
Source: CBSN; PharmaNet

Figure 29  Percent of Streptococcus pyogenes isolates (NCS-iPHIS) non-susceptible to erythromycin correlated to utilization of new macrolides, clarithromycin, azithromycin, telithromycin and spiramycin

Source: NCS-iPHIS linked dataset; PharmaNet

Figure 30  Percent of isolates (BC Biomedical Laboratories for MRSA, CBSN for S. Pneumoniae and NCS for S. Pyogenes) resistant to erythromycin correlated to utilization of new macrolides (clarithromycin, azithromycin and telithromycin)

*Streptococcus Pyogenes isolates form January to October were used for 2007

Source: BC Biomedical Laboratories; CBSN; NCS; PharmaNet
Percent of *Streptococcus Pyogenes*, *Streptococcus Pneumoniae* and Methicillin-Sensitive *Staphylococcus Aureus* Isolates Non-Susceptible to Clindamycin Correlated to the Utilization of Clindamycin

Figure 31  Percent of isolates (BC Biomedical Laboratories for MSSA, CBSN for *S. Pneumoniae* and NCS for *S. Pyogenes*) non-susceptible to clindamycin correlated to utilization of clindamycin

*Streptococcus Pyogenes* isolates form January to October were used for 2007

Source: BC Biomedical Laboratories; CBSN; NCS; PharmaNe
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 (24). These antimicrobials are classified as short-acting (e.g. tetracycline), intermediate-acting (e.g. demeclocycline), 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 (24). Resistance to tetracyclines can be either chromosomally or plasmid-mediated through the expression of *tet* genes. 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 (24).

Results
During the available time period, 1996 to 2007, the utilization rates decreased for all tetracyclines (p≤0.01) and the drug tetracycline (p≤0.01) while the utilization of doxycycline remained between 1.0 to 1.5 DDD/1000 inhabitant days (Figure 32). The utilization rate of minocycline increased slightly over the available time period, however it still remains under 1.0 DDD/1000/inhabitant days.

The percent of *N. gonorrhoeae* isolates resistant to tetracycline are positively correlated to the utilization of all tetracyclines (r=0.9, p=0.03; Figure 33). However, a negative correlation was demonstrated between the proportion of *N. gonorrhoeae* resistant to minocycline (r=-0.6) and minocycline (r=-0.7). These negative correlations are not statistically significant.

Conclusion
Overall, the utilization of tetracyclines decreased over the available time period. BC Biomedical Laboratories, the primary data source for this report, did not previously publish the percent of isolates non-susceptible to tetracycline in available antibiograms. As such, limited AMR trend data were available and correlations between AMR trends and antimicrobial utilization performed using BC Biomedical data were only available following September 2007. Significant positive correlations were observed for the percent of *N. gonorrhoeae* isolates from the BCCDC STI Clinic and utilization of all tetracyclines and tetracycline.
Figure 32  Defined daily rate of tetracycline utilization

Source: PharmaNet

Figure 33  Percent of Neisseria gonorrhoeae isolates (Laboratory Services, BCCDC) non-susceptible to tetracycline correlated to utilization of all tetracyclines

Source: Laboratory Services, BCCDC; BC PharmaNet
**Quinolones**

**Examples**
- Ciprofloxacin
- Levofoxacin
- Gatifloxacin
- Norfloxacin
- Nalidixic acid

**Background**

Quinolone antimicrobials are active against a broad-spectrum of both Gram-positive and Gram-negative bacteria. Most clinically used quinolones belong to the fluoroquinolone subclass of antimicrobials, named for the presence of a fluoro group attached to the parent molecule, nalidixic acid. Fluoroquinolones (e.g. ciprofloxacin and levofloxacin) are recommended therapies for urinary tract infections (UTI), gonorrheal infections, gastroenteritis, and respiratory infections such as pneumonia.

Quinolone antimicrobials bind to DNA supercoiling enzymes, DNA gyrase and topoisomerase IV, inhibit DNA synthesis, and consequently prevent bacterial replication. 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. The specificity and magnitude of the resistance is related to the number of mutations present in the DNA supercoiling genes. Due to the broad-spectrum of quinolone activity, resistance is common in both Gram-positive and Gram-negative bacteria.

**Results**

Ciprofloxacin constitutes the majority of fluoroquinolone prescriptions in BC; consequently, the increased utilization of ciprofloxacin drives the increase in overall fluoroquinolone utilization from 1996 to 2007 (p<0.01; Figure 34). Utilization of newer quinolones (gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin and tovafloxacin) increased over the available time period, as the utilization of the older fluoroquinolone, norfloxacin, decreased (p<0.01, Figure 34). The utilization rate of gatifloxacin, a newer quinolone, peaked in 2004 before falling once again in 2005.

Urinary tract infection pathogens such as *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae* all demonstrate a dramatic increase in the percent of isolates non-susceptible to ciprofloxacin between the years 1998 to 2007 according to data from BC Biomedical Laboratories (Figure 35). The increase of fluoroquinolone resistance by UTI pathogens correlates to the increase in ciprofloxacin utilization which occurred during the same time period. Although *Enterococcus* spp. isolates more frequently demonstrate resistance against ciprofloxacin, the percent of *Enterococcus* spp. isolates non-susceptible to ciprofloxacin did decrease between years 2002 and 2007, while the other presented UTI pathogens continued to increase.

*Neisseria gonorrhoeae* isolates also demonstrated increasing resistance against ciprofloxacin during the available time period. The increase in the percent of *N. gonorrhoeae* isolates resistant to ciprofloxacin is positively correlated to the utilization of fluoroquinolone (r=0.8; Figure 36).

Fluoroquinolone non-susceptibility in the streptococci remains minimal with less than 5% of *Streptococcus pneumoniae* isolates demonstrating ciprofloxacin or levofloxacin resistance for all available years using data from the CBSN. Using data from the NCS-IPHis linked database, less than 1% of all tested *S. pneumoniae* isolates were non-susceptible to levofloxacin between years 2002 to 2007 (data not shown). The increase in non-susceptibility to levofloxacin is significantly correlated to...
utilization of levofloxacin (r=1.0, p<0.01) but no significant correlations exist for ciprofloxacin non-susceptibility (Figure 37).

Fluoroquinolone non-susceptibility in the staphylococci varied dramatically between methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA). In 2008, 94.3% of MRSA isolates were also non-susceptible to ciprofloxacin, while only 9.0% of MSSA isolates were non-susceptible according the BC Biomedical data (data not shown).

**Conclusions**

Ciprofloxacin non-susceptibility is increasing amongst UTI pathogens. This trend should be monitored in subsequent years as ciprofloxacin is a recommended therapy for treating UTIs along with nitrofurantoin and TMP-SMX. *N. gonorrhoeae* isolates also demonstrate an increase in the percent of isolates non-susceptible to ciprofloxacin over the available time period.

The increase in the percent of isolates non-susceptible to fluoroquinolones may be due to the introduction of new generation fluoroquinolones (e.g. levofloxacin, moxifloxacin, and gatifloxacin) with longer half-lives in the mid-1990s. Newer generation antimicrobials may select for antimicrobial resistance phenotypes as they exist for longer periods of time in the body at suboptimal concentrations. The significant increase in the percent of *S. pneumoniae* isolates non-susceptible to levofloxacin following its introduction in the mid-1990s supports this hypothesis. Despite the observable increases, the majority of *S. pneumoniae* isolates remain susceptible to fluoroquinolone antimicrobials. These trends may be overemphasized due to the small number of *S. pneumoniae* isolates non-susceptible to fluoroquinolones.

**Figure 34** Defined daily rate of fluoroquinolone utilization

Source: PharmaNet
Figure 35  Percent of urinary tract infection pathogens (BC Biomedical Laboratories) non-susceptible to ciprofloxacin correlated to utilization of fluoroquinolone

Source: BC Biomedical Laboratories; PharmaNet

Figure 36  Percent of Neisseria gonorrhoeae isolates (STI Clinic, BCCDC) resistant to ciprofloxacin correlated to utilization of ciprofloxacin

Source: STI Clinic, BCCDC; PharmaNet
Figure 37 Percent of Streptococcus pneumoniae isolates (CBSN) (A) non-susceptible to ciprofloxacin correlated to utilization ciprofloxacin and (B) non-susceptible to levofloxacin correlated to utilization of fluoroquinolones

Source: CBSN; PharmaNet
Sulfonamides and Trimethoprim

Examples

Trimethoprim-sulfamethoxazole (TMP-SMX)

Background

First synthesized prior to World War II, sulfonamides, also known as Sulpha drugs, are amongst the oldest agents shown to have antimicrobial properties. These antimicrobials are active not only against gram-positive and gram-negative bacteria, but also protozoa. When combined with trimethoprim, sulfonamides are primarily used to treat urinary tract infections (UTIs) (17). Combinations of sulfonamides and trimethoprim inhibit folic acid synthesis and, consequently, impede bacterial growth. Sulfonamides compete with p-amino-benzoic acid (PABA) for binding dihydropteroate synthase, a critical enzyme in the folic acid synthesis pathway (24). Trimethoprim binds to dihydrofolate reductase, another critical enzyme in the folic acid synthesis pathway, and prevents the conversion of PABA to folic acid (24). Resistance mechanisms include the overproduction of PABA and modification of folic acid synthesis enzymes (24).

Results

Combinations of sulfonamides and trimethoprim, specifically trimethoprim-sulfamethoxazole (TMP-SMX), constitute the 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 0.1 DDD/1000 inhabitant days for all available years (data not shown). Utilization of TMP-SMX declined during the available time period, 1996 to 2007 (p=0.01; Figure 38).

Despite the decrease in TMP-SMX utilization, the percent of UTI pathogens non-susceptible to TMP-SMX increased between years 2002 to 2007 (data not shown). In contrast, the percent of gram-positive isolates non-susceptible to TMP-SMX dramatically decreased in same time period (data not shown). The percent of CBSN S. pneumoniae isolates non-susceptible to TMP-SMX are not significantly correlated to utilization of TMP-SMX (Figure 39).

![TMP-SMX Utilization Rate](image)

*Figure 38  Defined daily rate of TMP-SMX utilization*

Source: PharmaNet
Conclusions

The percent of gram-negative bacteria non-susceptible to TMP-SMX increased, while the percent of gram-positive bacteria non-susceptible to TMP-SMX decreased during the available time period, 2002 to 2007. An exception is the gram-negative *K. pneumonia* which remains stable with approximately 10% of isolates demonstrating TMP-SMX non-susceptibility.

Figure 39  Percent of *Streptococcus pneumoniae* isolates (CBSN) non-susceptible to TMP-SMX correlated to utilization of TMP-SMX

Source: CBSN; PharmaNet
Other Antimicrobials

Examples
- Vancomycin
- 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) (17). Similar to β-lactam antimicrobials, vancomycin interferes with cell wall synthesis by binding to peptidoglycan precursors, D-Ala-D-Ala (24). 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 (24). Vancomycin-resistant strains, especially *Enterococcus* spp. (VRE), are of concern due to the lack of 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) (17). Its mechanism of action is unknown, but is thought to damage DNA (24).

Results

Although both nitrofurantoin and metronidazole utilization rates have remained below 0.6 DDD/1000/inhabitants per day over the available years, the utilization of nitrofurantoin is increasing while that of metronidazole remains unstable (Figure 40 and Figure 41). The percent of *Enterococcus* spp. isolates non-susceptible to vancomycin remains low in BC. According to both the BC Biomedical and BCAMM data, no more than 1% of isolates demonstrated vancomycin resistance between 2002 and 2006 (data not shown). The percent of isolates non-susceptible to nitrofurantoin varies between UTI pathogens. Less than 4% of *Enterococcus* spp. and *Escherichia coli* isolates demonstrated resistance against nitrofurantoin in 2007. In contrast, 68.6% of *Klebsiella pneumoniae* isolates and 100% of *Proteus mirabilis* isolates demonstrated resistance against nitrofurantoin in 2007. No significant increasing or decreasing trends were observed for nitrofurantoin non-susceptibility in the UTI pathogens.

Conclusions

The percent of vancomycin-resistant *Enterococcus* (VRE) isolates remained less than 1% over the available time period, 2002 to 2006. This trend should be observed closely in subsequent years as vancomycin resistance genes are readily transmitted to other bacterial species, of particular concern methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin is one of the few remaining treatment options for MRSA.

The percent of UTI isolates non-susceptible to nitrofurantoin widely varies between bacterial species. Caution should be exercised when prescribing nitrofurantoin for UTIs until the pathogen is cultured and identified.
Nitrofurantoin Utilization Rate

Figure 40  Defined daily rate of nitrofurantoin utilization

Source: PharmaNet

Metronidazole Utilization Rate

Figure 41  Defined daily rate of metronidazole utilization

Source: PharmaNet
Conclusions

Three major antimicrobial resistance trends are apparent in BC and should be monitored closely in subsequent years: an increasing prevalence of methicillin-resistant *Staphylococcus aureus* especially in community-acquired infections, macrolide resistance in gram-positive bacteria, and fluoroquinolone resistance in urinary tract infection pathogens.

Both BC Biomedical Laboratories and the BCAMM report an increasing percent of *S. aureus* isolates demonstrating methicillin resistance, especially in isolates originating from community sources. Their antibiotic resistance profile and limited reference testing at BCCDC supports the conjecture that these isolates are genetically related to community-acquired strains worldwide.

Significant correlations exist between the utilization of new, long half-life macrolides, clarithromycin and azithromycin, and the percent of gram-positive bacterial isolates demonstrating macrolide resistance. This observation is concerning as the defined daily rate of new macrolide utilization continues to increase. Significant correlations between erythromycin non-susceptibility and antimicrobial classes in addition to macrolides suggest that multidrug resistant strains are prevalent in BC and that treatment with antimicrobials may promote cross-resistance.

Ciprofloxacin is often recommended as a treatment for urinary tract infections (UTIs) along with nitrofurantoin and trimethoprim-sulfamethoxazole (TMP-SMX). Non-susceptibility to all three of these antimicrobials increased in UTI pathogens over the available time period. Ciprofloxacin non-susceptibility especially, 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.

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 rather than a causative relationship.

This report does not take into consideration antimicrobial utilization in food-producing animals 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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(10) Canadian Nosocomial Infection Surveillance Program (CNISP). Surveillance for Methicillin-resistant Staphylococcus aureus (MRSA) 2006 Results. PHAC, editor. 1-5. 2006. Ref Type: Generic


Ref Type: Abstract


## Appendix A

**Table 2**  List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial Resistance</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Classification</td>
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<tr>
<td>BC</td>
<td>British Columbia</td>
</tr>
<tr>
<td>BCAMM</td>
<td>British Columbia Association of Medical Microbiologists</td>
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<tr>
<td>BCCDC</td>
<td>British Columbia Centre for Disease Control</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>Community-Acquired Methicillin-Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>CBSN</td>
<td>Canadian Bacterial Surveillance Network</td>
</tr>
<tr>
<td>CIPARS</td>
<td>Canadian Integrated Program for Antimicrobial Resistance Surveillance</td>
</tr>
<tr>
<td>CLSI</td>
<td>Canadian Laboratory Standards Institute</td>
</tr>
<tr>
<td>CNISP</td>
<td>Canadian Nosocomial Infection Control System</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>D-test</td>
<td>Double Disk Diffusion Test</td>
</tr>
<tr>
<td>ESBL</td>
<td>Extended-Spectrum β-lactamase</td>
</tr>
<tr>
<td>E-test</td>
<td>Epsilometer Test</td>
</tr>
<tr>
<td>GAS</td>
<td>Group A Streptococcus</td>
</tr>
<tr>
<td>GES</td>
<td>Generalized Estimation System</td>
</tr>
<tr>
<td>HA-MRSA</td>
<td>Hospital-Acquired Methicillin-Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>iPHIS</td>
<td>Integrated Public Health Information System</td>
</tr>
<tr>
<td>M</td>
<td>Macrolide Resistance</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
</tr>
<tr>
<td>MLS₉</td>
<td>Macrolide, Lincosamide, Streptogramin B Resistance</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MSSA</td>
<td>Methicillin-Susceptible <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>NAUTICA</td>
<td>North American Urinary Tract Infection Collaborative Alliance</td>
</tr>
<tr>
<td>NCS</td>
<td>National Centre for Streptococcus</td>
</tr>
<tr>
<td>NML</td>
<td>National Microbiology Laboratory</td>
</tr>
<tr>
<td>PABA</td>
<td>p-Amino-Benzoic Acid</td>
</tr>
<tr>
<td>PBP</td>
<td>Penicillin-Binding Protein</td>
</tr>
<tr>
<td>PEOPLE 31</td>
<td>Population Extrapolation for Organizational Planning with Less Error Projection 31</td>
</tr>
<tr>
<td>PFGE</td>
<td>Pulse Field Gel Electrophoresis</td>
</tr>
<tr>
<td>PPNG</td>
<td>Penicillinase-Producing <em>Neisseria Gonorrhoeae</em></td>
</tr>
<tr>
<td>SCC</td>
<td>Staphylococcal Cassette Chromosome</td>
</tr>
<tr>
<td>SMX</td>
<td>Sulfamethoxazole</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Trimethoprim-Sulfamethoxazole</td>
</tr>
<tr>
<td>TRID</td>
<td>Translational Research in Infectious Diseases</td>
</tr>
<tr>
<td>TRNG</td>
<td>Tetracycline-Resistant <em>Neisseria Gonorrhoeae</em></td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary Tract Infection</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin-Resistant <em>Enterococcus</em></td>
</tr>
<tr>
<td>VRSA</td>
<td>Vancomycin-Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
Table 3  Summary of antimicrobial modes of action and bacterial mechanisms of resistance. Adapted from Murray et al. 2003.

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Action</th>
<th>Antimicrobial Mechanism</th>
<th>Resistance Mechanism</th>
<th>Common bacteria exhibiting resistance mechanism</th>
</tr>
</thead>
</table>
| B-lactams           | 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       | 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) |
| Macrolides          | 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<sub>B</sub> phenotype) | 1. *S. pneumoniae*, *S. pyogenes*  
2. *S. aureus*, *S. pneumoniae*, *S. pyogenes* |
| Tetracyclines       | 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          | 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 TMP-SMX | Bactericidal | Prevent synthesis of folic acid; Sulfonamides - compete with p-amino-benzoic acid (PABA) by binding dihydropteroate synthase  
Trimethoprim – bind dihydrofolate reductase and prevent conversion of PABA to folic acid | 1. Mutations in folic acid synthesis enzymes causing reduced affinity for sulfonamides and trimethoprim  
2. Overproduction of target | 1. *S. aureus*, *S. pneumoniae*, Gram-negative bacteria  
2. *E. coli* |
| Nitrofurans         | Bactericidal | Unknown; Thought to damage DNA | 1. Unknown | 1. Urinary tract infection pathogens |