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Antimicrobial Resistance Trends in the Province of British Columbia

2012

Prepared for *the*
Do Bugs Need Drugs? Program

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Provincial Health Services Authority
Province-wide solutions. Better health.

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About This Report

This report aims to provide a comprehensive overview of antimicrobial resistance prevalence in British Columbia (BC), as part of the *Do Bugs Need Drugs?* (DBND) program evaluation. The DBND program is a community education program for health care professionals and the public geared towards decreasing antibiotic overuse and misuse and the spread of resistant organisms. It has been funded since its inception in BC (2005) by Pharmaceutical Services, BC Ministry of Health. This report is an update of the annual report "Antimicrobial Resistance Trends in the Province of British Columbia" which has been prepared at the BC Centre for Disease Control (BCCDC) since 2006. Data presented in this report may differ from previous years due to additional information regarding changes in testing methods or number of isolates tested. The most current report should be considered the most accurate.

Data were obtained from various provincial and national collaborators to provide a comprehensive overview of antimicrobial resistance surveillance in BC for clinically relevant bacteria. Line-listed data were provided by BC Biomedical Laboratories and the Canadian Bacterial Surveillance Network (CBSN), while aggregate data were provided by all other sources.

The WHO ATC/DDD System

Since the mid 1970s, The World Health Organisation (WHO) has advocated for the use of its classification system and standard unit of measurement in drug utilisation studies. While the Defined Daily Dose (DDD) was not required for this report, it is the standard technical unit of measurement for use in drug utilization studies, allowing for comparability of results internationally (1). The Anatomical Therapeutic Classification (ATC) is a system of categorizing active substances into groups at five different levels, starting with the organ or system on which they act. It is followed by the pharmacological, therapeutic or chemical properties of the drug. These properties are expanded upon in the third and fourth levels, while the fifth level identifies the chemical substance (1).

Important Notes

- Antimicrobial resistance refers to organism's ability to survive in the presence of one or more antimicrobial agents. Organisms are tested for susceptibility to antimicrobial agents in the laboratory using the minimum inhibitory concentration (MIC) breakpoints, as set out by the Clinical and Laboratory Standards Institute (CLSI) guidelines (2). The MIC breakpoint is the lowest concentration of the drug that will inhibit growth of the pathogen (2).
- Wherever possible, data are presented for isolates reaching both the resistant and intermediate MIC breakpoint threshold. Unless otherwise indicated, all other data presented combine both resistant and intermediate percentages, and are referred to as the percent of isolates non-susceptible to the specific antimicrobial.
- Antibiotic resistance and non-susceptibility trends are, in most cases, provided for antibiotics that are used as therapy for a particular organism.
- All resistance and non-susceptibility trends are reported on a per isolates basis with the exception of carbapenem-resistant Enterobacteriaceae (CRE) and *Mycobacterium tuberculosis* which are reported on a per patient basis.
- The antibiograms provided by LifeLabs Medical Laboratory Services include isolates collected from community-based patients across BC. The vast majority of these isolates are from patients in the Lower Mainland of BC and Vancouver Island. In keeping with the LifeLabs antibiogram terminology, the LifeLabs data presented in this report will be referenced following their terminology of 'Mainland' and 'Vancouver Island'.
- As resistance rates differed significantly between organisms, scale bars (vertical axes) on figures are not consistent between organisms. Caution should be exercised when interpreting and comparing figures across organisms.
- Analysis of temporal trends in resistance rates compared changes in the pattern of resistance between the years 2007 to 2012, unless otherwise specified, using the non-parametric Spearman Rank test.
- BCAMM data were only available up to the year 2011. Comparisons with the data source are made using data from 2011 for all sources.

- The α-level used for significance in this report is $p<0.05$.
- Please see Table 1 for a list of abbreviations used in the report.

Changes from Previous Reports

New to the report this year is aggregate antibiogram data from LifeLabs Medical Laboratory Services, a community-based laboratory which provides services to Vancouver Island and the Mainland (mainly in Vancouver Coastal and Fraser Health Authorities of BC). Additional community-based laboratory data, the majority of which was collected from the Fraser Health Authority of BC, were derived from line-listed monthly data extracts provided by BC Biomedical Laboratories. Also new to this year's report is a short section on carabapenem-resistant Enterobacteriaceae (CRE) within the extended-spectrum beta-lactamase (ESBL) section. Resistance and non-susceptibility results are reported for each drug based on data availability and empiric therapy guidelines as set out in the *Bugs and Drugs* antimicrobial and infectious disease reference manual (3).

This year's report focuses only on antimicrobial resistance. A separate report will present findings on antimicrobial utilization. This report will be available through the BCCDC website. Additionally, background information on each organism that was included in previous years, can be found in the supplemental report. The supplemental report is not comprehensive but briefly reviews the mechanisms of resistance and highlights some recent antimicrobial resistance findings for organisms of interest. It is also available on the BCCDC website: http://www.bccdc.ca/prevention/AntibioticResistance/ReportsandPublications/default.htm.

Table 1 - List of Abbreviations

Abbreviation	Definition
AMR	Antimicrobial Resistance
ATC	Anatomical Therapeutic Classification
BC	British Columbia
BCAMM	British Columbia Association of Medical Microbiologists
BCCDC	British Columbia Centre for Disease Control
CA-MRSA	Community-Associated Methicillin-Resistant *Staphylococcus aureus*
CANWARD	Canadian Ward Surveillance Study
CBSN	Canadian Bacterial Surveillance Network
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CLSI	Clinical and Laboratory Standards Institute
CNISP	Canadian Nosocomial Infection Surveillance Program
CRE	Carbapenems-resistant Enterobacteriaceae
DDD	Defined Daily Dose
DNA	Deoxyribonucleic acid
D-test	Double Disk Diffusion Test
ESBL	Extended-Spectrum β-lactamase
GAS	Group A Streptococcus
HA-MRSA	Hospital-Associated Methicillin-Resistant *Staphylococcus aureus*
iPHIS	Integrated Public Health Information System
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
NML	National Microbiology Laboratory
MTB	*Mycobacterium tuberculosis*
PHAC	Public Health Agency of Canada
TMP-SMX	Trimethoprim-Sulfamethoxazole
UTI	Urinary Tract Infection
VRE	Vancomycin-Resistant *Enterococcus*
WHO	World Health Organization

Executive Summary

This report aims to provide a comprehensive overview of antimicrobial resistance (AMR) trends in the province of British Columbia (BC). A summary of the results is presented below:

Gram Positive Organisms

- The proportion of ***Staphylococcus aureus*** isolates that were methicillin resistant (MRSA) ranged from 16.1% to 23.9% from 2008 to 2012, but remained below the peak rate observed in 2007 (30.5%). In 2012, rate of resistance to clindamycin, doxycycline (tetracyclines) and trimethoprim-sulfamethoxazole (TMP-SMX) among MRSA isolates were 38.0%, 6.7% and 1.8%, respectively. These data imply that clindamycin may not be an optimal choice for empirical treatment of suspected community-acquired MRSA when antibiotics are needed to treat complicated infections.
- ***Streptococcus pneumoniae*** isolates have demonstrated a stable rate of resistance to all antibiotics tested since 2007, with the exception of levofloxacin, to which resistance has declined ($p<0.01$). In 2012, 33.7% of all tested isolates demonstrated non-susceptibility against erythromycin - a finding relevant to all macrolides. *S. pneumoniae* isolates were also non-susceptible to penicillin and TMP-SMX at rates of 17.2% and 21.9%, respectively in 2012.
- From 2007 to 2010, non-susceptibility rates to erythromycin and clindamycin decreased in ***Streptococcus pyogenes*** isolates. However, as of 2012, non-susceptibility rates had significantly increased to 22.7% ($p<0.01$) and 22.3% ($p=0.03$), respectively. As of 2012, *S. pyogenes* isolates remain highly susceptible to penicillin, cephalothin and vancomycin, but fully resistant to TMP-SMX and ciprofloxacin.
- In 2012, ***Enterococcus* spp**. isolates remained highly susceptible to ampicillin (98.6%) and nitrofurantoin (98.8%). However, one quarter of all isolates tested were non-susceptible to ciprofloxacin (24.7%), largely due to increased resistance in individuals older than 70 years of age ($p<0.01$). Less than 1% of all *Enterococcus* spp. isolates were identified as vancomycin-resistant *Enterococcus* (VRE).

Gram Negative Organisms

- In 2012, ***Escherichia coli*** resistance to ciprofloxacin was 25.3%. These resistance rates increase with age, being highest in those aged 70 years or more ($p<0.001$). *E. coli* isolates have demonstrated moderate levels of resistance to TMP-SMX with 25.6% of isolates demonstrating resistance in 2012. Nitrofurantoin remains a highly effective empiric treatment for urinary infections caused by *E. coli* with approximately 97.1% of isolates exhibiting susceptibility to this drug class. This trend is reassuring as *E. coli* is the causative organism for the majority of uncomplicated UTI infections.
- Data from 2012 suggest that ciprofloxacin resistance in ***Klebsiella pneumoniae*** isolates remains low at 3.9%. Additionally, resistance to TMP-SMX for *K. pneumoniae* appears to be decreasing from 10.8% in 2007 to 8.2% in 2012 ($p<0.01$).
- In 2012, 20.5% of ***Proteus mirabilis*** isolates were non-susceptible to ciprofloxacin. Additionally, 31.3% of isolates demonstrated resistance to TMP-SMX.
- While 11.7% of *E. coli* isolates exhibited an **extended-spectrum β-lactamase-like (ESBL)** phenotype in 2012, only 3.3% of *K. pneumoniae* and 5.5% of *P. mirabilis* isolates exhibited this phenotype. Approximately half of all ESBL-like (*E. coli, K. pneumoniae* and *P. mirabilis*) isolates demonstrated non-susceptibility to at least two of the quinolones, aminoglycosides and TMP-SMX, while approximately 20% of isolates demonstrated non-susceptibility to antimicrobials in all three classes.
- Despite a slight increase in non-susceptibility to ciprofloxacin from 10.1% in 2011 to 11.7% in 2012 for ***Pseudomonas aeruginosa*** isolates, the non-susceptibility trend did not reach statistical significance ($p=0.09$). Isolates remain highly susceptible (>95%) to tobramycin, piperacillin, ceftazidime, meropenem and gentamicin.
- The percent of ***Haemophilus influenzae*** isolates resistant to ampicillin has remained between 14-20% from 2007 to 2012 ($p=0.70$). Resistance to ampicillin peaked in 2012 at 19.4%.

Other Organisms

- Rates of multi-drug and poly-drug resistance in patients infected with *Mycobacterium tuberculosis* (MTB) remains low at less than 1% of patients. No cases of extensively drug-resistant MTB were reported. Approximately 9% of patients were infected with MTB exhibiting resistance to one drug.

Introduction

Bacterial strains that develop or acquire resistance to one or more first-line antimicrobials pose numerous challenges to healthcare, including: increased patient morbidity and mortality, increased drug costs, prolonged illness duration, and more expensive disease control measures (4). These antimicrobial resistant (AMR) strains arise, in part, as a result of antimicrobial use that selects for resistant organisms (4). Inappropriate antimicrobial use therefore contributes unnecessarily to the rise in resistance. As AMR genes or plasmids can be readily transmitted between bacterial species, surveillance of AMR trends is critical for the rapid detection of new isolates and continuous monitoring of disease prevalence (4). This report aims to describe trends in AMR for clinically relevant Gram positive and Gram negative bacteria in the community in the province of British Columbia (BC) for all years where data are available. Background information on each organism described in this report can be found online in the Supplemental Background: Background on Antimicrobial Resistance Trends available online at: http://www.bccdc.ca/prevention/AntibioticResistance/ReportsandPublications/default.htm

Data sources

Data sources used for the compilation of this report are listed below along with the organism for which they provided data. Detailed descriptions of these sources can be found in Appendix B: Technical Notes

BC Association of Medical Microbiologists (BCAMM)
Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBL producing Enterobacteriaceae)

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

BC Public Health Microbiology & Reference Laboratory (BCPHMRL)
Methicillin-resistant *Staphylococcus aureus* (MRSA), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBL-producing Enterobacteriaceae), carbapenem-resistant Enterobacteriaceae (CRE), *Mycobacterium tuberculosis*

Canadian Bacterial Surveillance Network (CBSN)
Streptococcus pneumoniae

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

LifeLabs Medical Laboratory Services
Staphylococcus aureus, methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Haemophilus influenzae*

Antimicrobial Resistance (AMR) Trends

Gram-positive Organisms

1.1. Staphylococcus aureus

Staphylococcus aureus is a Gram positive organism that most commonly cause skin and soft tissue infections, but can also cause disease in other organ systems (e.g. pneumonia, sepsis) (5). Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are the most prevalent and most clinically important form of antimicrobial resistance among the staphylococci. Although MRSA infections were traditionally only acquired in the hospital setting, community-associated MRSA (CA-MRSA) strains have become prevalent both in hospitals and in the community (6). The epidemiological source of acquisition of infection was not determined for the purpose of this report. Methicillin-susceptible *S. aureus* (MSSA) reported here, represents all strains of *S. aureus* that are susceptible to the β-lactam class of antibiotics.

According to data from BC Biomedical Laboratories, the proportion of all *S. aureus* isolates resistant to methicillin (MRSA) has fluctuated between 16-30% from 2007 to 2012 (Figure 1). In 2012, MRSA made up 23.9% of all *S. aureus* isolates. According to the BCAMM data, which includes both hospital and community laboratory data, the proportion of MRSA in all *S. aureus* isolates increased from 9.1% in 2002 to a peak of 23.0% in 2006 (Figure 1). This figure has since declined and was most recently reported at 15.0% in 2011 (Figure 1). BCAMM has yet to publish data for 2012.

Data from BC Biomedical Laboratories indicate a higher proportion of *S. aureus* isolates being MRSA when compared to BCAMM. This may in part be due to the increasing prevalence of community-associated MRSA (CA-MRSA), which is likely represented in greater proportions within the BC Biomedical Laboratories' dataset as it is a community-based laboratory. LifeLabs data was available for Vancouver Island and the Mainland. Vancouver Island was found to have the lowest rate of MRSA isolates in the community at 13.3% in 2012, while the Mainland showed a similar rate to that of BC Biomedical (Figure 1).

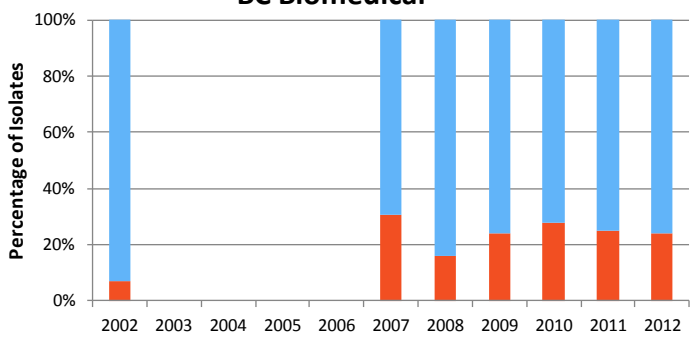
Nationally, the Canadian Nosocomial Infection Surveillance Program (CNISP) has monitored the prevalence of MRSA from 1995 to 2009. CNISP reports that the overall incidence of both MRSA colonization and MRSA infection increased from 0.65 to 12.4 cases per 10,000 patient-days from 1995 to 2007 (7). CNISP also reports that infection with community-associated MRSA strains rose significantly from 6 percent in 1995 to 23 percent in 2007 (7).

Among MRSA isolates, resistance to trimethoprim-sulfamethoxazole (TMP-SMX) and erythromycin significantly declined from 2007 to 2012 (TMP-SMX: $p<0.001$; erythromycin: $p<0.001$), while clindamycin resistance did not change ($p=0.562$) (Figure 2). In 2012, more than 95% of MRSA isolates continued to be susceptible to vancomycin and mupirocin (data not shown). According to data from BC Biomedical Laboratories, the proportion of isolates resistant to clindamycin, erythromycin, and TMP-SMX was significantly higher for MRSA isolates compared to methicillin-susceptible *S. aureus* (MSSA) isolates (clindamycin: $p<0.001$; erythromycin: $p<0.001$; TMP-SMX: $p<0.001$) (Figure 2).

The decrease in non-susceptibility rates of MRSA for many of the tested antimicrobials between 2002 and 2012 likely reflects an increased proportion of CA-MRSA strains, which are typically more susceptible to antimicrobials than their hospital-associated counterparts (6-11). In the CANWARD study, 27,123 isolates were collected across Canada from tertiary hospitals from 2007 to 2011, of which 16.8% of isolates were from BC (12). Of the 27,123 isolates, 5,443 were *S. aureus*; of which, 1,266 (23.3%) were identified as MRSA, and of those 366 (28.9%) were found to be CA-MRSA, while 868 (68.6%) were found to be HA-MRSA (12). Nationally, the CANWARD study found that while 85.6% and 27.8% of HA-MRSA were susceptible to TMP-SMX and clindamycin, respectively, 100% and 86.1% of CA-MRSA were susceptible to the same drugs (6;12). Similar relationships were found with several other antibiotics (6;13). It should be noted that these trends represent resistance seen in Canadian hospitals only and do not include community isolates. Consequently, differences in rates may be in part due to demographic and geographic differences in data sources. CA-MRSA isolates should be managed according to susceptibility results if antibiotic treatment is required.

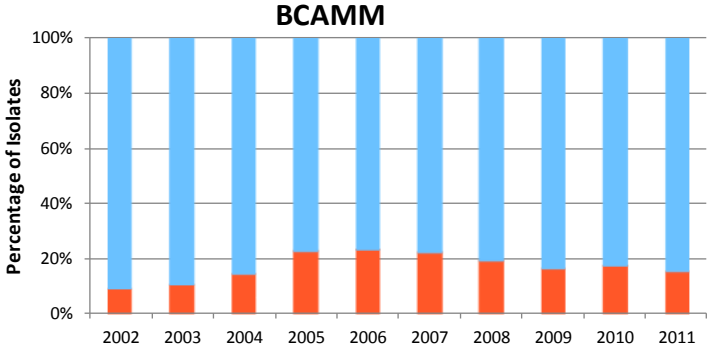
Among MSSA, resistance to clindamycin and erythromycin has remained stable from 2007 to 2012 (clindamycin: $p=0.129$; erythromycin: $p=0.329$), but resistance to TMP-SMX decreased during this period, reaching 0.8% in 2012 ($p<0.001$) (Figure 2). In 2012, 99.9% of MSSA isolates were susceptible to cephalothin (data not shown). Additionally, all *S. aureus* isolates were susceptible to vancomycin.

BC Biomedical



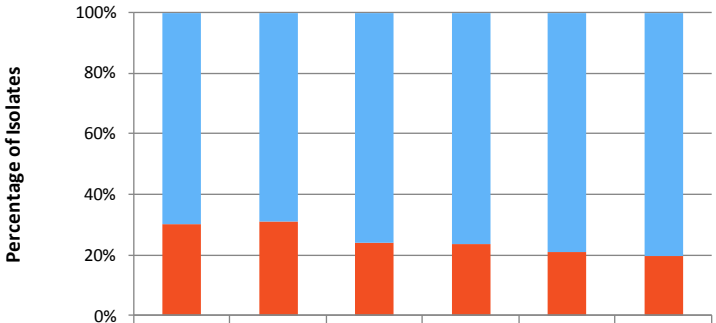
	2002	2007	2008	2009	2010	2011	2012
MSSA	92.8%	69.5%	83.9%	76.1%	72.1%	75.1%	76.1%
MRSA	7.2%	30.5%	16.1%	23.9%	27.9%	24.9%	23.9%
Total Isolates	4,587	7,668	6,636	7,006	6,731	5,873	5,659

BCAMM

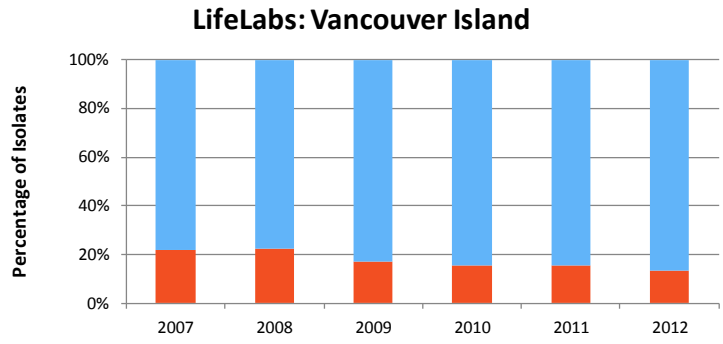


	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
MSSA	90.9%	89.6%	85.6%	77.4%	77.0%	78.0%	81.0%	84.0%	83.0%	85.0%
MRSA	9.1%	10.4%	14.4%	22.6%	23.0%	22.0%	19.0%	16.0%	17.0%	15.0%
Total Isolates	27,641	29,991	33,079	39,471	43,694	50,226	52,604	48,126	47,220	50,367

LifeLabs: Mainland



	2007	2008	2009	2010	2011	2012
MSSA	69.9%	69.1%	76.0%	76.6%	79.1%	80.5%
MRSA	30.1%	30.9%	24.0%	23.4%	20.9%	19.5%
Total Isolates	7780	8129	6548	6322	6316	6257

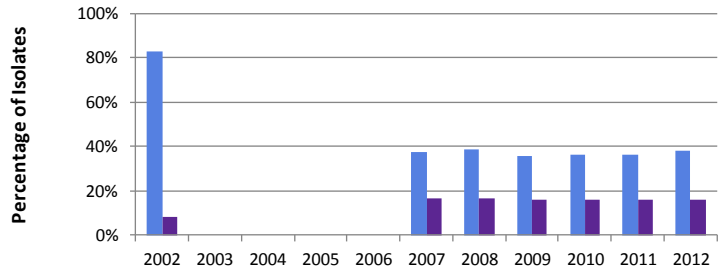


	2007	2008	2009	2010	2011	2012
MSSA	78.1%	77.8%	82.6%	84.2%	84.6%	86.7%
MRSA	21.9%	22.2%	17.4%	15.8%	15.4%	13.3%
Total Isolates	4210	4210	3270	3037	3166	3055

Figure 1 - Proportion of *Staphylococcus aureus isolates* methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) (2002-2012)
Source: BC Biomedical Laboratories; BCAMM(14); LifeLabs

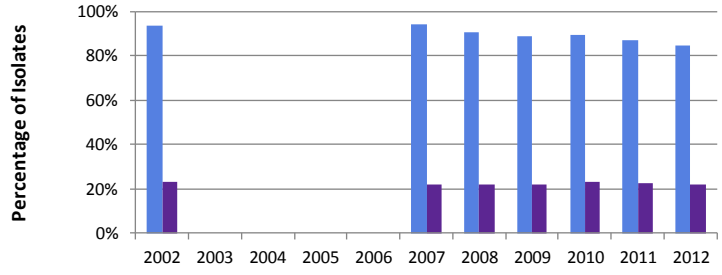
Please note: BCAMM data was only available up to 2011.

Clindamycin



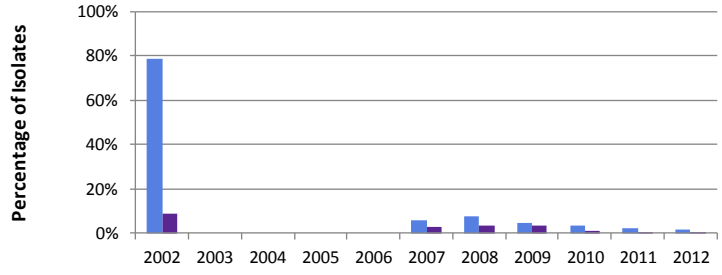
	2002	2007	2008	2009	2010	2011	2012
MRSA	83.0%	37.7%	39.0%	35.7%	36.7%	36.3%	38.0%
MSSA	8.0%	16.8%	16.7%	16.1%	16.1%	15.8%	15.9%
MRSA Isolates	328	2,234	1,004	1,589	1,778	1,387	1,219
MSSA Isolates	4,529	4,981	5,212	4,922	4,438	4,055	3,995

Erythromycin

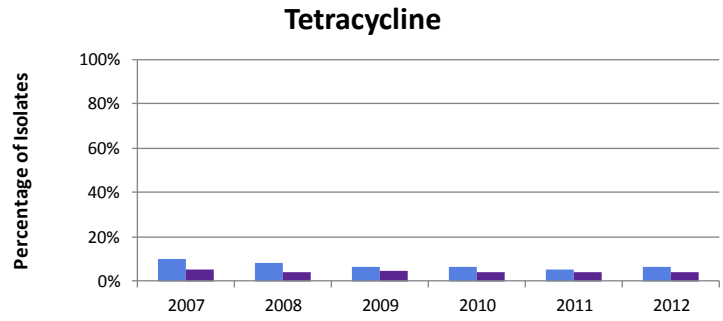


	2002	2007	2008	2009	2010	2011	2012
MRSA	94.0%	94.2%	90.5%	89.2%	89.3%	87.0%	84.8%
MSSA	23.0%	21.8%	22.1%	22.2%	23.4%	22.7%	22.1%
MRSA Isolates	328	2,234	1,004	1,589	1,778	1,387	1,219
MSSA Isolates	4,529	4,981	5,212	4,922	4,438	4,055	3,995

TMP-SMX



	2002	2007	2008	2009	2010	2011	2012
MRSA	79.0%	5.9%	7.5%	4.7%	3.5%	2.2%	1.8%
MSSA	9.0%	2.6%	3.5%	3.6%	0.9%	0.8%	0.6%
MRSA Isolates	328	2,234	1,004	1,589	1,778	1,387	1,219
MSSA Isolates	4,529	4,981	5,212	4,922	4,438	4,055	3,995



	2007	2008	2009	2010	2011	2012
MRSA	9.9%	8.5%	6.3%	6.8%	5.1%	6.7%
MSSA	5.3%	4.2%	4.4%	4.3%	4.3%	4.1%
MRSA Isolates	836	1,065	1,673	1,878	1,464	511
MSSA Isolates	1,805	5,452	5,308	4,821	4,401	1,679

Figure 2 - Proportion of MRSA and MSSA isolates resistant to clindamycin, erythromycin and TMP-SMX and tetracycline (2002-2012)
Source: BC Biomedical Laboratories

Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 were obtained from aggregate antibiograms.

1.2. *Streptococcus pneumoniae*

Streptococcus pneumoniae (pneumococcus) is the leading cause of community acquired pneumonia (CAP), but also commonly presents as acute otitis media, bacteremia, and meningitis.

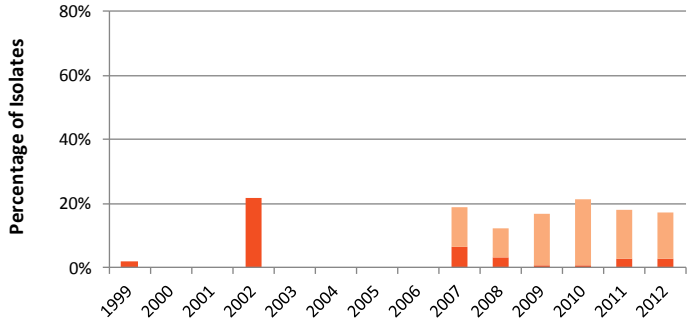
According to BC Biomedical Laboratories data, 17.2% of *S. pneumoniae* were non-susceptible to penicillin in 2012, the majority of which showed intermediate resistance (Figure 3). The proportion of *S. pneumoniae* non-susceptible to erythromycin remained stable around 30% from 2007 to 2012 (p=0.427) (Figure 3). Since 2007, clindamycin non-susceptibility has fluctuated around 15% (p=0.850), and is currently reported at 15.8% (Figure 3). Similarly, non-susceptibility towards TMP-SMX has appeared to remain stable at approximately 20% of isolates for 2002, and 2007 to 2012 (p=0.287). However, this rate is substantially lower than the antibiogram rate reported in 1999 (66%) (Figure 3). Tetracycline non-susceptibility has exhibited similar trends, with non-susceptibility rates fluctuating between 15% and 20% from 2007 to 2012 (p=0.504) (Figure 3). Levofloxacin non-susceptibility has remained less than 5% of isolates since 2007 and currently sits at 0.9% (data not shown). All isolates were susceptible to ceftriaxone and vancomycin in 2012 and all isolates were fully resistant to cefixime (data not shown).

Data from the CBSN suggest a general increase in the percent of isolates non-susceptible to clindamycin, tetracycline, and erythromycin between 1994 and 2012 (clindamycin: p=0.001; tetracycline: p<0.001; erythromycin: p<0.001), a trend not observed in BC Biomedical data (Figure 4). Penicillin non-susceptibility has fluctuated quite drastically between less than 5% to more than 20% for the period of 1994 to 2012 (p=0.473). From 2009 to 2011, it appeared as though the rate of isolates non-susceptible to penicillin was decreasing from 20.0% to 8.2%; however, non-susceptibility increased again in 2012 and was reported at 15.3%, a rate similar to BC Biomedical Laboratories (Figure 4). TMP-SMX non-susceptibility had remained stable, just above 25.0%, from 2009 to 2011 but decreased by more than ten percent in 2012 to 15.3% (p=0.270) (Figure 4). Ceftriaxone non-susceptibility remained low in 2012 at 1.9% of isolates, similar to the rate seen in 2011 (Figure 4). Non-susceptibility to moxifloxacin exhibited a similar trend to the observed non-susceptibility for levofloxacin for most years with 1.9% of *S. pneumoniae* isolates showing resistance to moxifloxacin and to levofloxacin in 2012 (Figure 4).

LifeLabs data suggest higher non-susceptibility rates in *S. pneumoniae* isolates from the Mainland when compared to Vancouver Island. In 2012, non-susceptibility to TMP-SMX was 24.0% for Mainland isolates and 21.0% for Vancouver Island isolates (data not shown), as compared to 21.9% of isolates based on BC Biomedical data. Penicillin non-susceptibility rates among LifeLabs isolates from the Mainland and Vancouver Island were 16.0% and 15.0%, respectively, similar to the BC Biomedical rate (17.2%). The rate of tetracycline non-susceptibility was highest on the Mainland at 41.0%, while 15.0% of isolates on Vancouver Island were non-susceptible (data not shown).

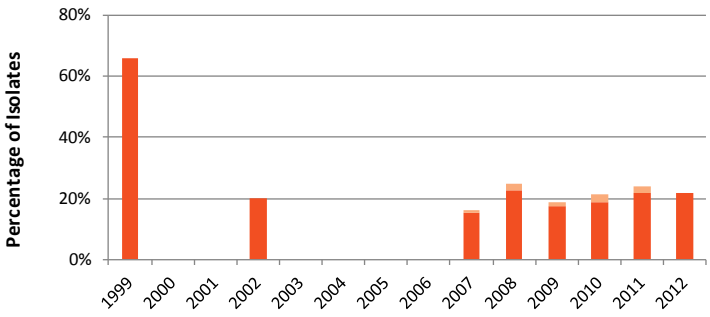
Discrepancies between the data sources may be due to the differences in the site of data collection. BC Biomedical Laboratories collects isolates from community sources throughout the Lower Mainland of BC while CBSN obtains isolates from several hospitals in BC. For 2010 to 2012, susceptibility results from one and two hospitals were available at time of publication. It should also be noted that for LifeLabs data in 2012, susceptibility testing was performed on only 33 of *S. pneumoniae* isolates from Vancouver Island, while more than 100 isolates from the Mainland were tested. BC Biomedical Laboratories also had over 100 isolates tested for susceptibility.

Penicillin



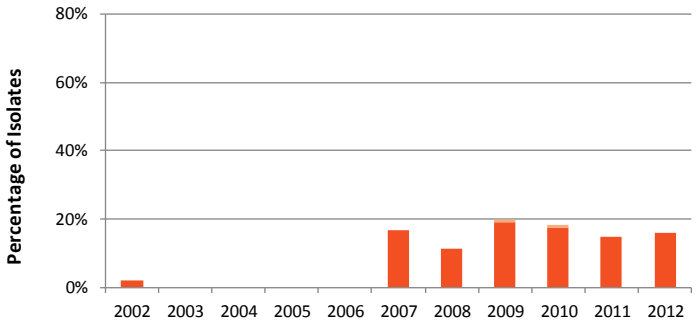
	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	12.3%	8.8%	16.3%	20.7%	15.0%	14.5%
Resistant	2.0%	22.0%	6.5%	3.4%	0.8%	0.9%	3.0%	2.7%
Total Isolates	N/A	100	154	148	129	116	133	110

TMP-SMX

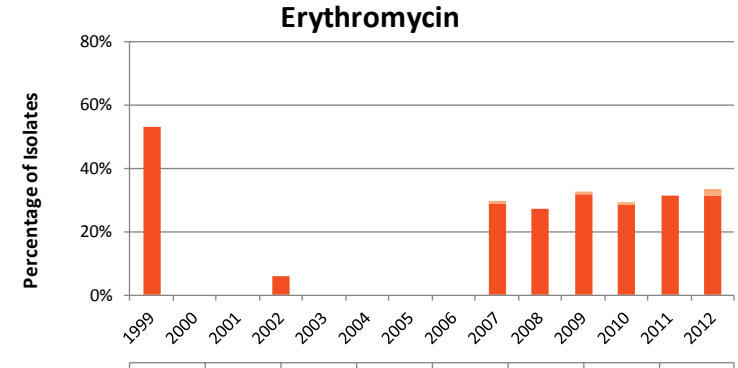


	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.6%	1.9%	1.5%	2.6%	2.2%	0.0%
Resistant	66.0%	20.0%	15.5%	22.7%	17.4%	18.8%	21.6%	21.9%
Total Isolates	N/A	100	155	154	132	117	134	114

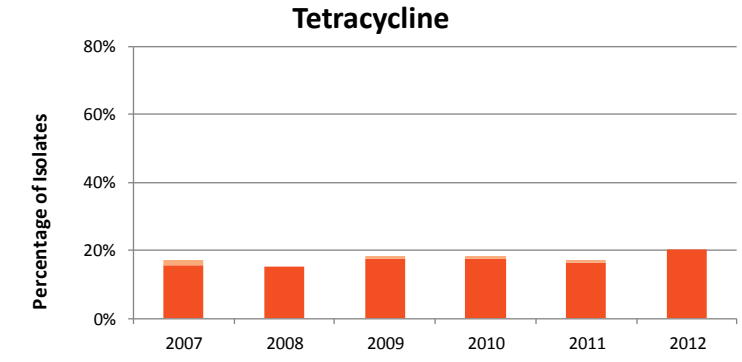
Clindamycin



	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	0.0%	0.0%	0.8%	1.0%	0.0%	0.0%
Resistant	2.0%	16.9%	11.3%	18.9%	17.3%	14.9%	15.8%
Total Isolates	100	148	141	122	104	121	95



	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.7%	0.0%	0.8%	1.0%	0.0%	2.1%
Resistant	53.0%	6.0%	29.1%	27.3%	32.0%	28.6%	31.4%	31.6%
Total Isolates	N/A	100	148	143	122	105	121	95

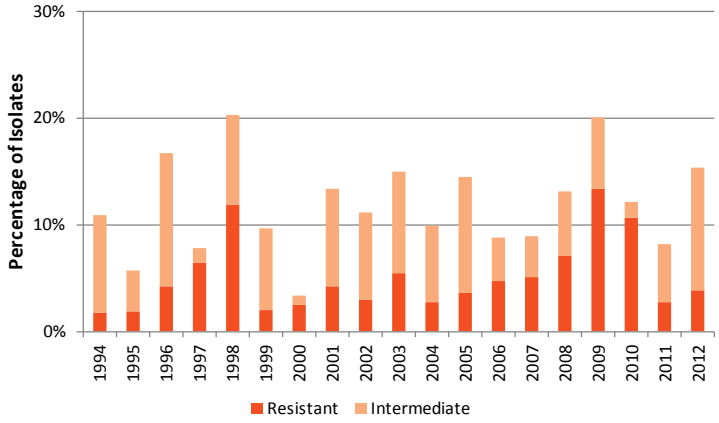


	2007	2008	2009	2010	2011	2012
Intermediate	1.4%	0.0%	0.8%	1.0%	0.8%	0.0%
Resistant	15.7%	15.4%	17.5%	17.5%	16.5%	20.2%
Total Isolates	140	136	120	103	121	94

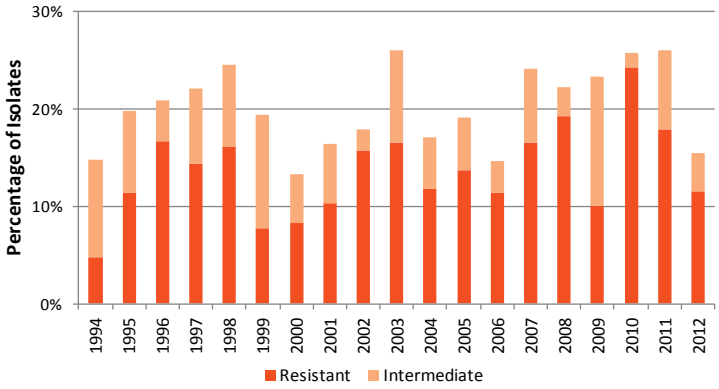
Figure 3 - Proportion of *Streptococcus pneumoniae* isolates non-susceptible to penicillin, TMP-SMX, clindamycin, erythromycin and tetracycline (1999-2012)
Source: BC Biomedical Laboratories

Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 were obtained from aggregate antibiograms.

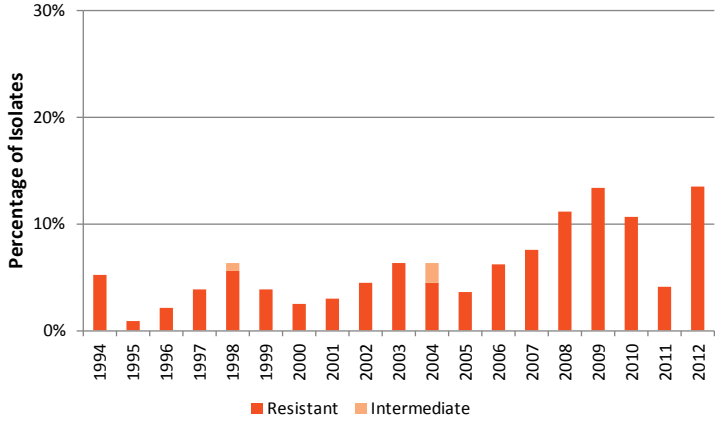
Penicillin

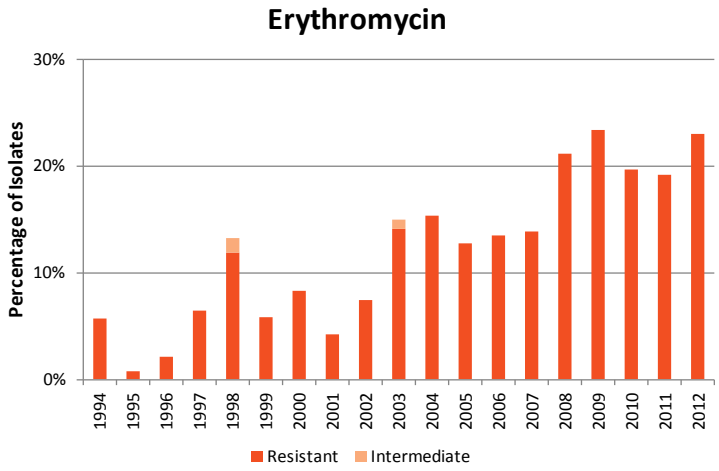


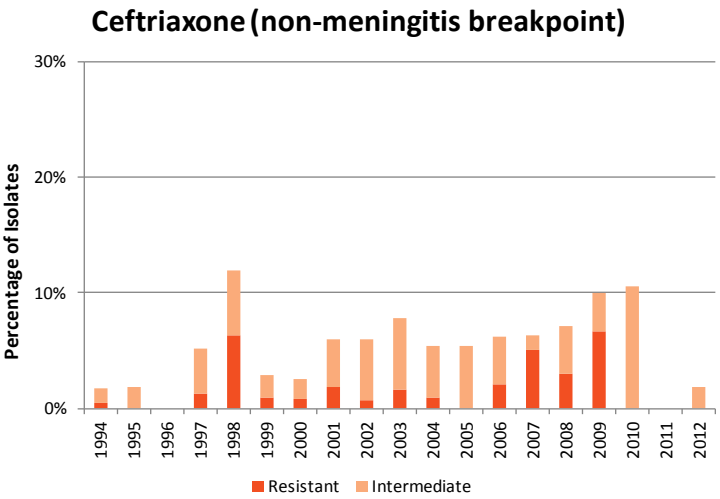
TMP-SMX

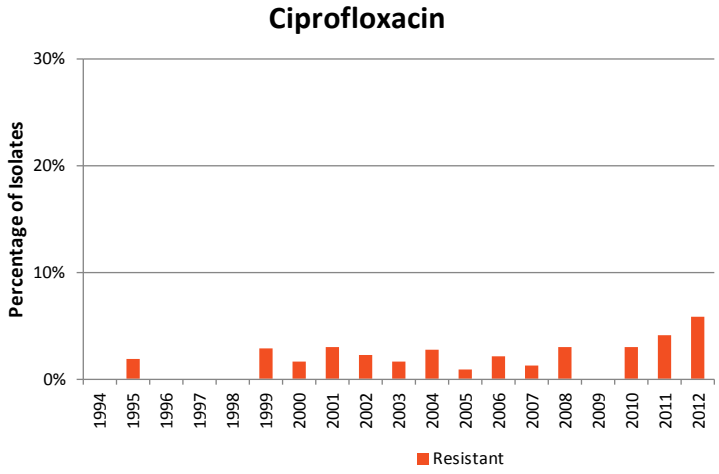


Clindamycin




Erythromycin
30%
20%
10%
0%
Percentage of Isolates
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Resistant
Intermediate


Ceftriaxone (non-meningitis breakpoint)
30%
20%
10%
0%
Percentage of Isolates
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Resistant
Intermediate


Ciprofloxacin
30%
20%
10%
0%
Percentage of Isolates
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Resistant

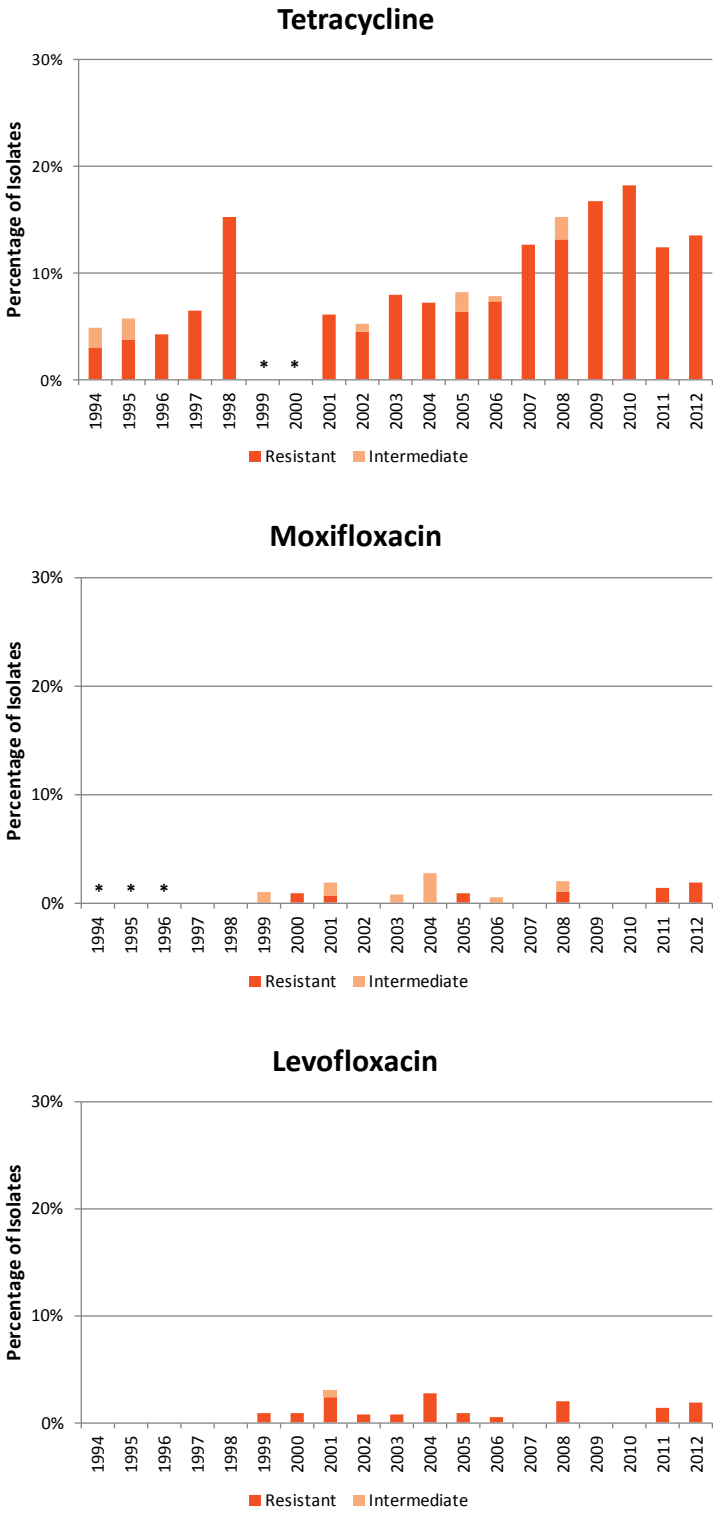


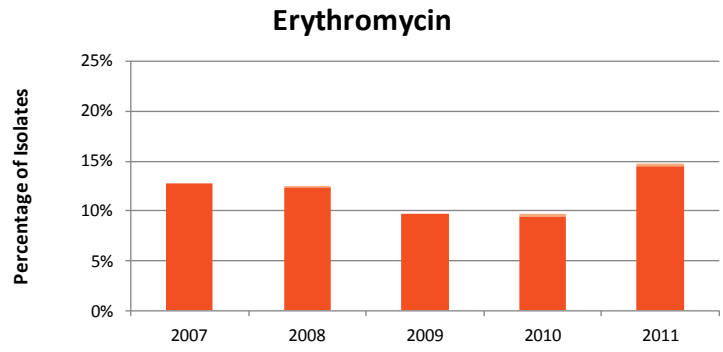
Figure 4 - Proportion of *Streptococcus pneumoniae* isolates non-susceptible to penicillin, TMP-SMX, clindamycin, erythromycin, ceftriaxone, ciprofloxacin, tetracycline, moxifloxacin and levofloxacin (1994-2012)
*Fewer than 40 isolates tested
Source: CBSN

1.3. Streptococcus pyogenes

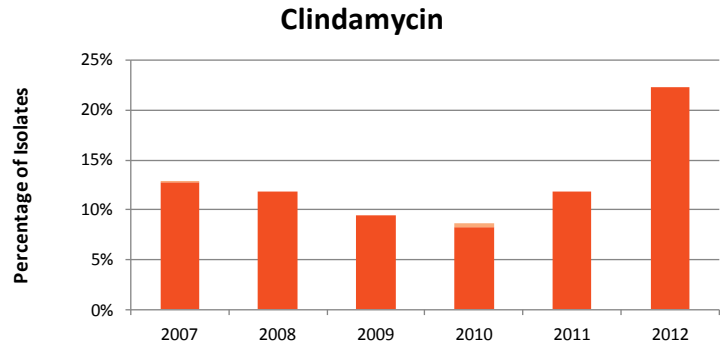
Streptococcus pyogenes, also known as β-hemolytic Group A Streptococci (GAS), typically presents as a relatively mild, non-invasive throat infection ("Strep throat"), but can also cause more serious invasive infections including necrotizing fasciitis and toxic shock syndrome (15). Recommended therapies for GAS infections include penicillin, clindamycin, azithromycin, clarithromycin and cephalexin (3).

BC Biomedical Laboratories data include both invasive and non-invasive GAS isolates for all years available. All isolates remained susceptible to penicillin, amoxicillin-clavulanate and cephalothin as of 2012 (data not shown). The percent of isolates non-susceptible to erythromycin had appeared to be decreasing from 2007 to 2010 but have since increased, peaking at 22.7% non-susceptibility in 2012 (p=0.002) (Figure 5). Clindamycin non-susceptibility shows a similar trend to erythromycin non-susceptibility for all years (2007-2012), and has increased to 22.3% non-susceptibility in 2012 (p=0.032) (Figure 5). All isolates were non-susceptible to ciprofloxacin and TMP-SMX (data not shown).

The CANWARD study found that from 2007 to 2011, less than 2% of *S. pyogenes* isolates nationally were non-susceptible to clindamycin – a number far lower than any rate observed in BC over the same time period (12). This difference in resistance may be related to differences in the source of isolates, as rates derived from the CANWARD study reflect national, hospital-based isolates.



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



	2007	2008	2009	2010	2011	2012
Intermediate	0.2%	0.0%	0.0%	0.4%	0.0%	0.0%
Resistant	12.7%	11.8%	9.4%	8.3%	11.9%	22.3%
Total Isolates	866	946	615	483	446	431

Figure 5 - Proportion of *Streptococcus pyogenes* isolates resistant to erythromycin and with inducible clindamycin non-susceptibility (as determined by the D-test in the presence of erythromycin) (2007-2012)
Source: BC Biomedical Laboratories

1.4. Enterococcus spp.

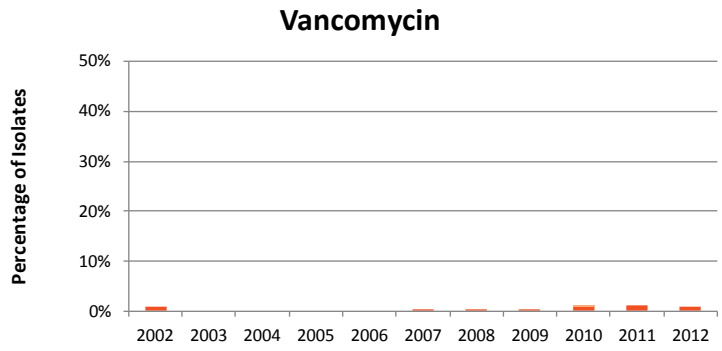
A prominent nosocomial pathogen, enterococci, more specifically *Enterococcus faecalis* and *Enterococcus faecium*, are normal enteric flora bacteria that may cause urinary tract infections (UTIs), intra-abdominal infections, and bacteremia. Most enterococcus strains are intrinsically resistant to macrolides, lincosamides, TMP-SMX, and β-lactams including cephalosporins and some penicillins (16).

Resistance in *Enterococcus* isolates to ampicillin has increased from approximately 1.0% in 2007 to 2.6% in 2012 ($p<0.001$) (Figure 6). LifeLabs data showed similar non-susceptibility rates as those from BC Biomedical for 2012, with 1% and 2% of isolates being non-susceptible to ampicillin for Mainland and Vancouver Island isolates, respectively (data not shown).

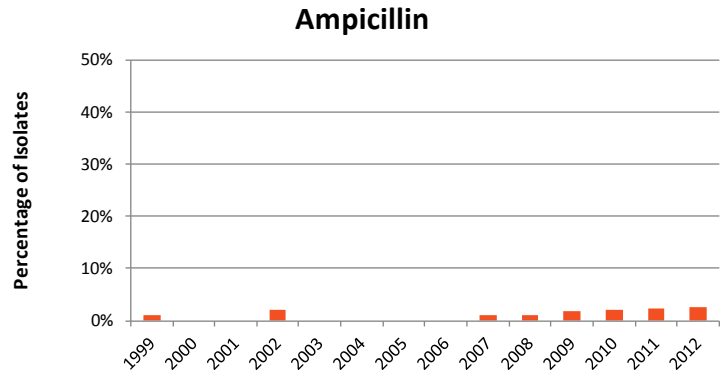
According to BC Biomedical Laboratories data, the proportion of *Enterococcus* spp. isolates resistant to nitrofurantoin and vancomycin remained under 2% (Figure 6). Nitrofurantoin resistance has increased over the last six years, but remained low with 1.4% of isolates displaying resistance in 2012 ($p<0.001$) (Figure 6). The national CANWARD study found that 32.7% of vancomycin-resistance *Enterococcus* (VRE) were susceptibly to nitrofurantoin from 2007 to 2011, and 94.1% of VRE were susceptible to linezolid (12).

Between years 2002 and 2007, BCAMM estimated that the proportion of VRE in BC remained less than 1% (14). While a numeric estimate is not available for 2008 to 2011 due to uncertainty in the denominator, rates of VRE are thought to remain low in BC. Despite a decrease of 24% in number of patients with new VRE infections from 2008 to 2010, the number of cases reported in 2011 was similar to counts in 2008, the so-called 'peak year' (14). However, with a total of only five cases, BCAMM indicated that VRE continues to be rare in the community.

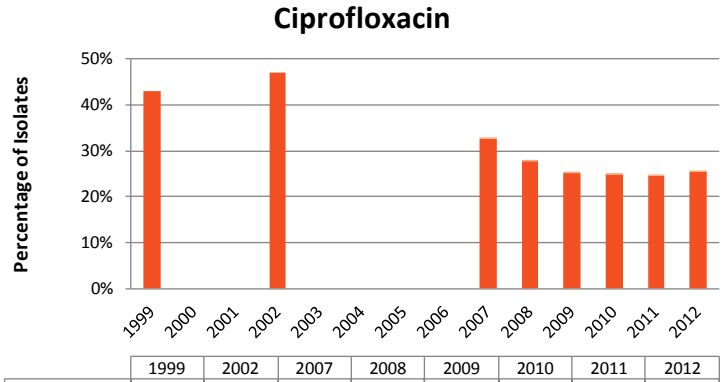
Ciprofloxacin non-susceptibility shows a declining trend from 2007 to 2012 using data from BC Biomedical and LifeLabs; yet, approximately one fourth of isolates showed non-susceptibility in 2012. In 2012, non-susceptibility rates ranged from 18% for LifeLabs isolates from Vancouver Island, to 25.4% for BC Biomedical isolates. The trend over time within the BC Biomedical data suggested a small, but significant decline since 2007 ($p<0.001$) (Figure 6). When resistance to ciprofloxacin of urinary *Enterococcus* isolates is broken down into ten-year age groups, an increase in the proportion of isolates resistant to ciprofloxacin is observed among older individuals, particularly those aged 70 and older (Figure 7). A similar trend is observed in the data from BC Biomedical Laboratories for *E. coli* isolates. The higher rates of resistance among older adults may be explained by the greater lifetime cumulative exposure to ciprofloxacin and other antibiotics and, consequently a greater selection for resistance (17).



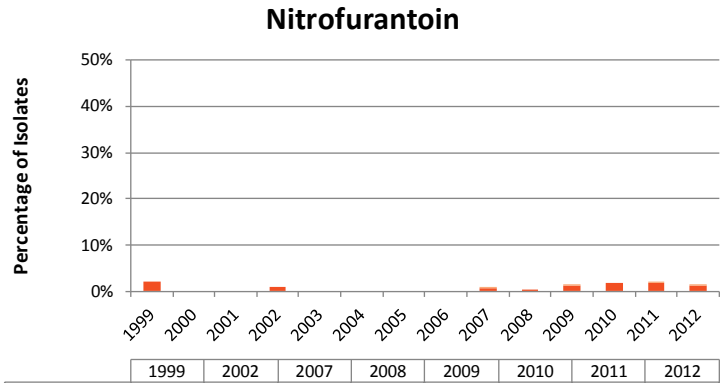
	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%
Resistant	1.0%	0.2%	0.1%	0.2%	1.0%	1.1%	0.9%
Total Isolates	2,140	3,460	3,228	3,298	3,641	2,944	3,015



	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	1.0%	2.0%	1.1%	1.0%	1.7%	2.0%	2.4%	2.6%
Total Isolates	N/A	2,140	3,460	3,229	3,297	3,648	2,945	3,058



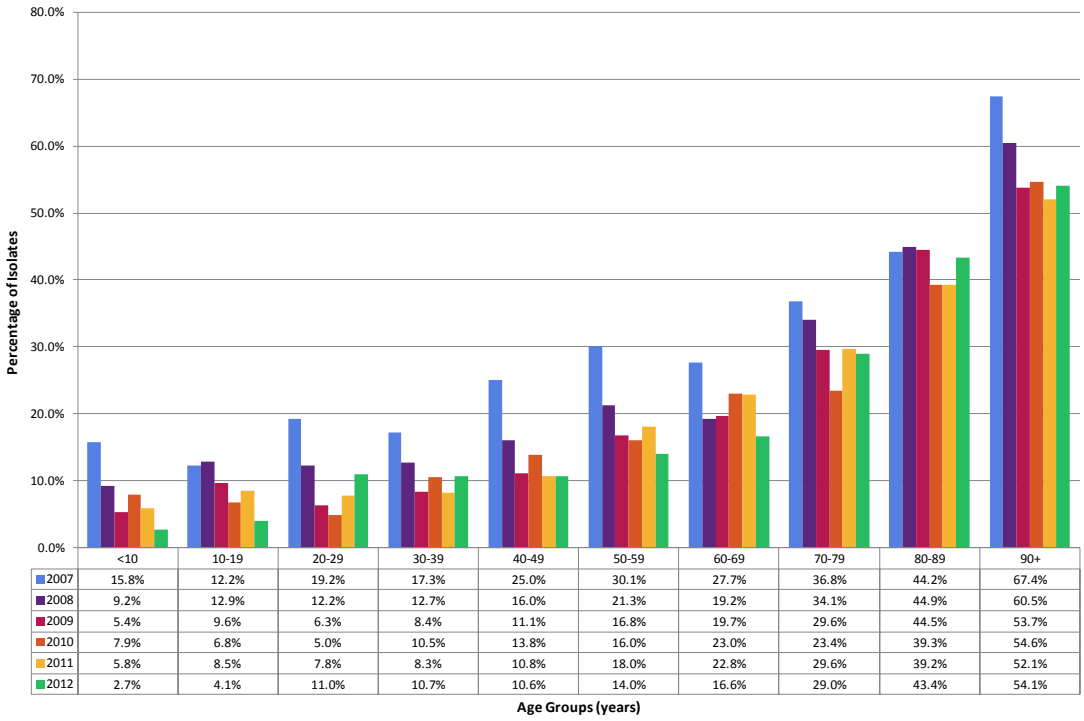
	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.3%	0.3%	0.3%	0.3%	0.1%	0.1%
Resistant	43.0%	47.0%	32.6%	27.8%	25.2%	24.9%	24.7%	25.3%
Total Isolates	N/A	2,140	3,458	3,226	3,296	3,643	2,941	3,057



	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.0%	0.0%	0.1%	0.0%	0.0%	0.1%
Resistant	2.0%	1.0%	0.6%	0.4%	1.2%	1.8%	1.7%	1.3%
Total Isolates	N/A	2,140	3,460	3,221	3,293	3,633	2,929	3,054

Figure 6 - Proportion of *Enterococcus* spp. isolates resistant to vancomycin, ampicillin and nitrofurantoin and non-susceptible to ciprofloxacin (1999-2012)
Source: BC Biomedical Laboratories

Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 were obtained from aggregate antibiograms.



	<10	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
2007	15.8%	12.2%	19.2%	17.3%	25.0%	30.1%	27.7%	36.8%	44.2%	67.4%
2008	9.2%	12.9%	12.2%	12.7%	16.0%	21.3%	19.2%	34.1%	44.9%	60.5%
2009	5.4%	9.6%	6.3%	8.4%	11.1%	16.8%	19.7%	29.6%	44.5%	53.7%
2010	7.9%	6.8%	5.0%	10.5%	13.8%	16.0%	23.0%	23.4%	39.3%	54.6%
2011	5.8%	8.5%	7.8%	8.3%	10.8%	18.0%	22.8%	29.6%	39.2%	52.1%
2012	2.7%	4.1%	11.0%	10.7%	10.6%	14.0%	16.6%	29.0%	43.4%	54.1%

Figure 7 - Proportion of *Enterococcus* spp. urinary isolates non-susceptible to ciprofloxacin by age of patient (2007-2012)
Source: BC Biomedical Laboratories

Gram-negative Organisms

1.5. Escherichia coli

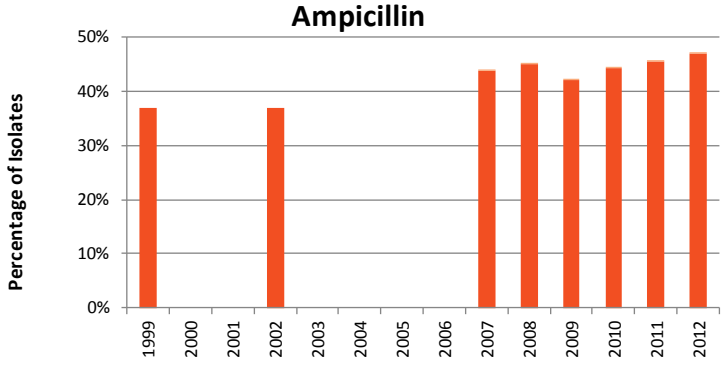
Escherichia coli is a pathogen that causes sepsis, gastrointestinal infections, and approximately 85 - 90% of urinary tract infections (UTIs) (18). Treatment for *E. coli* infections usually consists of nitrofurantoin, TMP-SMX or aminoglycosides (3;19;20).

The highest proportion of non-susceptible isolates occurred for ampicillin, with 47.0% of isolates showing non-susceptibility in 2012 (Figure 8). Approximately one-fourth of isolates were non-susceptible to TMP-SMX (25.6%) (Figure 8). The number of *E. coli* isolates non-susceptible to ampicillin and gentamicin significantly increased between the years 2007 and 2012 (ampicillin: $p<0.001$; gentamicin: $p=0.025$), while TMP-SMX and nitrofurantoin showed no significant change in non-susceptibility since 2007 (TMP-SMX: $p=0.379$; nitrofurantoin: $p=0.244$). Rates of *E. coli* non-susceptibility from LifeLabs data for ampicillin, nitrofurantoin and TMP-SMX were similar to those derived using BC Biomedical data (data not shown).

The most noticeable increase in non-susceptibility among *E. coli* isolates occurred with ciprofloxacin, where an almost nine-fold increase was demonstrated between 1999 and 2012 for BC Biomedical (Figure 8). Resistance rates appeared to be stable between 2007 and 2009 at 22.3%, but increased in 2010, and are currently reported at 25.3% ($p<0.001$) (Figure 8). The long-term increase from 3.0% to 25.3% in BC Biomedical data was greater than the increase observed in the adult sample of an American study of UTI *E. coli* isolates from 2000 to 2010 (+9.4%), but similar to the increase observed in the older adult sample (+23.5%) (21). According to the LifeLabs antibiograms, 14.0% of Mainland isolates and 10.0% of Vancouver Island isolates were non-susceptible to ciprofloxacin in 2012. BC Biomedical data showed a non-susceptibility rate for ciprofloxacin that was more than 10% higher than LifeLabs Mainland isolates and 15% higher than Vancouver Island isolates (data not shown).

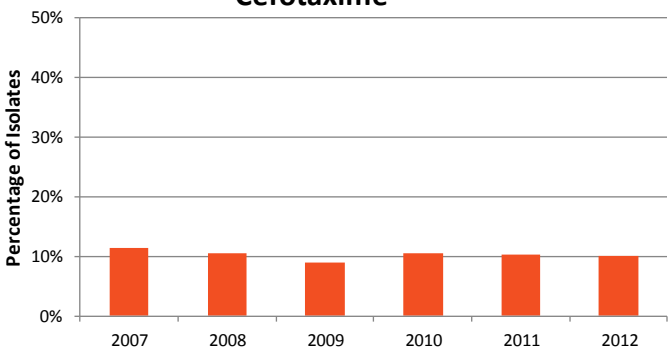
When resistance to ciprofloxacin of urinary *E. coli* isolates is broken down by ten-year age groups, the proportion of resistance increases with increasing patient age, particularly after age 50 (Figure 9). This is similar to the trend observed in *Enterococcus* isolates, and could be explained by the general tendency for greater cumulative lifetime exposure to ciprofloxacin and other antibiotics among older adults, and greater selection for resistance (17). An American study by Sanchez et al. found that resistance to ciprofloxacin increased at a faster rate over a ten year period for geriatric outpatients when compared with non-geriatric adults (21). The increasing likelihood of UTIs in the geriatric population was attributed to changing physiology, while increases in the number and duration of antibiotic therapy prescriptions in this population likely lead to selective pressures for resistant *E. coli* strains (21).

Ampicillin



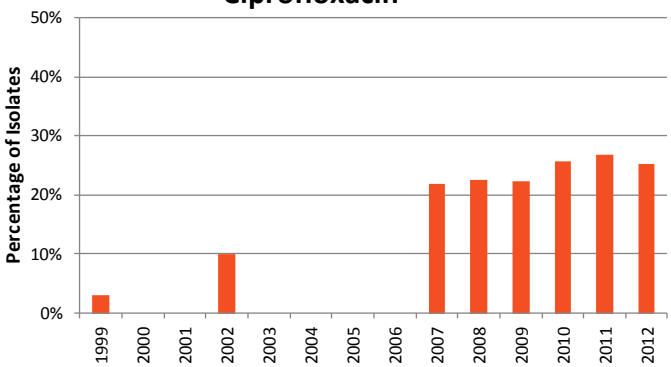
	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.2%	0.2%	0.2%	0.3%	0.2%	0.1%
Resistant	37.0%	37.0%	43.9%	45.1%	42.1%	44.3%	45.6%	46.9%
Total Isolates	N/A	15,000	24,363	24,568	24,849	27,511	24,444	26,288

Cefotaxime

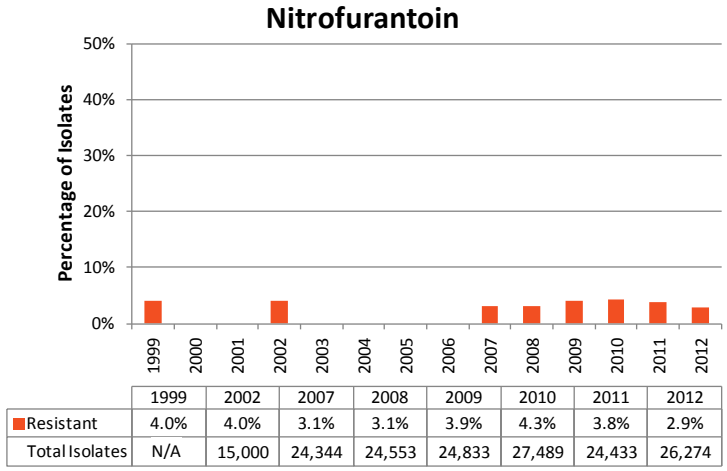


	2007	2008	2009	2010	2011	2012
Resistant	11.5%	10.6%	9.1%	10.4%	10.4%	10.0%
Total Isolates	24,348	24,560	24,848	27,510	24,448	26,289

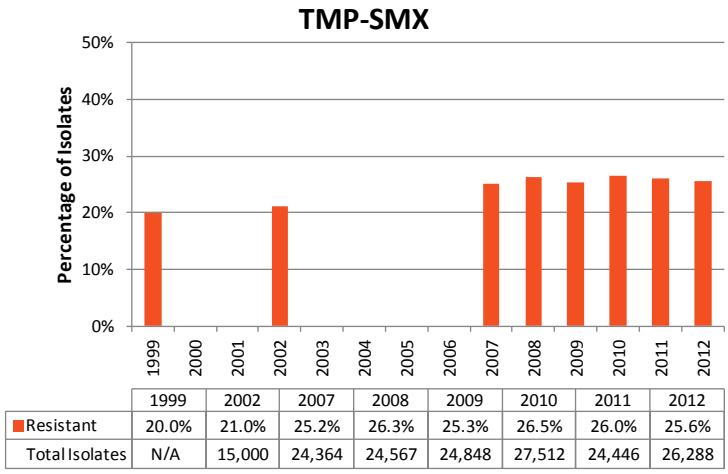
Ciprofloxacin



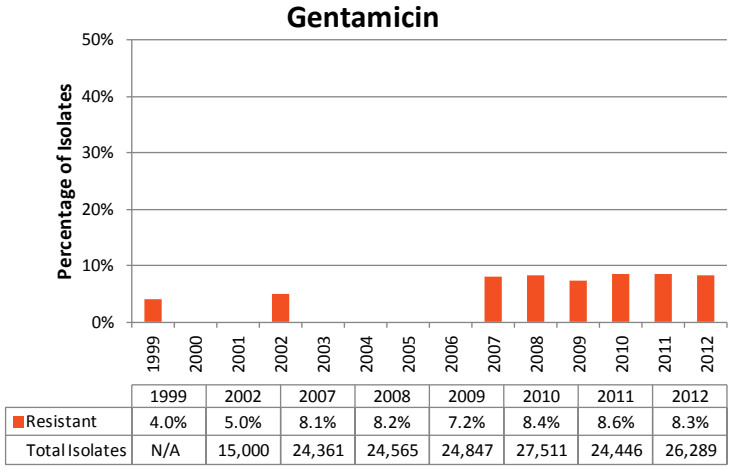
	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	3.0%	10.0%	21.8%	22.5%	22.3%	25.7%	26.8%	25.3%
Total Isolates	N/A	15,000	24,362	24,568	24,848	27,511	24,439	26,288



	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	4.0%	4.0%	3.1%	3.1%	3.9%	4.3%	3.8%	2.9%
Total Isolates	N/A	15,000	24,344	24,553	24,833	27,489	24,433	26,274



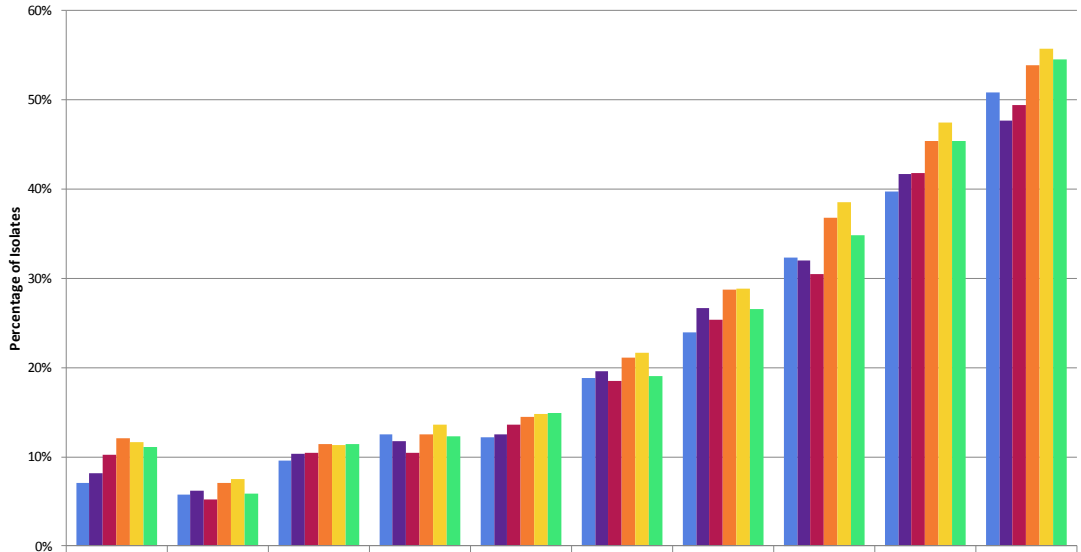
	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	20.0%	21.0%	25.2%	26.3%	25.3%	26.5%	26.0%	25.6%
Total Isolates	N/A	15,000	24,364	24,567	24,848	27,512	24,446	26,288



	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	4.0%	5.0%	8.1%	8.2%	7.2%	8.4%	8.6%	8.3%
Total Isolates	N/A	15,000	24,361	24,565	24,847	27,511	24,446	26,289

Figure 8 - Proportion of *Escherichia coli* isolates resistant to ciprofloxacin, gentamicin, nitrofurantoin, TMP-SMX and third generation cephalosporins, and non-susceptible to ampicillin (1999-2012)
Source: BC Biomedical Laboratories

Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 was obtained from aggregate antibiogram data.



	<10	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
2007	7.1%	5.8%	9.6%	12.5%	12.2%	18.8%	24.0%	32.3%	39.7%	50.8%
2008	8.2%	6.2%	10.4%	11.7%	12.5%	19.6%	26.7%	32.0%	41.6%	47.7%
2009	10.2%	5.2%	10.4%	10.5%	13.6%	18.4%	25.3%	30.5%	41.8%	49.4%
2010	12.0%	7.1%	11.4%	12.5%	14.5%	21.1%	28.8%	36.7%	45.4%	53.9%
2011	11.6%	7.5%	11.4%	13.6%	14.7%	21.6%	28.9%	38.5%	47.4%	55.7%
2012	11.1%	5.9%	11.4%	12.3%	14.9%	19.1%	26.5%	34.9%	45.4%	54.5%

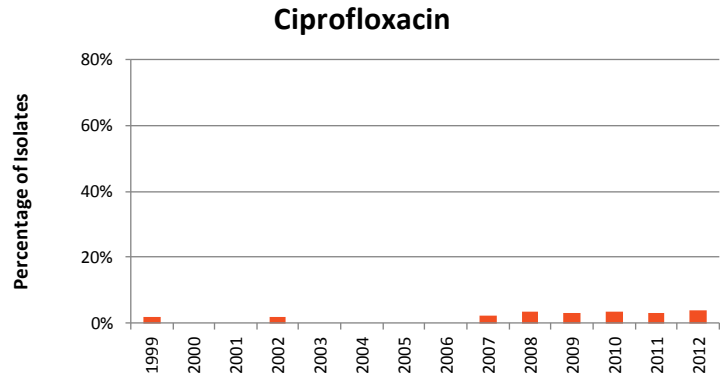
Age Groups (years)

Figure 9 - Proportion of *Escherichia coli* urinary isolates non-susceptible to ciprofloxacin by age of patient (2007-2012)
Source: BC Biomedical Laboratories

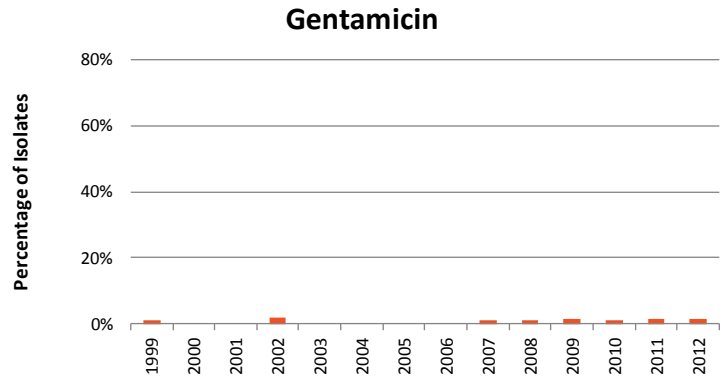
1.6. *Klebsiella pneumoniae*

Klebsiella pneumoniae, another cause of UTIs**,** can also lead to pneumonia, bacteremia, and skin and soft tissue infections (22). There have been no significant changes in resistance rates to ciprofloxacin and gentamicin since 2007, which remain under 5% (ciprofloxacin: p=0.068; gentamicin: p=0.247) (Figure 10). Similar rates of non-susceptibility have been reported by LifeLabs in their antibiograms for Vancouver Island and the Mainland (data not shown). The rate of non-susceptibility for ciprofloxacin was slightly higher (7.8%) in the CANWARD study and may be related to differences in the source of isolates, as rates derived from the CANWARD study reflect national, hospital-based isolates (12).

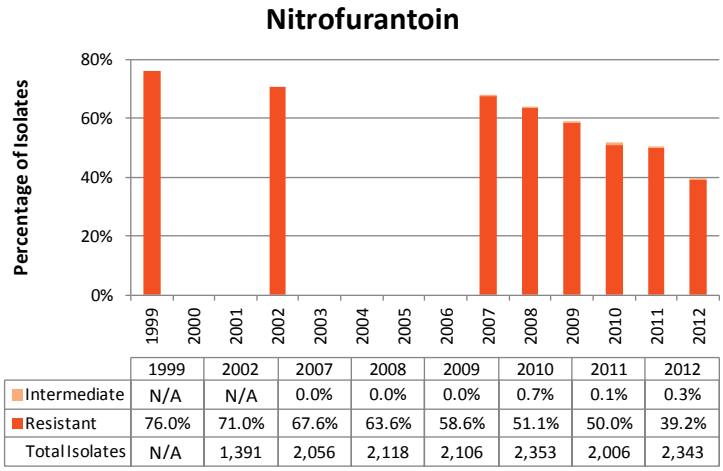
The proportion of *K. pneumoniae* isolates resistant to TMP-SMX has continued to decrease from 12.0% in 2008 to 8.2% in 2012, a nadir for all available years (p<0.001) (Figure 10). Resistance of isolates to nitrofurantoin dropped more than 10% from 2011 to 2012, continuing the downward trend in resistance that has been observed since 1999. Resistance to nitrofurantoin decreased from a peak of 76.0% in 1999 to 67.6% in 2007. Since then, it has significantly decreased to 39.2% in 2012 (p<0.001) (Figure 10). Rates of nitrofurantoin resistance, as reported by LifeLabs appear to be higher: 62% of Vancouver Island isolates and 73% of Mainland isolates were resistant in 2012 (Figure 11). These rates are similar to the rate of 63.8% reported in the national CANWARD study for 2007 to 2011 (12).



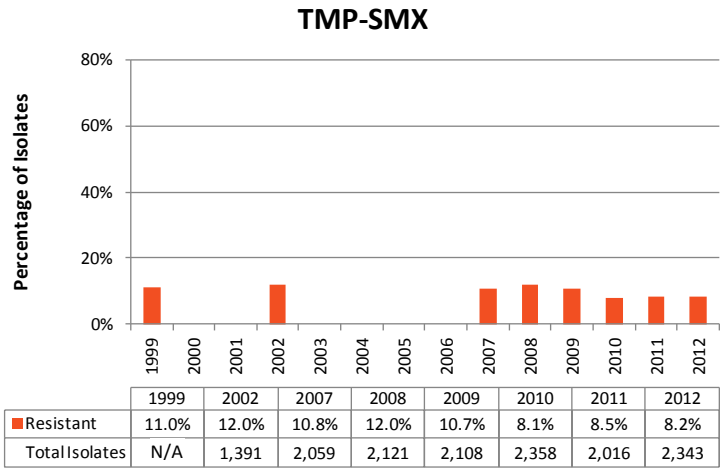
	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	2.0%	2.0%	2.4%	3.7%	3.0%	3.4%	3.0%	3.9%
Total Isolates	N/A	1,391	2,059	2,121	2,108	2,358	2,015	2,342



	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	1.0%	2.0%	1.2%	0.9%	1.6%	1.2%	1.5%	1.4%
Total Isolates	N/A	1,391	2,059	2,121	2,107	2,358	2,016	2,343



	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.0%	0.0%	0.0%	0.7%	0.1%	0.3%
Resistant	76.0%	71.0%	67.6%	63.6%	58.6%	51.1%	50.0%	39.2%
Total Isolates	N/A	1,391	2,056	2,118	2,106	2,353	2,006	2,343

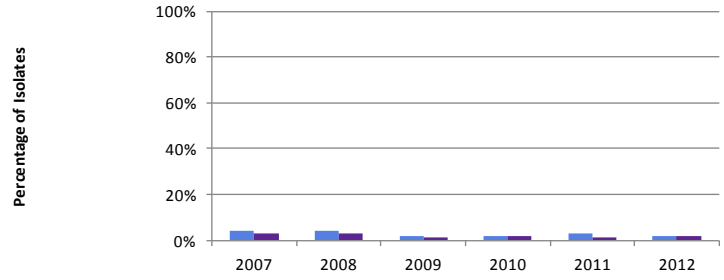


	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	11.0%	12.0%	10.8%	12.0%	10.7%	8.1%	8.5%	8.2%
Total Isolates	N/A	1,391	2,059	2,121	2,108	2,358	2,016	2,343

Figure 10 - Proportion of *Klebsiella pneumoniae* isolates resistant to ciprofloxacin, gentamicin, nitrofurantoin, and TMP-SMX (1999-2012)
Source: BC Biomedical Laboratories

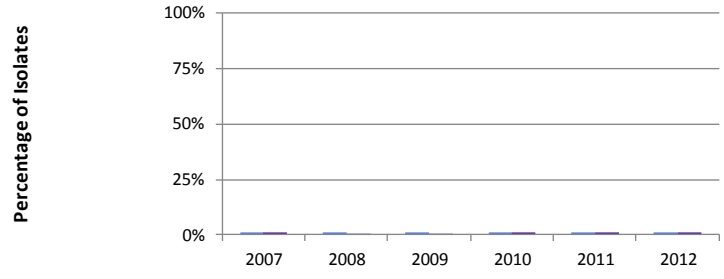
Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 were obtained from aggregate antibiograms.

Ciprofloxacin



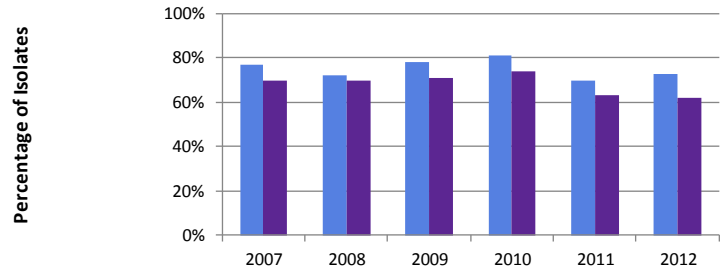
	2007	2008	2009	2010	2011	2012
Mainland	4.0%	4.0%	2.0%	2.0%	3.0%	2.0%
Vancouver Island	3.0%	3.0%	1.0%	2.0%	1.0%	2.0%
Mainland Isolates	1896	2000	1436	1564	1671	1789
Vancouver Island Isolates	1142	1304	932	899	853	880

Gentamicin

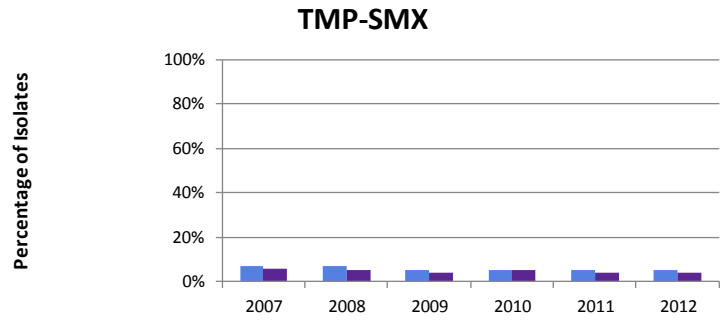


	2007	2008	2009	2010	2011	2012
Mainland	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
Vancouver Island	1.0%	0.5%	0.5%	1.0%	1.0%	1.0%
Mainland Isolates	1896	2000	1436	1564	1671	1789
Vancouver Island Isolates	1142	1304	932	899	853	880

Nitrofurantoin



	2007	2008	2009	2010	2011	2012
Mainland	77.0%	72.0%	78.0%	81.0%	70.0%	73.0%
Vancouver Island	70.0%	70.0%	71.0%	74.0%	63.0%	62.0%
Mainland Isolates	1896	2000	1436	1564	1671	1789
Vancouver Island Isolates	1142	1304	932	899	853	880



	2007	2008	2009	2010	2011	2012
Mainland	7.0%	7.0%	5.0%	5.0%	5.0%	5.0%
Vancouver Island	6.0%	5.0%	4.0%	5.0%	4.0%	4.0%
Mainland Isolates	1896	2000	1436	1564	1671	1789
Vancouver Island Isolates	1142	1304	932	899	853	880

Figure 11 - Proportion of *Klebsiella pneumoniae* isolates resistant to ciprofloxacin, gentamicin, nitrofurantoin, and TMP-SMX (2007-2012)
Source: LifeLabs

1.7. *Proteus mirabilis*

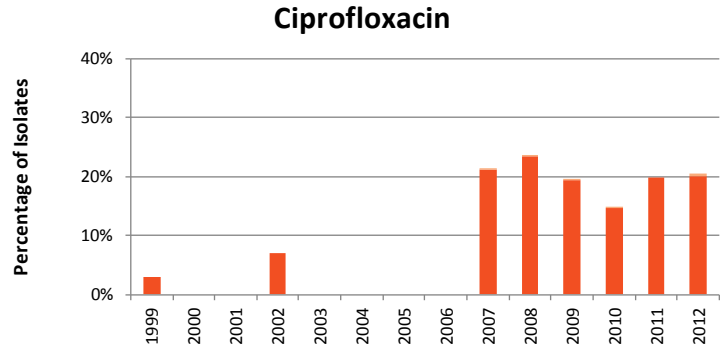
Proteus mirabilis is an enteric bacterium that causes approximately 2% of UTIs (18). In the past, TMP-SMX was the first-line treatment for UTIs; however, use of fluoroquinolones (e.g. ciprofloxacin) and aminoglycosides (e.g. gentamicin) has become more common over the years (3;23). High percentages of *P. mirabilis* isolates demonstrated non-susceptibility against ampicillin, ciprofloxacin, TMP-SMX, and nitrofurantoin. In 2012, approximately one out of three *P. mirabilis* isolates demonstrated non-susceptibility to ampicillin and TMP-SMX, while one in five isolates exhibited non-susceptibility to ciprofloxacin (Figure 12).

The percent of isolates non-susceptible to ampicillin has remained relatively stable since 2007, currently reported at 32.5% (p=0.403) (Figure 12). Hospital isolates from the national CANWARD study were reported to have non-susceptibility of less than 5% for most β-lactam antibiotics (12).

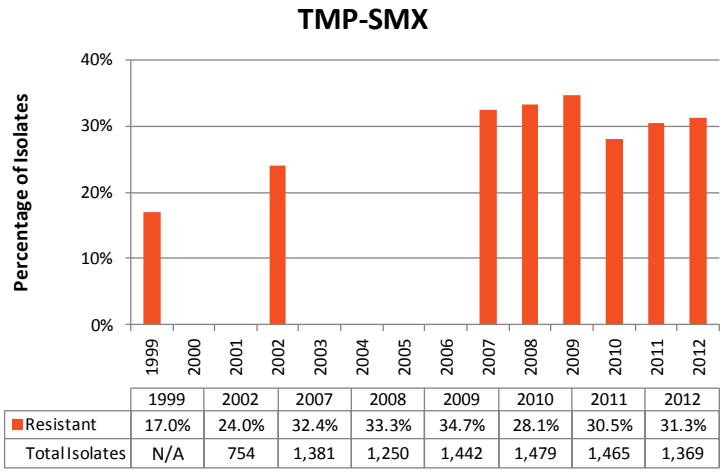
The percent of *P. mirabilis* isolates resistant to TMP-SMX increased from 1999 to 2009 during which time resistance had more than doubled from 17.0% in 1999 to 34.7% in 2009 (Figure 12). The percent of *P. mirabilis* isolates resistant to TMP-SMX has since fluctuated around 30%, and was reported at 31.3% in 2012 (Figure 12). Nationally, hospital isolates, as reported by the CANWARD study, appear to have lower non-susceptibility to TMP-SMX (15.9%) when compared with community isolates from BC Biomedical (12).

Non-susceptibility rates to ciprofloxacin have shown a small, but significant decline since 2007, dropping from 21.3% in 2007 to 20.5% in 2012 (p=0.031) (Figure 12). The CANWARD study reported 14.5% of national hospital isolates to be non-susceptible to ciprofloxacin, a rate slightly lower than BC Biomedical data (12).

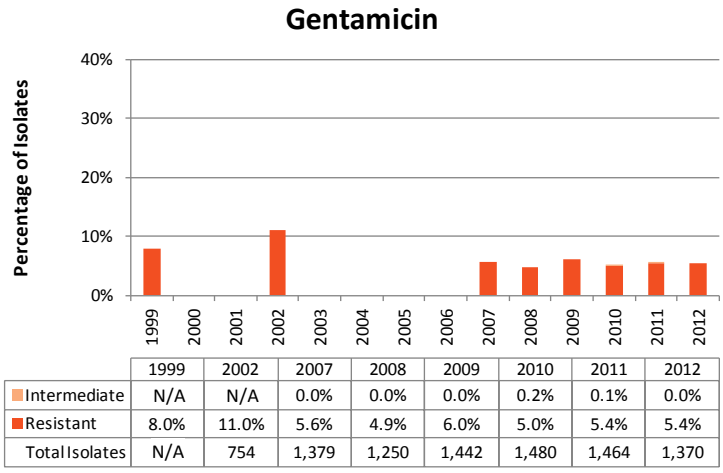
The percent of isolates resistant to gentamicin decreased by nearly half from 2002 to 2007, falling from 11.0% in 2002 to 5.6% in 2007. However, since 2007, non-susceptibility rates have remained stable (p=0.966) (Figure 12). The CANWARD study found similar rates of non-susceptibility to gentamicin (4.9%) in *P. mirabilis* hospital isolates from 2007 to 2011 (12). All isolates are inherently resistant to nitrofurantoin (data not shown).



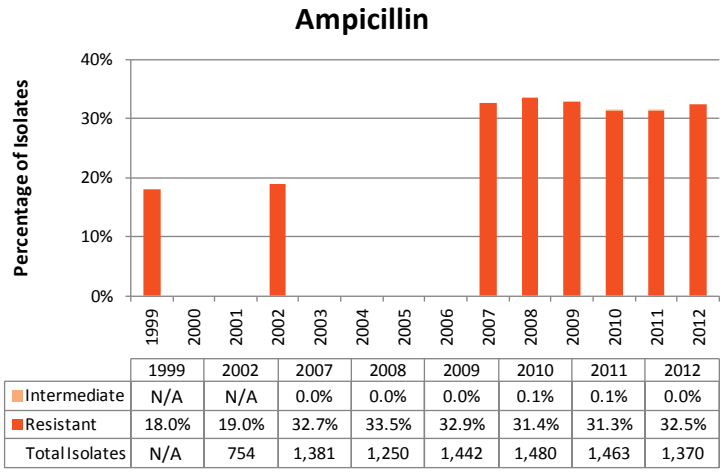
	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.1%	0.1%	0.1%	0.1%	0.0%	0.4%
Resistant	3.0%	7.0%	21.2%	23.4%	19.5%	14.6%	19.8%	20.1%
Total Isolates	N/A	754	1,381	1,249	1,442	1,478	1,464	1,369



	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	17.0%	24.0%	32.4%	33.3%	34.7%	28.1%	30.5%	31.3%
Total Isolates	N/A	754	1,381	1,250	1,442	1,479	1,465	1,369



	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.0%	0.0%	0.0%	0.2%	0.1%	0.0%
Resistant	8.0%	11.0%	5.6%	4.9%	6.0%	5.0%	5.4%	5.4%
Total Isolates	N/A	754	1,379	1,250	1,442	1,480	1,464	1,370



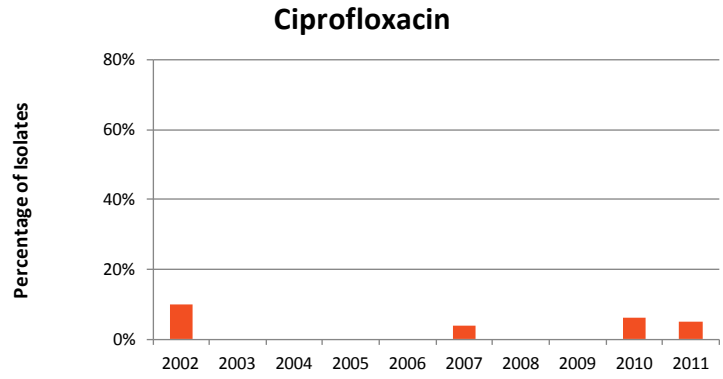
	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%
Resistant	18.0%	19.0%	32.7%	33.5%	32.9%	31.4%	31.3%	32.5%
Total Isolates	N/A	754	1,381	1,250	1,442	1,480	1,463	1,370

Figure 12 - Proportion of *Proteus mirabilis* isolates non-susceptible to ciprofloxacin and resistant to TMP-SMX, gentamicin and ampicillin (1999-2012)
Source: BC Biomedical Laboratories

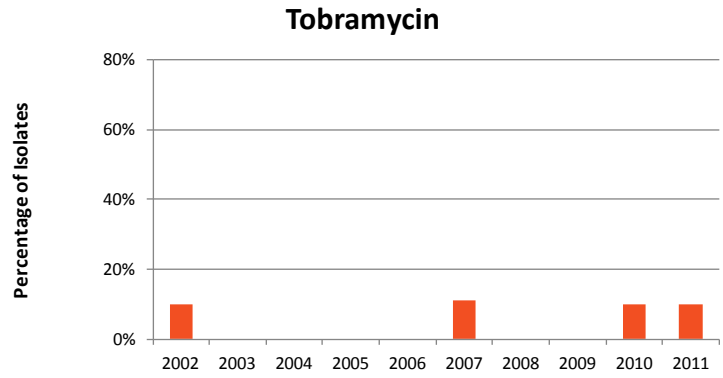
Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 were obtained from aggregate antibiograms.

1.8. Serratia, Providencia, Morganella, Citrobacter, and *Enterobacter* spp.

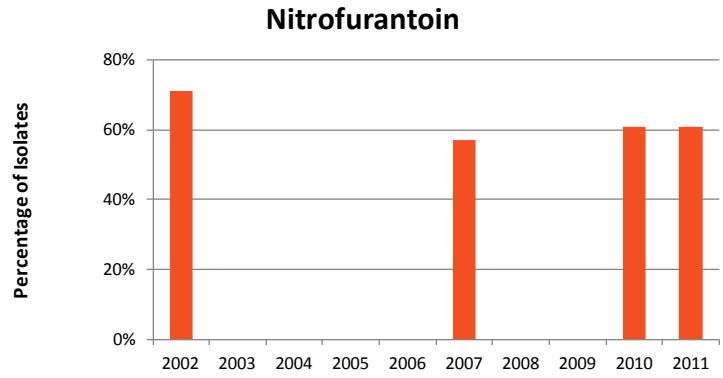
Serratia spp., *Providencia* spp., *Morganella* spp., *Citrobacter* spp., and *Enterobacter* spp. are collectively referred to as the SPICE organisms or 'ESCPM' group (24). Most SPICE organisms are opportunistic nosocomial pathogens that commonly cause urinary tract or respiratory infections (25;26). The number of SPICE organism isolates resistant to the tested antimicrobials with the exception of nitrofurantoin, have remained relatively low during the testing period (i.e., less than 15%) (Figure 13). Resistance towards nitrofurantoin displayed the most fluctuation and occurred most frequently, with 61% of isolates demonstrating non-susceptibility in 2010 and 2011 (Figure 13). SPICE organisms remain highly susceptible to ciprofloxacin and gentamicin with less than 5% of isolates exhibiting resistance. All tested isolates were non-susceptible to β-lactams (penicillins and cephalexin) in 2011 (data not shown).



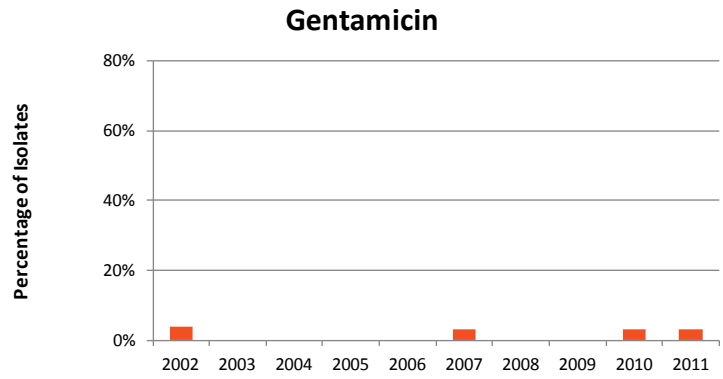
	2002	2007	2010	2011
Non-susceptible	10.0%	4.0%	6.0%	5.0%
Total Isolates	1123	1028	644	1325



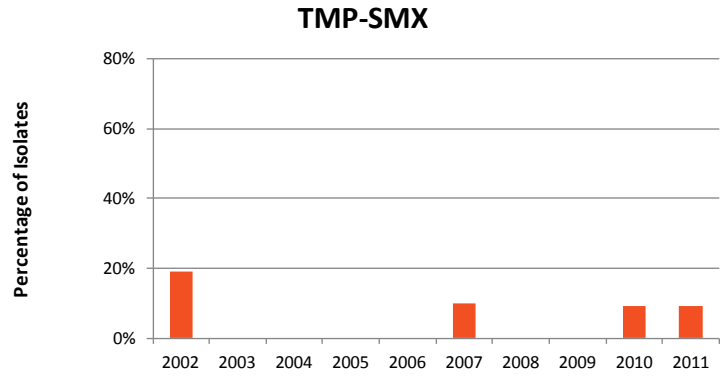
	2002	2007	2010	2011
Non-susceptible	10.0%	11.0%	10.0%	10.0%
Total Isolates	1123	1028	644	1325



	2002	2007	2010	2011
Non-susceptible	71.0%	57.0%	61.0%	61.0%
Total Isolates	1123	1028	644	1325



	2002	2007	2010	2011
Non-susceptible	4.0%	3.0%	3.0%	3.0%
Total Isolates	1123	1028	644	1325



	2002	2007	2010	2011
Non-susceptible	19.0%	10.0%	9.0%	9.0%
Total Isolates	1123	1028	644	1325

Figure 13 - Proportion of SPICE (Serratia, Providencia, Morganella, Citrobacter, and Enterobacter) organism isolates resistant to ciprofloxacin, tobramycin, gentamicin, nitrofurantoin, and TMP-SMX (2002, 2007, 2010, 2011)
Source: BC Biomedical Laboratories
Please note: Data from 2010 only represent the months of July to December.

1.9. Extended spectrum β-lactamase producing Enterobacteriaceae

Extended spectrum β-lactamases (ESBLs) are enzymes often associated with bacteria within the *Enterobacteriaceae* family that hydrolyze antibiotics belonging to the penicillin and cephalosporin classes (27). Laboratories detect the presence of ESBLs by evaluating the organism's phenotypic resistance patterns to different antibiotics (28). An ESBL-producing organism must demonstrate resistance to a third generation cephalosporin (e.g. cefotaxime, ceftriaxone or ceftazidime) but not cephamycins (e.g. cefoxitin) or carbapenems (e.g. imipenem, meropenem or ertapenem) (28). In addition, it must also demonstrate a change in susceptibility to third generation cephalosporin in the presence of a β-lactamase inhibitor (e.g. clavulanic acid, tazobactam or sulbactam) (28).

The estimated number of ESBL-producing *E. coli* and *K. pneumoniae* isolates have remained low in BC in 2011, according to the BCAMM 2011 report (14). In 2011, the estimated percentage of isolates demonstrating an ESBL phenotype varied from 2.5% - 10% for *E. coli* and 0% - 8% for *K. pneumoniae* for all laboratories (Table 2). While the BCAMM estimates for community laboratories were lower, they appear to be increasing over time. For the 450 clinical Enterobacteriaceae isolates that underwent genotypic testing methods, from October 2009 to October 4, 2012, the detected ESBL genes included TEM, CTX-M and OXA-1.

Data from BC Biomedical Laboratories suggest that the majority of ESBL-like isolates were *E. coli*, while *K. pneumoniae* and *P. mirabilis* made up similar but substantially lower proportions of all ESBL-like isolates in 2012 ( ). Currently, approximately, 11.7% of *E. coli* isolates exhibit an ESBL-like phenotype, a rate which has not changed drastically over the past six years (p=0.208) (Figure 14 - Distribution of ESBL- like phenotypes between Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis (2012)

Source: BC Biomedical Laboratories). The percent of *K. pneumoniae* isolates demonstrating an ESBL-like phenotype decreased substantially from 8.5% in 2007 to 3.3% in 2012 (p=0.019), while the percent of *P. mirabilis* isolates demonstrating an ESBL-like phenotype decreased from 12.5% in 2007 to 5.5% in 2012 (p=0.019) (Figure 14 - Distribution of ESBL- like phenotypes between Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis (2012)

Source: BC Biomedical Laboratories). As these rates represent estimates of ESBL-like phenotypes, rates are higher than those reported by BCAMM which are based on direct genotypic laboratory confirmation. These differences may be due to differences in prevalence of ESBLs in geographic areas where BC Biomedical Laboratories are present or in the case of *E. coli,* may be due to the overestimation of these data without direct confirmation.

Data for *E. coli, K. pneumoniae* and *P. mirabilis* isolates with phenotypes compatible with ESBLs were analyzed for their resistance to quinolones (i.e. ciprofloxacin or levofloxacin), aminglycosides (i.e. gentamicin, amikacin or tobramycin) and TMP-SMX, as well as combinations of these drugs (i.e. 2 classes or all 3 classes) (Figure 16).

Non-susceptibility rates for ESBL-like *E. coli* isolates have remained relatively stable over the past six years for quinolones, aminoglycoside and TMP-SMX. In 2012, nearly 73% of ESBL-like *E. coli* isolates were non-susceptible to quinolones; a non-significant increase of nearly 7% from 2007 to 2012 (p=0.156) (Figure 16). Aminoglycoside and TMP-SMX non-susceptibility rates were estimated at 27.7% and 56.7%, respectively for ESBL-like *E. coli* isolates (Figure 16). From 2007 to 2011, the CANWARD study found 231 of 5451 hospital *E. coli* isolates were EBSL (4.2%), with 70.0% showing resistance to TMP-SMX, and at least 48.9% and 89.2% showing non-susceptibility to aminoglycosides and quinolones, respectively (12).

Non-susceptibility to quinolones in ESBL-like *K. pneumoniae* isolates showed a positive upward trend from 2007 to 2012, with 56.4% of isolates showing non-susceptibility in 2012 (p<0.001) (Figure 16). Similarly, a strong positive trend was also observed for aminoglycosides non-susceptibility with nearly a four-fold increase in the non-susceptibility rate from 2007 to 2012 (p=0.005) (Figure 16). In 2012, non-susceptibility rates to TMP-SMX for ESBL-like *K. pneumoniae* isolates remained high at 62.8% (p=0.957) (Figure 16).

P. mirabilis isolates with an ESBL-like phenotype exhibited an increase in non-susceptibility from 18.9% in 2011 to 38.2% in 2012 for quinolones, and 29.7% to 44.7%, for TMP-SMX. Yet, these rates remained lower than the rates observed in 2007 (Figure 16). Contrastingly, aminoglycoside non-susceptibility has increased nearly three-fold since 2007 to 31.6% of ESBL-like *P. mirabilis* isolates (p=0.019) (Figure 16).

When looking at multi-drug non-susceptibility, the proportion of ESBL-like *E. coli* isolates non-susceptible to more than one class of antimicrobial has remained relatively stable from 2007 to 2012, while the proportion of ESBL-like *K. pneumoniae* isolates non-susceptible to two or more classes appears to be increasing (*E. coli*: p=0.042; *K. pneumoniae*: p=0.019) (Figure 16). The proportion of ESBL-like *P. mirabilis* isolates that are non-susceptible to all three classes of antibiotics (i.e. aminoglycosides, quinolones and TMP-SMX) has increased from 1.7% in 2007, to 21.1% in 2012 (p=0.019) (Figure 16).

Carbapenem-resistant Enterobacteriaceae (CRE)

According to the BCPHMRL *Lab Trends* report, thirty-nine patients have been found to carry carbapenem-resistant Enterobacteriaceae (CRE) since 2010, with more cases being identified each year (29). Previous to 2010, only one patient in 2008 and 2009 harboured a CRE isolate; however, in 2012, 22 patients harboured a CRE (29). The most common organism to harbour carbapenem-resistance genes was *K. pneumoniae* (70%), followed by *E. coli* (20%). The majority of patients (64%) were infected with the New Delhi Metallo-B-lactamase-1-gene (NDM-1), and 26% of patients harbored the OXA-48 carbapenemase. Two patients provided isolates with both NDM-1 and OXA-48 carbapenemase genes. More than three-fourths of patients were over the age of 60 years (85%) (29). Organisms that carried CRE genes included *E. coli, K. pneumoniae, P. aeruginosa, C. freundii, M. morganii, E. cloacae* and *A. baumannii* (14).

AmpC

AmpC genes are inducible genes that are triggered in response to the presence of a β-lactam. These genes can also be found on transmissible plasmids, allowing the gene to be transferred between bacteria (2). The gene codes for the production of β-lactamase enzymes, allowing the organism to break down penicillins, cephalosporins and other β-lactam drugs (30). Forty-four isolates were found to harbour an AmpC gene in isolation of other resistance mechanisms while all other AmpC genes were found in combination with ESBLs or CREs. *E. coli*, *Morganella* spp. and *Proteus* spp. isolates had the highest number of AmpC genes (14).

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

Year	*E. coli* ESBL estimates	*K. pneumoniae* ESBL estimates
2007	0.7% – 5%	0% – 3%
2008	1% – 13%	0.3% – 6%
2009 (All laboratories)	1% – 7.8%	0.3% – 6%
2010 (All laboratories)	0.7% – 10%	0% – 8%
2011 All Laboratories	2.5 – 11%	<1 – 7%
2009 (Community laboratories)	1% – 1.7%	0.3% – 1%
2010 (Community laboratories)	0.7% – 2.5%	0.5%
2011 (Community laboratories)	3%	5%

Source: BCAMM 2011 Report (14)

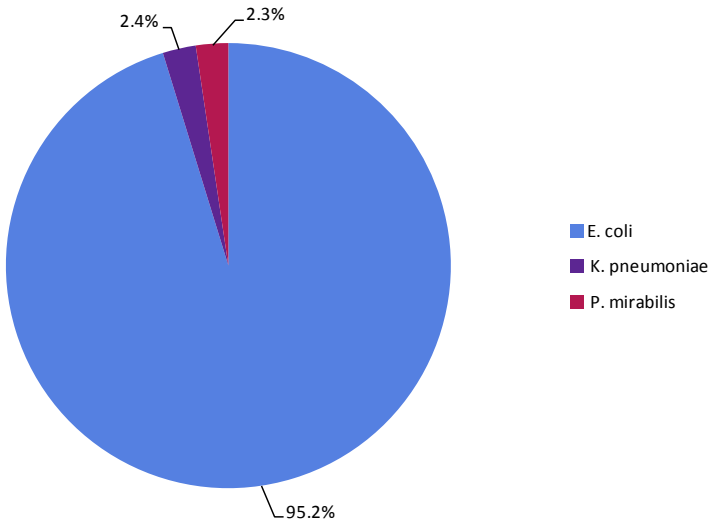
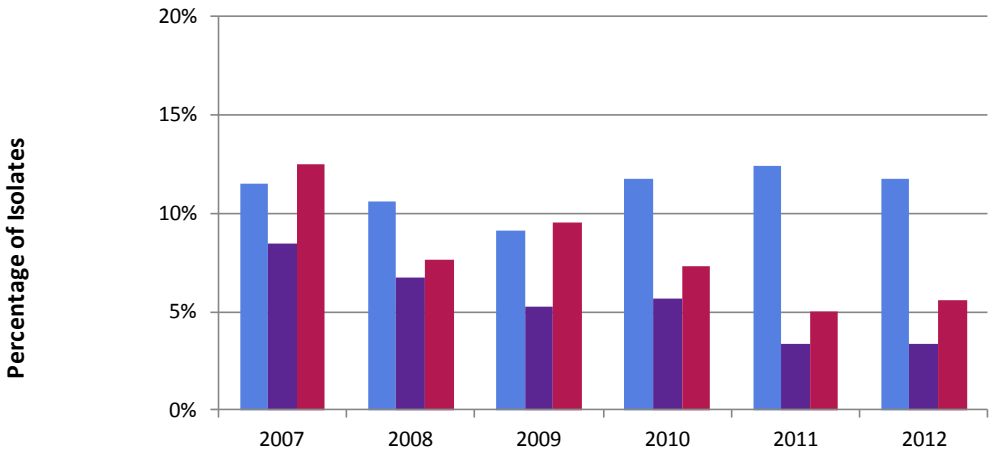


Figure 14 - Distribution of ESBL- like phenotypes between *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis (*2012)
Source: BC Biomedical Laboratories

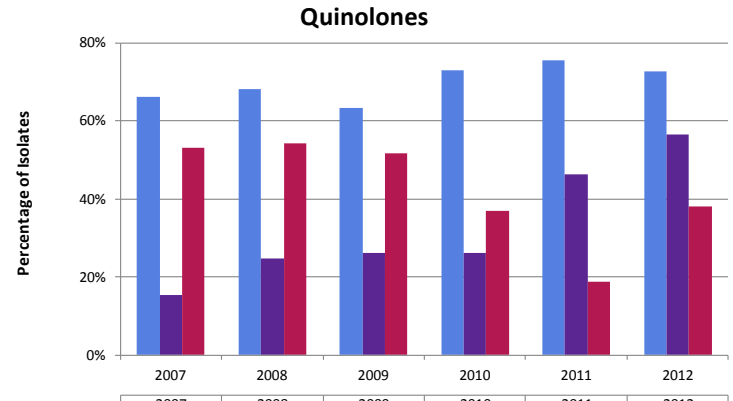


	2007	2008	2009	2010	2011	2012
E.coli	11.5%	10.6%	9.1%	11.8%	12.4%	11.7%
K. pneumoniae	8.5%	6.7%	5.3%	5.6%	3.3%	3.3%
P. mirabilis	12.5%	7.7%	9.5%	7.3%	5.0%	5.5%
Total E. coli Isolates	24,365	24,569	24,851	27,514	24,448	26,289
Total K. pneumoniae Isolates	2,059	2,121	2,108	2,358	2,016	2,343
Total P. mirabilis Isolates	1,381	1,251	1,442	1,480	1,468	1,370

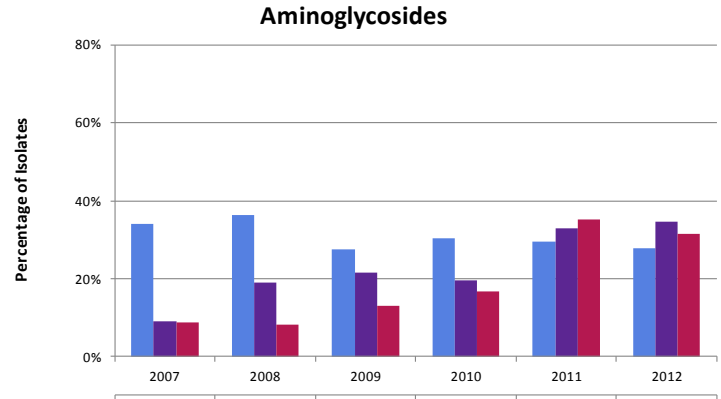
Figure 15 - Proportion of *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis* isolates demonstrating ESBL-compatible phenotype (2007-2012)
Source: BC Biomedical Laboratories

Please note: The numerator and denominator data used to create Figure 14 **- Distribution of ESBL- like phenotypes between Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis (2012)**

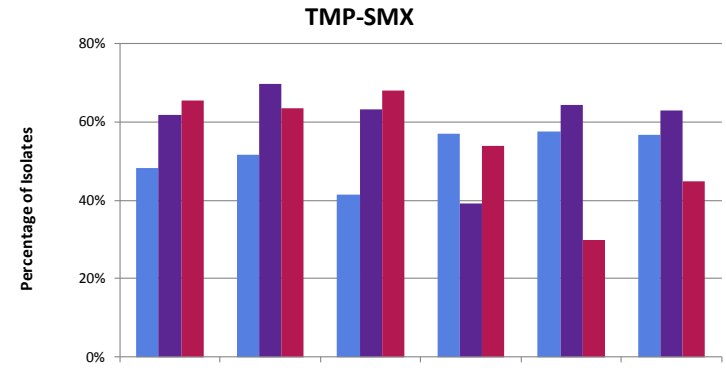
Source: BC Biomedical Laboratories can be found in Appendix A: Supplemental Tables



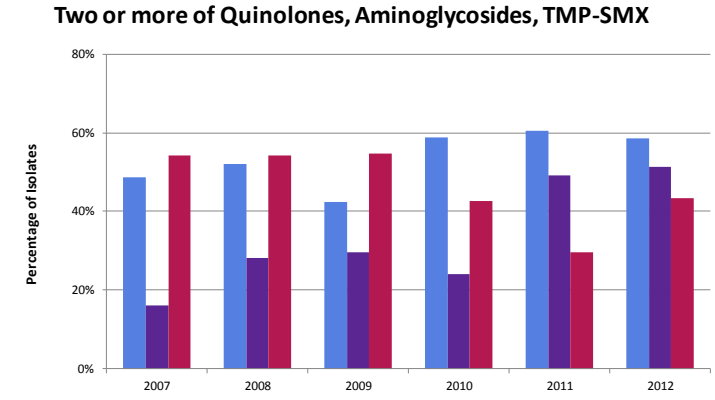
	2007	2008	2009	2010	2011	2012
E.coli	66.1%	68.2%	63.3%	73.1%	75.5%	72.8%
K. pneumoniae	15.4%	24.6%	26.1%	26.3%	46.3%	56.4%
P. mirabilis	53.2%	54.2%	51.8%	37.0%	18.9%	38.2%



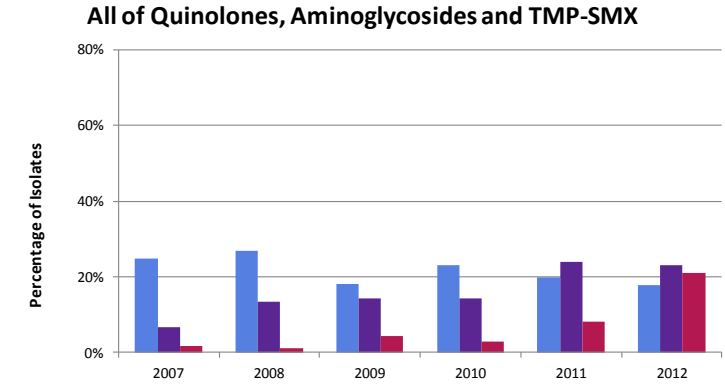
	2007	2008	2009	2010	2011	2012
E. coli	34.2%	36.2%	27.6%	30.3%	29.4%	27.7%
K. pneumoniae	9.1%	19.0%	21.6%	19.5%	32.8%	34.6%
P. mirabilis	8.7%	8.3%	13.1%	16.7%	35.1%	31.6%



	2007	2008	2009	2010	2011	2012
E. coli	48.2%	51.6%	41.3%	57.1%	57.6%	56.7%
K. pneumoniae	61.7%	69.7%	63.1%	39.1%	64.2%	62.8%
P. mirabilis	65.3%	63.5%	67.9%	53.7%	29.7%	44.7%



	2007	2008	2009	2010	2011	2012
E. coli	48.6%	52.1%	42.5%	58.7%	60.5%	58.5%
K. pneumoniae	16.0%	28.2%	29.7%	24.1%	49.3%	51.3%
P. mirabilis	54.3%	54.2%	54.7%	42.6%	29.7%	43.4%



	2007	2008	2009	2010	2011	2012
E. coli	24.9%	26.8%	18.1%	23.0%	19.9%	17.7%
K. pneumoniae	6.9%	13.4%	14.4%	14.3%	23.9%	23.1%
P. mirabilis	1.7%	1.0%	4.4%	2.8%	8.1%	21.1%

Figure 16 - Proportion of *ESBL-like Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis* isolates demonstrating non-susceptibility to quinolones, aminoglycosides or TMP-SMX, two or more, and three of quinolones, aminoglycosides and TMP-SMX (2007-2012)
Source: BC Biomedical Laboratories

Please note: The numerator and denominator data used to create Figure 16 can be found in Appendix A: Supplemental Tables

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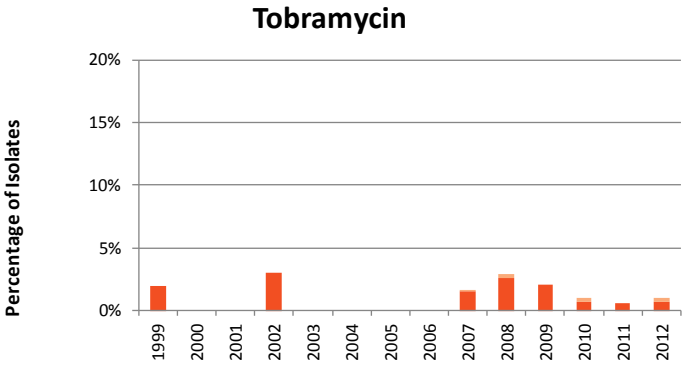
1.10. *Pseudomonas aeruginosa*

Pseudomonas aeruginosa are prominent nosocomial pathogens that infect numerous sites including the respiratory tract, urinary tract, blood, skin and soft tissue. Treatment for *P. aeruginosa* infections typically includes piperacillin, tobramycin, ceftazidime, carbapenems, fluoroquinolones, and aminoglycosides (3).

The percent of *P. aeruginosa* isolates in BC Biomedical data that were non-susceptible to aminoglycosides (tobramycin and gentamicin) remained low in 2012, continuing the downward trend seen since 2008 (tobramycin: p=0.004; gentamicin: p=0.034) (Figure 17). Fourteen percent (14%) of isolates from the Mainland, as reported by LifeLabs, were non-susceptible to gentamicin in 2011 (data not shown).

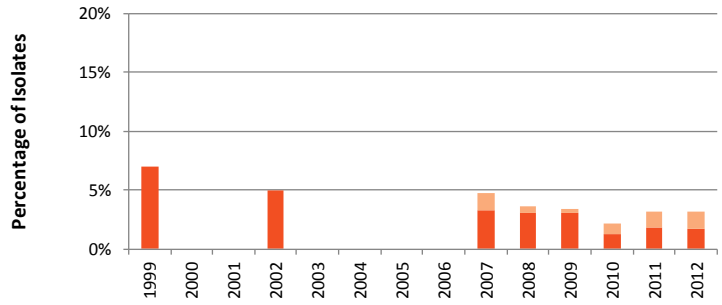
Non-susceptibility rates to ciprofloxacin have remained relatively stable over the years and were 11.7% in 2012, as reported by BC Biomedical (Figure 17). LifeLabs data for the Mainland showed a similar rate of non-susceptibility (9%) in 2011 (data not shown). According to BC Biomedical, over the testing period not more than 4% of isolates in any year (2.1% in 2012) were non-susceptible to ceftazidime and less than or equal to 3% (2.7% in 2012) for piperacillin (Figure 17). Ceftazidime non-susceptibility, as reported by LifeLabs has declined since 2007, from 8% to 2% in 2011 for the Mainland (data not shown).

LifeLabs susceptibility data for *P. aeruginosa* isolates from Vancouver Island have not been reported since 2009; data for *P. aeruginosa* for the Mainland was not reported in the 2012 antibiogram.



	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.1%	0.4%	0.0%	0.4%	0.0%	0.3%
Resistant	2.0%	3.0%	1.5%	2.6%	2.0%	0.6%	0.6%	0.7%
Total Isolates	N/A	919	915	848	888	781	695	685

Gentamicin

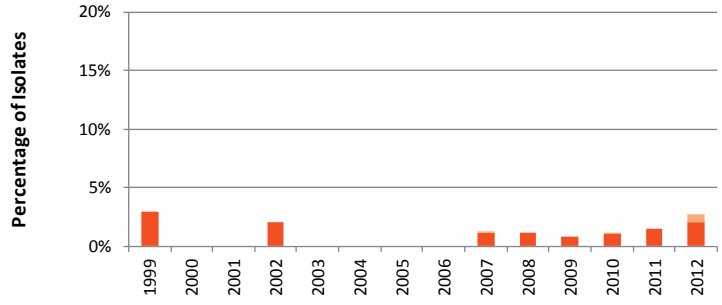


	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	1.4%	0.6%	0.3%	0.9%	1.3%	1.5%
Resistant	7.0%	5.0%	3.3%	3.1%	3.0%	1.3%	1.9%	1.7%
Total Isolates	N/A	919	915	848	889	782	695	687

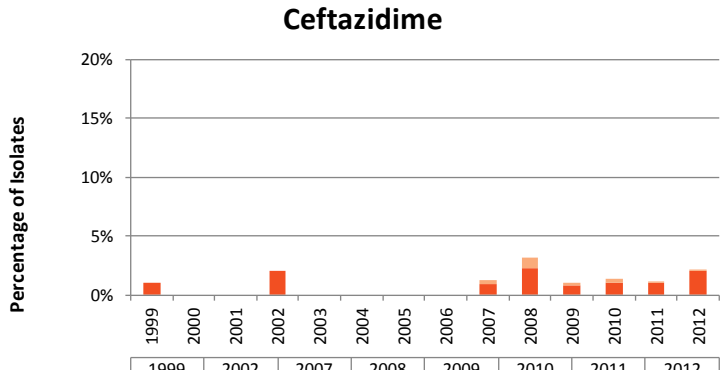
Ciprofloxacin

	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	3.1%	1.9%	1.3%	2.6%	3.5%	2.9%
Resistant	11.0%	14.0%	9.0%	12.5%	10.0%	7.7%	6.6%	8.8%
Total Isolates	N/A	919	915	848	889	782	695	685

Piperacillin



	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.1%	0.0%	0.0%	0.1%	0.0%	0.7%
Resistant	3.0%	2.0%	1.2%	1.2%	0.8%	1.0%	1.4%	2.0%
Total Isolates	N/A	919	915	848	887	781	695	686



	1999	2002	2007	2008	2009	2010	2011	2012
Intermediate	N/A	N/A	0.4%	0.9%	0.2%	0.4%	0.1%	0.1%
Resistant	1.0%	2.0%	0.9%	2.3%	0.8%	1.0%	1.0%	2.0%
Total Isolates	N/A	919	912	844	886	777	692	685

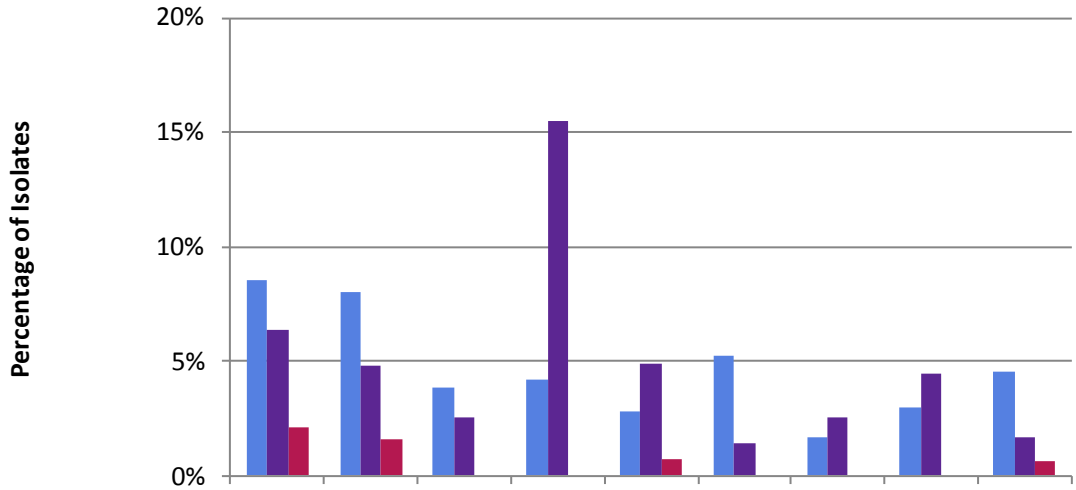
Figure 17 - Proportion of *Pseudomonas aeruginosa* isolates non-susceptible to tobramycin, gentamicin, ciprofloxacin, piperacillin, and ceftazidime (1999-2012)
Source: BC Biomedical Laboratories

Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 were obtained from aggregate antibiograms.

1.11. Salmonella Enteritidis

*Salmonell*a is a common cause of gastroenteritis in Canada. *Salmonella* is usually a food-borne pathogen that is transmitted through contaminated or uncooked food products, but can also be transmitted through contaminated water or person-to-person contact (31). Of the antimicrobials tested in 2011, isolates demonstrated 100% susceptibility to ceftriaxone, ciprofloxacin, TMP-SMX and azithromycin (data not shown). Resistance to ampicillin was reported at 4.5% in 2011, which remains lower than rates seen in 2003 and 2004 (Figure 18). Following a large increase from 2.6% in 2005 to 15.5% in 2006, tetracycline resistance rates returned to rates seen prior to 2006 and were reported at 1.7% in 2011 (Figure 18). The jump in tetracycline resistance observed in 2006 may be related to an increase in isolates acquired during travel. Resistance to chloramphenicol has remained below 2.0% since 2004 and only one isolate has been identified as resistant since 2008 (Figure 18).

From 2009 to 2011, the number of isolates exhibiting a resistance pattern that included only one antimicrobial class ranged between 5.9% and 11.9% of isolates (data not shown). Additionally, in 2011, less than five percent of isolates exhibited resistance to more than one antimicrobial class; however, no isolates were observed with resistance to more than five antimicrobial classes in BC (data not shown).

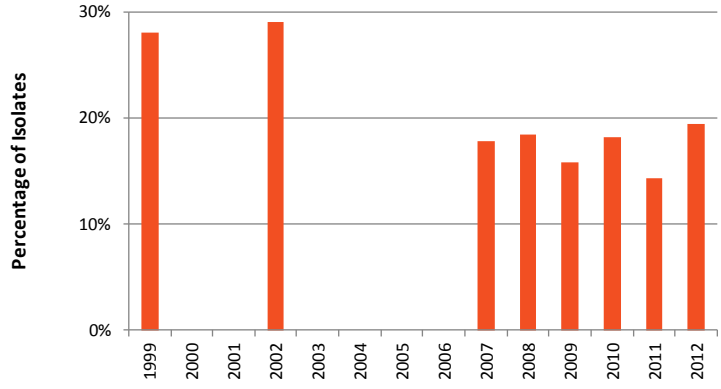


	2003	2004	2005	2006	2007	2008	2009	2010	2011
Ampicillin	8.5%	8.1%	3.8%	4.2%	2.8%	5.2%	1.7%	3.0%	4.5%
Tetracycline	6.4%	4.8%	2.6%	15.5%	4.9%	1.4%	2.5%	4.4%	1.7%
Chloramphenicol	2.1%	1.6%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.6%

Figure 18 - Proportion of *Salmonella* Enteritidis isolates resistant to ampicillin, tetracycline, and chloramphenicol (2003-2011)
Source: CIPARS

1.12. *Haemophilus influenzae*

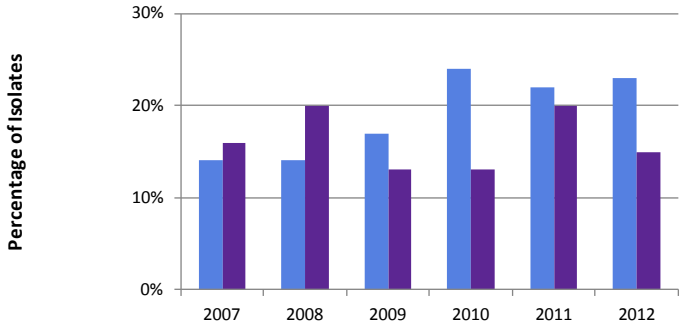
Haemophilus influenzae is a respiratory tract Gram negative bacterium that causes numerous invasive diseases including bacterial meningitis, bacterial pneumonia, epiglottitis, septic arthritis, cellulitis, and pericarditis. According to BC Biomedical Laboratories data, ampicillin resistance fluctuated around 18.0% from 2007 to 2012 with the exception of a temporary drop to 15.8% in 2009 and 14.3% in 2011 (p=0.697). In 2012, resistance was reported at 19.4% of all isolates (Figure 19). LifeLabs data for *H. influenzae* isolates from Vancouver Island and the Mainland regions showed non-susceptibility rates similar to BC Biomedical data for 2012 with 15.0% and 23.0% of isolates demonstrating non-susceptibility, respectively (Figure 20). The national CANWARD study reported that 18.8% of hospital isolates were non-susceptible to ampicillin between 2007 and 2011 (12).



	1999	2002	2007	2008	2009	2010	2011	2012
Resistant	28.0%	29.0%	17.8%	18.4%	15.8%	18.2%	14.3%	19.4%
Total Isolates	N/A	N/A	580	522	404	391	307	252

Figure 19 - Proportion of *Haemophilus influenzae* isolates resistant to ampicillin (1999-2012)
Source: BC Biomedical Laboratories

Please note: BC Biomedical data from 2007 and onwards was derived using line-listed data. Data prior to 2007 were obtained from aggregate antibiograms.



	2007	2008	2009	2010	2011	2012
Mainland	14.0%	14.0%	17.0%	24.0%	22.0%	23.0%
Vancouver Island	16.0%	20.0%	13.0%	13.0%	20.0%	15.0%
Mainland Isolates	301	315	216	207	203	142
Vancouver Island Isolates	179	190	130	110	127	85

Figure 20 – Proportion of *Haemophilus influenzae* isolates resistant to ampicillin (2007-2012)
Source: LifeLabs

Other organisms

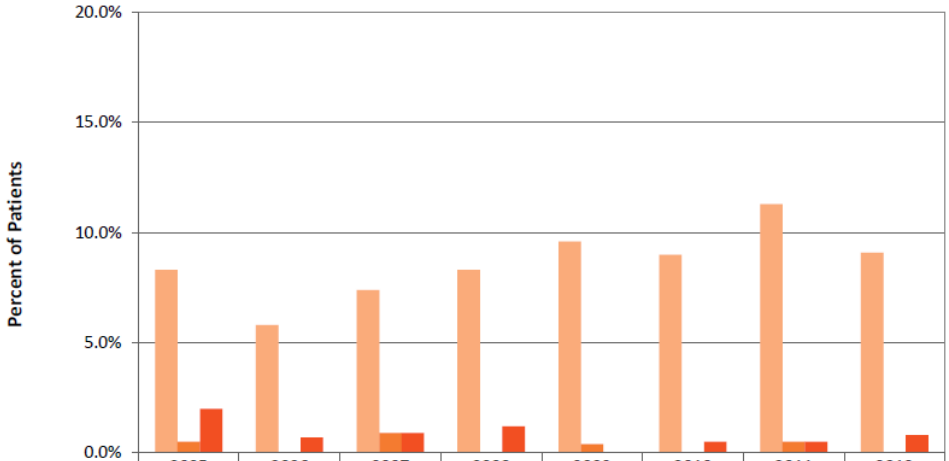
1.13. Mycobacterium tuberculosis

Mycobacterium tuberculosis (MTB) is a slow-growing, aerobic, acid-fast bacterium that is the causative agent for tuberculosis (TB) (32). The infection usually causes disease in the lungs (pulmonary TB), but the bacteria can travel through the bloodstream to other parts of the body (extrapulmonary TB) (32). In British Columbia, there are about 300 cases of TB disease each year with an average incidence rate of 7.0 cases per 100,000 people (33).

Mono-resistant TB is defined as resistance to one drug only, most often isoniazid (INH). Multi-drug resistant TB (MDR-TB) is caused by MTB resistant to at least INH and rifampin, the most effective anti-TB drugs (34). Poly-resistant TB is caused by MTB resistant to more than one anti-TB drug, but not both INH and rifampin (34). Extensively drug-resistant TB (XDR-TB) is a form of TB caused by MTB resistant to INH and rifampin (i.e. MDR-TB), as well as any fluoroquinolone and any of the second-line anti-TB injectable drugs (amikacin, kanamycin or capreomycin) (34).

Susceptibility data for TB is presented as per patient rather than per isolate in order to maintain consistency with reporting to the Public Health Agency of Canada. A total of 1852 patients with culture-confirmed TB strains and drug susceptibility testing (DST) results were reported between 2005 and 2012 by the BCPHMRL. In BC, MDR-TB was found in 0.8% of cases over the eight years. For the same time period (2005-2012), mono-resistance occurred in 8.1% of BC cases while poly-resistance was noted in 0.3% of patients (Figure 21). While the annual proportion of MDR-TB cases has fluctuated over the eight-year period, the proportions of mono-resistant TB cases have increased, making up 9.1% of patients in 2012 (Figure 21). There were no cases of extensively drug resistant TB (XDR) diagnosed in BC from 2005 to 2012.

Rates in BC are comparable to national rates for 2011 with the exception of MDR-TB (1.4%) which was reported to be approximately half the national rate in 2011 (data not shown). BC had the third highest number of TB cases in Canada in 2011, following Ontario and Quebec (34). For more information on TB, the most recent BCCDC report can be found online at: http://www.bccdc.ca/dis-cond/a-z/_t/Tuberculosis/statsres/default.htm.



	2005	2006	2007	2008	2009	2010	2011	2012
Mono-resistant	8.3%	5.8%	7.4%	8.3%	9.6%	9.0%	11.3%	9.1%
Poly-resistant	0.5%	0.0%	0.9%	0.0%	0.4%	0.0%	0.5%	0.0%
Multi-resistant	2.0%	0.7%	0.9%	1.2%	0.0%	0.5%	0.5%	0.8%
Number of Mono-resistant strains	17	16	17	21	23	18	22	21
Number of Poly-resistant strains	1	0	2	0	1	0	1	0
Number of Multi-resistant strains	4	2	2	3	0	1	1	2
Total Number of Tested Patients	204	275	231	254	239	201	194	254

Figure 21 - Proportion and number of *M. tuberculosis* complex patients that are mono-resistant, poly-resistant and multi-drug resistant in British Columbia, Canada (2005-2012)
Source: BCPHMRL

Please note: Data provided by the BCPHMRL represent patients with tuberculosis caused by species within the *Mycobacterium tuberculosis* complex including, but not limited to, *Mycobacterium tuberculosis.*

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Appendix A: Supplemental Tables

Table 3 - Proportion of *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis* isolates demonstrating ESBL-compatible phenotype and their resistance to one, two and three antibiotics (quinolones, aminoglycosides and TMP-SMX) (2007-2012)

	2007	2008	2009	2010	2011	2012
Proportion of all Isolates (Count)						
ESBL-like *E. coli*	11.5% (2,811)	10.6% (2,598)	9.1% (2,266)	11.8% (3,233)	12.4% (3,043)	11.7% (3,082)
ESBL-like *K. pneumoniae*	8.5% (175)	6.7% (142)	5.3% (111)	5.6% (133)	3.3% (67)	3.3% (78)
ESBL-like *P. mirabilis*	12.5% (173)	7.7% (96)	9.5% (137)	7.3% (108)	5.0% (74)	5.5% (76)
Proportion of ESBL-like Isolates exhibiting Quinolones Non-susceptibility (Count)						
ESBL-like *E. coli*	66.1% (1,859)	68.2% (1,773)	63.3% (1,434)	73.1% (2,364)	75.5% (2,296)	72.8% (2,243)
ESBL-like *K. pneumoniae*	15.4% (27)	24.6% (35)	26.1% (29)	26.3% (35)	46.3% (31)	56.4% (44)
ESBL-like *P. mirabilis*	53.2% (92)	54.2% (52)	51.8% (71)	37.0% (40)	18.9% (14)	38.2% (29
Proportion of ESBL-like Isolates exhibiting Aminoglycosides Non-susceptibility (Count)						
ESBL-like *E. coli*	34.2% (960)	36.2% (940)	27.6% (626)	30.3% (981)	29.4% (895	27.7% (854)
ESBL-like *K. pneumoniae*	9.1% (16)	19.0% (27)	21.6% (24)	19.5% (26)	32.8% (22)	34.6% (27)
ESBL-like *P. mirabilis*	8.7% (15)	8.3% (8)	13.1% (18)	16.7% (18)	35.1% (26)	31.6% (24)
Proportion of ESBL-like Isolates exhibiting TMP-SMX Non-susceptibility (Count)						
ESBL-like *E. coli*	48.2% (1,356)	51.6% (1,340)	41.3% (936)	57.1% (1,845)	57.6% (1,752)	56.7% (1,746)
ESBL-like *K. pneumoniae*	61.7% (108)	69.7% (99)	63.1% (70)	39.1% (52)	64.2% (43)	62.8% (49)
ESBL-like *P. mirabilis*	65.3% (113)	63.5% (61)	67.9% (93)	53.7% (58)	29.7% (22)	44.7% (34)
Proportion of ESBL-like Isolates exhibiting Non-susceptibility to at least two of quinolones, aminoglycosides and TMP-SMX (Count)						
ESBL-like *E. coli*	48.6% (1,367)	52.1% (1,354)	42.5% (963)	58.7% (1,899)	60.5% (1,841)	58.5% (1, 803)
ESBL-like *K. pneumoniae*	16.0% (28)	28.2% (40)	29.7% (33)	24.1% (32)	49.3% (33)	51.3% (40)
ESBL-like *P. mirabilis*	54.3% (94)	54.2% (52)	54.7% (75)	42.6% (46)	29.7% (22)	43.4% (33)
Proportion of ESBL-like Isolates exhibiting Non-susceptibility quinolones, aminoglycosides and TMP-SMX (Count)						
ESBL-like *E. coli*	24.9% (700)	26.8% (695)	18.1% (411)	23.0% (745)	19.9% (606)	17.7% (546)
ESBL-like *K. pneumoniae*	6.9% (12)	13.4% (19)	14.4% (16)	14.3% (19)	23.9% (16)	23.1% (18)
ESBL-like *P. mirabilis*	1.7% (3)	1.0% (1)	4.4% (6)	2.8% (3)	8.1% (6)	21.1% (16)

Source: BC Biomedical Laboratories

Appendix B: Technical Notes

Data Sources

The data sources used for the compilation of this report are discussed below. The specific bacterial species provided by each data source are indicated. Organisms are tested for susceptibility to antimicrobial agents in the laboratory using the minimum inhibitory concentration (MIC) breakpoints, as set out by the Clinical and Laboratory Standards Institute (CLSI) guidelines (2).

BC Association of Medical Microbiologists (BCAMM)
Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), Extended spectrum β-lactamase-producing Enterobacteriaceae (ESBL producing Enterobacteriaceae)

The BC Association of Medical Microbiologists (BCAMM) collects data from a representative sample of community-based and hospital-based laboratories in BC. Refer to the BCAMM 2011 Report for a complete list of all participating laboratories (14). Data for 2012 was not available at the time of this report. Note that the participating community-based laboratories include BC Biomedical Laboratories and Life Labs, which provide most of the out-patient coverage for the province and are also included in this report. Limitations of the BCAMM data include the possibility of more than one isolate from the same patient being tested and included by different participating sites, re-testing of isolates at certain sites, the lack of denominator data for enterococci as they are part of normal enteric flora and often non-pathogenic, and the inability to differentiate community-acquired and hospital-acquired infections. Aggregated data were provided for years 2002 to 2011.

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

BC Biomedical Laboratories collected isolates from 45 community-based patient service centres located throughout the Lower Mainland of BC. Due to the clustering of patient services in the Vancouver Coastal and Fraser Health Authorities, isolates may not be representative of the entire province. BC Biomedical Laboratories published empiric therapy antibiograms from which earlier data for this report were obtained. For the years 1999 and 2002, the percent of isolates for each organism susceptible to a particular antimicrobial was reported in yearly aggregated form. If susceptibility data are similar between years, a new antibiogram is not published for the subsequent year. Therefore, antibiograms were only available for years 1999, 2002, 2007, 2011 and 2012. The 2011 and 2012 empiric therapy antibiograms are currently available on the BC Biomedical Laboratories' website (25;26). Since 2007, anonymous monthly datasets were analysed in collaboration with the *Do Bugs Need Drugs?* (DBND) program in BC.

The data shown for *E. coli, K. pneumoniae* and *P. mirabilis* isolates with phenotype compatible with ESBLs in the present report were not provided directly from the BC Biomedical Laboratories. Instead, these isolates were identified based on resistance to third generation cephalosporins (e.g. ceftriaxone, cefotaxime, ceftazidime, or cefixime). However, because cephamycin results were not available, true identification of ESBL producing *E. coli*, *K. pneumoniae* and *P. mirabilis* isolates was not possible and an overestimation is expected. Without direct confirmation, these isolated will be identified as extended spectrum beta-lactamase-like (ESBL) producers or "isolates with phenotype compatible with ESBLs."

BC Public Health Microbiology & Reference Laboratory (BCPHMRL)
Methicillin-resistant *Staphylococcus aureus* (MRSA), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBL-producing Enterobacteriaceae), Carbapenem-resistant Enterobacteriaceae (CRE), *Mycobacterium tuberculosis*

Since the fall of 2010, the BCPHMRL implemented genotypic methods for testing Enterobacteriaceae isolates in order to confirm antibiotic susceptibility profiles for isolates with unusual phenotypic profiles submitted from front-line microbiology laboratories. In particular, the BCPHRML looks for gene targets associated with ESBL (SHV, TEM, CTX-M and OXA-1), AmpC (CMY-2, CMY-1/MOX, CMY-2/LAT, DHA, ACC, MIR/ACT and FOX) and carbapenem (KPC, NDM, IMP and VIM) resistance. These data are reported in the BCAMM report. Additionally, in March 2013,

the BCPHMRL also released their monthly *Lab Trends* report with a section on carbapenem-resistant Enterobacteriaceae (CRE) (29).

Tuberculosis data from 2005 to 2011 were provided directly from the BCPHMRL. The BCCDC is informed of tuberculosis cases directly from providers and laboratories throughout the province. All new cases of TB with confirmatory testing in BC and bacterial isolate available (approximately 80% of all cases) are tested for susceptibility against anti-tuberculosis agents. Data used for analysis are extracted from iPHIS (Integrated Public Health Information System). Please note, that unlike previous reports, data on TB is now displayed on a per patient basis, rather than a per isolate basis for consistency with Public Health Agency of Canada (PHAC) reporting. Drug resistance is noted for patients with isolates that were mono-resistant, multi-drug resistant (MDR-TB) and poly-resistant.

Canadian Bacterial Surveillance Network (CBSN)
Streptococcus pneumoniae

The Canadian Bacterial Surveillance Network (CBSN) received isolates from one or more hospitals located in BC each year (nine different hospitals in total since 1994). From participating hospitals, CBSN collects a set of consecutive clinically relevant *Streptococcus pneumoniae* isolates (from any site) as well as isolates from a sterile site. Limitations that may affect the data are the collection method being from any site, and isolate submission being voluntary with only two hospitals having submitted isolates for 2010 and 2012, and only one for 2011. Aggregated data for *Streptococcus pneumoniae* were available for years 1994 to 2009 and line-listed data was provided for years 2010 to 2012. Please note that the oral penicillin and non-meningitis ceftriaxone CLSI breakpoints are used in this report.

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

Salmonella isolates from the BC Public Health Microbiology and Reference Laboratory (BCPHMRL) were forwarded to the National Microbiology Laboratory (NML) in Winnipeg, Manitoba for susceptibility testing. Only isolates from the first fifteen days of each month were sent to CIPARS with the exception of *Salmonella* Typhi and *Salmonella* Newport, for which all isolates are submitted. For *Salmonella* Enteriditis, due to the large number of isolates submitted by the larger Canadian provinces (British Columbia, Alberta, Ontario and Québec), only half of the isolates received during the first 15 days of the month were tested for antimicrobial susceptibility. The remaining isolates were stored and tested as resources were available. Consequently, the tested isolates represent approximately half of all non-typhoidal *Salmonella* cases in BC. The twelfth edition of the Performance Standards for Antimicrobial Resistance Testing from the CLSI was used to classify MIC breakpoints for resistance (4). Aggregated data were available for years 2003 to 2011. Data for 2009 to 2011 were obtained from short (preliminary) reports as the final reports were not available at the time of writing.

LifeLabs Medical Laboratory Services
Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Haemophilus influenzae

LifeLabs collected isolates from 80 community-based patient service centres located throughout Vancouver Island and the Mainland of BC. Due to the clustering of patient services in the Vancouver Island and Vancouver Coastal Health Authorities, isolates may not be representative of the entire province. LifeLabs has provided yearly aggregate susceptibility data from 2007 to 2012. The 2011 and 2012 empiric therapy antibiograms are currently available on the LifeLabs website (35;36).

Data analysis

Data were analyzed using SPSS 14.0 and R Studio for Windows. Microsoft Excel 2007 was used in the creation of all figures and tables. Where appropriate, the trend of non-susceptibility over time was tested for significance using the two-sided non-parametric Spearman Rank test. Please note that for BC Biomedical data, the trend over time was only tested for significance between 2007 and 2012. CBSN data for *S. pneumoniae* was also analyzed using the Spearman Rank. All available years were included in the analysis. Additionally, the chi-square test was used to compare differences in non-susceptibility rates between MRSA and MSSA. The significance level for this report was set at $p<0.05$.

Organism Specific Notes

Streptococcus pyogenes

Clindamycin susceptibility is determined using the double disk diffusion test (D-test). The D-test determines whether clindamycin non-susceptibility can be induced when *S. pyogenes* bacteria are grown in the presence of erythromycin.

SPICE Organisms

It should be noted that data for 2010 were only available for the months of July to December 2010. The data for 2011 can be found as part of the 2012 BC Bio Empiric Therapy Antibiogram (25) online at: http://www.bcbio.com/images/pdfs/antibiogram2012.pdf

Extended Spectrum β–Lactamase Producers

In BC, laboratory testing for ESBL-producing *E. coli* and *K. pneumoniae* is done routinely by phenotypic methods. An estimate of the percentage of ESBL-producing *E. coli* and *K. pneumoniae* was reported in the BCAMM report. These percentages represent the range of ESBL-producing *E. coli* and *K. pneumoniae* observed in all BC Biomedical Laboratories and LifeLabs community laboratories, and 23 health organizations' hospital laboratories across BC (14). The results are presented for both community and hospital settings from 2009 to 2011, in order to reflect the potential differences in prevalence within the respective settings.

The following information is taken directly from page 6 of the 2011 BCAMM report (14):

"Phenotypic testing methods cannot always identify and differentiate between specific resistance mechanisms, i.e., ESBLs, AmpC (also known as cephalosporinases) and carbapenemases; hence, genotypic methods were implemented at the BCCDC Public Health and Reference Laboratory in the fall of 2010. From October 2009 to October 4, 2012, 450 clinical Enterobacteriaceae isolates, (an additional 327 isolates since the 2010 BCAMM ARO report) were submitted based on unusual phenotypic antibiotic susceptibility profiles that required confirmation. Duplicate isolates from the same source and collection dates were removed … The phenotypic screening methods and decisions for submitting isolates were at the discretion of frontline medical microbiology laboratories."

The CLSI does not recommend confirming ESBLs and consequently, BC Biomedical Laboratories does not directly confirm potential ESBL isolates. BC Biomedical Laboratories refers to isolates exhibiting cephalosporin resistance as broad-spectrum beta-lactamase producers. Consequently, data from BC Biomedical Laboratories were used to estimate extended spectrum β-lactamase-like (ESBL-like) producers, determined through resistance to third generation cephalosporins (e.g. ceftriaxone, cefotaxime, ceftazidime, or cefixime). This method is likely to overestimate the proportion of isolates that are ESBL-like producers. Although data from BC Biomedical Laboratories would represent an overestimation of true ESBL numbers, the data are still useful as they will include all possible ESBL-producing *E. coli, K. pneumonia* and *P. mirabilis* isolates. Thus, it is still meaningful to represent the data in this report in order to use this denominator to identify multi-drug resistance patterns associated with *E. coli, K. pneumoniae* and *P. mirabilis* isolates with phenotype compatible with ESBLs, and to monitor for any changing trends.

While the gene targets associated with ESBL are not comprehensively tested at the BCCDC they include SHV, TEM, CTX-M, and OXA-1. Of the resistance mechanisms detected amongst tested isolates, ESBL resistance genes were the most common (14).

Please note that small sample sizes for the *K. pneumoniae* and *P. mirabilis* ESBL-like isolates may have caused some trends to be labeled as non-significant.

Carbapenem-resistant Enterobacteriaceae (CRE)

BCCDC tests for KPC, NDM-1, IMP and VIM carbapenem resistance genes. The additional plasmid-encoded carbapenemase gene OXA-48 were tested by the National Microbiology Laboratory (14).

AmpC

BCCDC tests for seven gene targets associated with AmpC resistance: CMY-2, CMY-1/MOX, CMY-2/LAT, DHA, ACC, MIR/ACT and FOX.

Haemophilus influenzae

CBSN reported susceptibility for *Haemophilus influenzae* from 2001 to 2008. The data from 2008 suggested nearly 40% of isolates were producing β-lactamases, which was the greatest proportion recorded during their surveillance activities. As the data on *H. influenzae* have not been updated since 2008, this information is no longer be included in this report

Mycobacterium tuberculosis

Please note that the data and figures (provided by BCPHMRL) represent patients with tuberculosis caused by species within the *Mycobacterium tuberculosis* complex including, but not limited to, *Mycobacterium tuberculosis*.