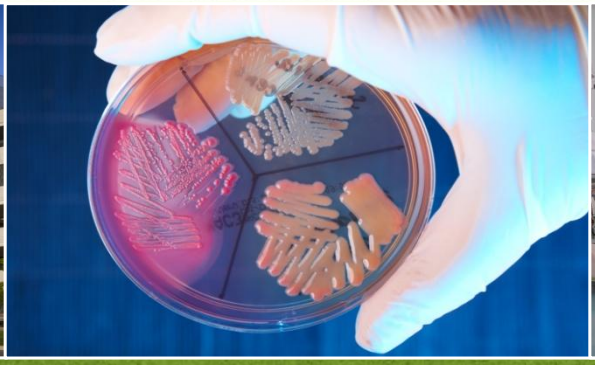
CARBAPENEM-RESISTANT GRAM-NEGATIVE BACILLI IN CANADIAN ACUTE-CARE HOSPITALS

SURVEILLANCE REPORT JANUARY 1, 2010 TO DECEMBER 31, 2012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Information to the reader of *Carbapenem-Resistant Gram-Negative Bacilli in Canada*

On behalf of the Public Health Agency of Canada, we would like to present you with a report entitled *Carbapenem-Resistant Gram-Negative Bacilli in Canadian acute-care hospitals: Surveillance Report January 1, 2010 to December 31, 2012.* This is the first report providing a review of available carbapenem resistant Gram-negative bacilli (CRGNB) surveillance data in Canada.

The Healthcare-Associated Infections Section is part of the Surveillance and Epidemiology Division, which is located in the Public Health Agency of Canada's Centre for Communicable Diseases and Infection Control. This Section is responsible for the data collection and management, analysis and report production related to this *Carbapenem-Resistant Gram-Negative Bacilli in Canadian acute-care hospitals* report. In addition, we continue to improve data quality, define and set surveillance standards, as well as support the use of these data to inform public health and policy action.

The Public Health Agency of Canada collects national data on various healthcare-associated infections, including CRGNB through the Canadian Nosocomial Infection Surveillance Program (CNISP), a collaborative effort of the Centre for Communicable Diseases and Infection Control, the National Microbiology Laboratory (NML) and sentinel hospitals across Canada who participate as members of the Canadian Hospital Epidemiology Committee (a subcommittee of the Association of Medical Microbiology and Infectious Disease Canada). As of December 2012, CNISP conducted surveillance in 54 large, university-affiliated tertiary care hospitals (i.e., major hospitals that offer a range of specialist services such as burn units, transplant units, trauma centres, specialized cardiac surgery etc. to which patients are referred from smaller hospitals). Thirty-eight of these hospitals participated in CRGNB surveillance. CNISP surveillance provides key information that informs the development of federal, provincial and territorial infection prevention and control programs and policies.

Highlights of the findings are outlined in the section entitled 'At a Glance' while the main findings of the surveillance data are outlined in the section entitled 'Results'. Data sources and references are available in the Appendices.

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Highlights of the findings are outlined in the section entitled 'At a Glance' while the main findings of the surveillance data are outlined in the section entitled 'Results'. Data sources and references are available in the Appendices.

Executive Summary

Gram-negative bacilli (GNB) cause a variety of diseases, ranging from pneumonia to urinary tract infections, to serious bloodstream or wound infections. The symptoms vary depending on the disease. GNB infections and colonization typically occur in ill patients with exposure to acute and long-term care setting. The most common GNB causing infections in the health care setting are *Klebsiella pneumonia*, *Escherichia coli* and *Acinetobacter*. GNB that have acquired resistance to carbapenems are called carbapenem-resistant Gram-negative bacilli (CRGNB).

This report provides a comprehensive look at CRGNB and carbapenemase-producing organisms (CPO) in Canadian acute-care hospitals since 2010 through the Canadian Nosocomial Infection Surveillance Program (CNISP). In Canada, carbapenemase-producing organisms (CPO) remain relatively uncommon in most acute-care hospitals in Canada, especially in the eastern region. CPOs represents a subset of CRGNB that have acquired resistance to carbapenem by the ability to produce carbapenemase; an enzyme that breaks down carbapenem. Carbapenemase producers are mainly identified among *Klebsiella pneumoniae* and found mostly in hospital settings.

The regional differences in CPO rates are observed across Canada. A major contributor to this variation is an outbreak of the *Klebsiella pneumoniae* carbapenemase (KPC) subtype reported in the central region. Regional variation of rates has also been reported by the United States and among European countries. Factors which may influence the regional emergence and spread of carbapenemases include local antimicrobial usage patterns, different policies or implementation of infection control measures, the role of interfacility transfers as well as differences in screening practices and detection methods across hospitals and laboratories. Importation of carbapenemases from other countries as a consequence of travel and medical tourism may also play an important role in the regional distribution of cases as hospitals in larger, urban cities may serve patients who are more likely to have travelled internationally.

In conclusion, the burden of CRGNB and CPO among Canadian acute-care hospitals remains low, yet the global dissemination of gram-negative bacilli that have acquired carbapenemase genes is a growing public health concern. Moreover, the significant proportion of non-travel associated CPO positive patients suggests the local establishment and spread of carbapenemase-producing organisms in Canada. Thus, the continued surveillance of carbapenem resistant and carbapenemase-producing organisms will enable the Agency to continue to monitor the spread and burden of these types of antimicrobial resistance in Canadian acute-care hospitals.

Abbreviations and Acronyms

CHEC	Canadian Hospital Epidemiology Committee
CLSI	Clinical and Laboratory Standards Institute
CNISP	Canadian Nosocomial Infection Surveillance Program
COPD	Chronic obstructive pulmonary disease
CPO	Carbapenemase-producing organisms
CRA	Carbapenem-Resistant Acinetobacter
CRE	Carbapenem-resistant enterobacteriaceae
CRGNB	Carbapenem-resistant gram-negative
EIP	Emerging Infections Program
ICP	Infection Control Practitioners
ICU	Intensive care unit
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	multiple drug resistant
MIC	Minimum inhibitory concentration
MLST	Multilocus sequence typing
NDM	New Delhi metallo-beta-lactamase
NHSN	National Healthcare Safety Network
NML	National Microbiology Laboratory
NNIS	National Nosocomial Infection Surveillance Program
OXA	Oxacillinase gene
PCR	Polymerase chain reaction
PFGE	Pulsed-field gel electrophoresis
SHV	Sulfhydryl-variable extended-spectrum beta-lactamase gene
VIM	Verona integron-encoded metallo-beta-lactamase
TEM	Temoneira extended-spectrum beta-lactamase gene

At a Glance

The Public Health Agency of Canada (Agency) has collected data on inpatients and outpatients with Carbapenem-Resistant Gram-Negative bacilli (CRGNB) in Canadian acute-care hospitals since 2010 through the Canadian Nosocomial Infection Surveillance Program (CNISP). Detailed epidemiologic data were consistently collected only for the subset of carbapenemase-producing organisms (CPO) among all carbapenen-resistant gram-negative isolates. Therefore, the epidemiologic and microbiological data summarized in this report only includes CPO cases. The following are highlights of this surveillance report.

- Rates of CRGNB in hospitals participating in CNISP remain low. In 2012, 0.14 cases per 1,000 patient admissions of carbapenem-resistant Enterobacteriaceae and 0.02 cases per 1,000 patient admissions of carbapenem-resistant *Acinetobacter* were identified among 38 hospitals.

- The number of CPO cases (154 cases between January 1, 2010 and December 31, 2012) in Canada remains low and the rates have remained stable over the three years since the Agency began conducting surveillance

- 44.8% of cases were colonized; 31.8% of cases were infected and status was unknown for 23.4% of cases.

- The central region of Canada reported the highest number of cases, the majority of which are likely due to an outbreak reporting at one hospital.

- Only twenty-three cases (14.9%) reported international travel within the 12 months prior to diagnosis and of those 16 cases sought medical care while abroad.

- No cases were admitted to the intensive care unit due to CPO while three deaths were determined to be attributed to CPO.

- For all three years, CPO subtype $bla_{\text{KPC-type}}$ (*Klebsiella pneumonia* carbapenemase) were observed in the highest proportion followed by CPO subtype $bla_{\text{NDM-1}}$ (New Delhi Metallo-beta-lactamase)

Background

Gram-negative bacilli (GNB) commonly encountered in healthcare settings include species such as *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas maltophilia*, and species belonging to the Enterobacteriaceae family, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. GNB are often resistant to many commonly prescribed antibiotics but may remain susceptible to one or more antibiotics. The carbapenem group of antimicrobials is a safe and generally effective treatment for GNB when resistance to other classes of antimicrobials is present. When resistance to carbapenems occurs, there are often few alternative treatments available.

GNB cause a variety of diseases, ranging from pneumonia to urinary tract infections, to serious bloodstream infections. The symptoms vary depending on the disease. GNB infections (microorganism causing disease in a person) and colonisations (microorganism found on or in a person without causing a disease) are more likely to occur in ill patients with exposure to acute and long-term care settings.

GNB are most commonly spread person-to-person in healthcare settings via the hands of healthcare providers. GNB can cause infections when they enter the body, often through medical devices such as intravenous catheters, urinary catheters, or through wounds caused by injury or surgery. Some people might be colonized rather than infected with GNB and may not require any treatment.

GNB that are resistant to carbapenem antimicrobials are known as carbapenem-resistant Gram-negative bacilli (CRGNB) and include carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant Acinetobacter (CRA). Carbapenem-resistance in GNB can occur by a number of different mechanisms. One mechanism of carbapenem resistance is due to changes in the permeability of the organism to the antibiotic. Another mechanism is via the production of enzymes, called carbapenamase, that break down carbapenem. These organisms are called carbapenamase-producing organisms (CPO). The majority of CPOs are resistant to at least one carbapenem, though some CPO exhibit only intermediate resistance to carbapenem.

An example of a recently identified carbapenemase is the New Delhi metallo beta-lactamase (NDM-1 enzyme) which has recently been identified in India and Pakistan and in patients hospitalized in other countries after receiving health care in India and Pakistan. CPOs are of particular concern because of their ability to transfer resistance easily across different genus and species of bacteria. They are quickly becoming a public health problem not only because of the ability to cause healthcare associated infections but because of the potential for colonizing both inpatient and outpatient populations creating a reservoir of bacterial resistance. For these reasons, the Canadian Nosocomial Infection Surveillance Program (CNISP) is specifically involved in the surveillance of the CPO subset of the CRGNB.

The Public Health Agency of Canada (the Agency) has developed a document to provide infection prevention and control guidance for healthcare workers in the management of patients colonized or infected with CRGNB, including CPO. It can be found at http://www.phac-aspc.gc.ca/nois-sinp/guide/ipcm-mpci/pdf/guide-eng.pdf[1].

Methods

Surveillance network

During 2010 to 2012, the Agency collected data on inpatients and outpatients with CRGNB identified by acute-care hospitals participating CNISP. Surveillance of CRGNB at participating hospitals is considered to be within the mandate of hospital infection prevention and control programs and does not constitute human research. Therefore in participating hospitals this surveillance activity does not require Institutional Review Board (IRB) review.

A CRGNB working group comprised of nine Canadian Hospital Epidemiology Committee (CHEC) members from participating hospitals and representative from the Agency's National Microbiology Laboratory (NML) and an epidemiologist are responsible for developing and regularly updating the surveillance protocol which includes standardized data collection forms and a data dictionary. In-service sessions are organised at the beginning of each surveillance year by the Agency for all participating hospitals. The purpose of the in-service sessions is to provide training to Infection Control Practitioners (ICPs) on how to follow the surveillance protocol and complete the data collection forms, and to establish consistency across the participating hospitals in the understanding of each question on the data collection forms. This ensures that the data are comparable between the participating hospitals and between the provinces and regions.

Study eligibility inclusion

Hospitalized patients as well as individuals identified in outpatient settings such as emergency departments and clinics with a laboratory confirmed CRGNB were included in the surveillance. Patients infected or colonized with *Pseudomonas* spp. were not included in the CRGNB surveillance.

From January 1, 2010 to August 31, 2010 any patient with an *Enterobacteriaceae* that exhibited a minimum inhibitory concentration (MIC) value ≥ 2 μg/ml for any of three carbapenem antimicrobials (imipenem, meropenem, ertapenem); or a disk diffusion diameter ≤ 21mm was eligible for inclusion. Subsequently, from September 1, 2010 to December 31, 2012, the MIC for ertapenem was decreased to ≥0.5 μg/ml and a disk diffusion diameter for any carbapenem ≤ 22 mm was considered eligible for inclusion.

From January 1, 2010 to August 31, 2010, *Acinetobacter* required a MIC value ≥ 16 μg/ml for imipenem and meropenem (or a disk diffusion diameter ≤ 13 mm) for inclusion which was revised to ≥8μg/ml or a disk diffusion diameter of ≤15mm for September 1, 2010 to December 31, 2012.

All submitted isolates confirmed to be either intermediate or fully resistant to carbapenem were tested by polymerase chain reaction (PCR) for detection of the following carbapenemase genes: NDM, KPC, IMP, VIM, GES, OXA-48-type, NMC/IMI and SME. Additionally all isolate were

also tested for the common beta-lactamase genes: SHV, TEM, CTX-M, OXA-1 and CMY-2. All *Pseudomonas* spp. were excluded from further laboratory analysis.

Isolates that tested positive for a carbapenemase gene by PCR were further characterized by multilocus sequence typing (MLST) macro-restriction analysis by pulsed-field gel electrophoresis (PFGE), antimicrobial susceptibility testing and analysis of plasmids harboring carbapenemase genes. BioNumerics software (version 3.5; Applied Maths, Saint Lartens-Latem, Belgium) were used to analyze PFGE fingerprints. Antimicrobial susceptibility testing was performed using Vitek2 (AST-GN25 and AST-N219) with the 2013 Clinical Laboratory Standard Institute (CLSI) breakpoints.

Primary laboratory detection and identification was conducted by either the hospital or provincial laboratories using standard diagnostic laboratory procedures in accordance with CLSI guidelines. All eligible isolates were sent to the NML for MIC confirmation using ertapenem, meropenem and imipenem Etest strips (bioMerieux, St. Laurent, QC, Canada).

Standard National Healthcare Safety Network (NHSN) surveillance definitions that include both laboratory and clinical criteria were used to determine infection. Cases that did not exhibit infection-associated clinical signs were determined to be colonized.

Data collection and submission

All isolates submitted to the NML included a minimum dataset which includes: age, sex, date of admission, date of positive culture, organism, ward, and site of isolation. If an isolate was determined to be a carbapenemase producer by the NML, a standardized patient questionnaire was completed. The standardized patient questionnaire included patient demographics and clinical information, date and site of positive culture, microorganisms isolated, travel history, treatment and outcome information. Cases that died within 30 days of diagnosis were reviewed by a CHEC physician or a delegate to determine whether CPO was the primary cause of death, contributed to death, or was unrelated to the death.

Detailed epidemiologic data were collected only for CPO. Epidemiological data were submitted by each participating hospital to the Agency for data entry, storage and statistical analysis.

Denominator data

Participating hospitals also provide the Agency with the number of patient-admissions and the number of patients-days for the corresponding surveillance year. Patient admissions are defined as the total number of patients admitted to the participating hospitals during a surveillance year. Patient-days are defined as the cumulative total number of days hospitalised for all patients during a surveillance year. The denominator data only includes data from inpatient settings. It does not account for denominators from outpatient settings such as emergency departments and clinics. Due to the small number of cases in Canada with CPOs, these outpatient settings were still included in the numerator. The denominator data received

from the participating hospitals is used as a proxy or substitute for the entire patient population under surveillance. These denominator data are used to calculate the annual incidence rates presented in this report.

Data analysis

Data submitted to the Agency both (epidemiologic and clinical data) by participating hospitals and the NML (results of laboratory analysis) are extracted, validated and statistically analysed as appropriate.

Annual incidence rates are calculated using patient admissions and patient-days. For reporting purposes and to ensure confidentiality, the provinces are grouped into three regions: Western (British Columbia, Alberta, Saskatchewan and Manitoba), Central (Ontario and Quebec), and Eastern (Nova Scotia, New Brunswick, Prince Edward Island and Newfoundland and Labrador). The territories do not currently submit data to the Agency and Prince Edward Island only began submitting data in 2011.

Results

From January 1, 2010 to December 31, 2012, thirty-eight (38) acute-care hospitals across Canada participated in CRGNB surveillance. 603 isolates were submitted for confirmatory testing to the NML from 21 acute-care hospitals (the remaining hospitals reported no cases). A total of 439 (72.8%) isolates were confirmed to be either intermediate or fully resistant to carbapenem according to the criteria described in the methods. Of these, 231 (52.5%) were carbapenem-resistant Enterobacteriaceae (CRE)**,** and 22 (5.0%) were carbapenem-resistant *Acinetobacter* (CRA). The remaining 186 isolates were *Pseudomonas* spp. (n= 123) or carbapenem intermediate resistant GNB (n = 63). All *Pseudomonas* spp. isolates were excluded from further analysis as per the surveillance protocol.

All CRE, CRA and carbapenem intermediate resistant GNB (n = 316) were tested for the presence of a carbapenamase. A total of 154 carbapenamase producers (CPO) were identified.

Carbapenem-Resistant Enterobacteriaceae

Table 1 to 2 provides the number of carbapenem-resistant Enterobacteriaceae (CRE) cases and rates by year. These data were included in this report to facilitate the comparison of Canadian and international data, however no epidemiologic or microbiological data are provided.

The overall incidence rate of CRE in hospitals participating in CNISP increased by over 60% from 2010 to 2011 (0.11 vs. 0.18 cases per 1,000 patient admissions in 2010 and 2011, respectively, p = 0.004). The rate decreased in 2012 by 22% but remains higher than the rate reported in 2010 (p = 0.048)

Table 1. Overall number of CRE* cases and incidence rates per 1,000 patient-admissions and 10,000 patient-days from January 1, 2010 to December 31, 2012 (n=231)

National	2010	2011	2012
No. of cases	51	96	84
No. of total patient admissions	452,094	520,134	588,832
No. of total patient-days	3,360,026	4,125,721	4,650,233
Rate per 1,000 patient admissions	**0.11**	**0.18**	**0.14**
Rate per 10,000 patient-days	**0.15**	**0.23**	**0.18**
No. of reporting hospitals	33	37	38

*CRE=Carbapenem-Resistant Enterobacteriaceae

The incidence rate for CRE by region is shown in Table 2. Incidence rates have increased significantly over the three year surveillance in the Western region (p = 0.003). The incidence rate in the Central region almost doubled between 2010 and 2011 (0.14 vs. 0.27 cases per 1,000 patients admissions, respectively, p <0.0001). The rate decreased in 2012 to 0.16 cases per 1,000 patient admissions, representing an overall increase of less than 20% in this region. The increase in the rate observed in 2011 is likely due to outbreaks of CRE that were reported in two hospitals in the Central region.

CRE remains rare in the Eastern region. Only five cases reported in the three-year surveillance period. The rate of CRE in 2012 was 0.03 per 1,000 patient admissions. No cases of CRE were reported in the Eastern region in 2011.

Table 2. Number of CRE* cases and incidence rates per 1,000 patient admissions and 10,000 patient-days, by region, from January 1, 2010 to December 31, 2012 (n=231)

Region	2010	2011	2012
Western			
No. of cases	17	19	27
No. of total patient admissions	140,472	140,472	150,417
No. of total patient-days	1,148,779	1,207,701	1,237,910
Rate per 1,000 patient admissions	**0.12**	**0.13**	**0.18**
Rate per 10,000 patient-days	**0.15**	**0.16**	**0.22**
No. of reporting hospitals	7	7	7
Central			
No. of cases	32	77	54
No. of total patient admissions	228,347	285,634	347,129
No. of total patient-days	1,448,172	2,100,545	2,575,613
Rate per 1,000 patient admissions	**0.14**	**0.27**	**0.16**
Rate per 10,000 patient-days	**0.22**	**0.37**	**0.21**
No. of reporting hospitals	20	23	24
Eastern			
No. of cases	2	0	3
No. of total patient admissions	83,275	87,095	91,286
No. of total patient-days	763,075	817,475	836,710
Rate per 1,000 patient admissions	**0.02**	**0.00**	**0.03**
Rate per 10,000 patient-days	**0.03**	**0.00**	**0.04**
No. of reporting hospitals	6	7	7

*CRE=Carbapenem-Resistant Enterobacteriaceae

Carbapenem-Resistant *Acinetobacter*

Table 3 to 4 provides the number of carbapenem-resistant *Acinetobacter* (CRA) cases and rates by year. These data were included in this report to facilitate the comparison of Canadian and international data, however no epidemiologic or microbiological data are provided.

CRA remains rare in Canada; 22 cases were reported between January 1, 2010 and December 31, 2012. The incidence rate of CRA in 2012 was 0.02 cases per 1,000 patient admissions and 0.02 cases per 10,000 patient-days. The incidence rate reported in 2012 is similar to the incidence rate reported in 2010 (0.02 cases per 1,000 patient admissions in 2010); however the incidence rate decreased significantly in 2011 before returning to the baseline in 2012. In 2011, the overall incidence rate of CRA was 0.004 cases per 1,000 patient admissions and 0.005 cases per 10,000 patient-days, representing a decrease of 80% (p = 0.018).

Table 3. Overall number of CRA* cases and incidence rates per 1,000 patient-admissions and 10,000 patient-days from January 1, 2010 to December 31, 2012 (n=22)

National	2010	2011	2012
No. of cases	9	2	11
No. of total patient admissions	452,094	520,134	588,832
No. of total patient-days	3,360,026	4,125,721	4,650,233
Rate per 1,000 patient admissions	**0.02**	**0.004**	**0.02**
Rate per 10,000 patient-days	**0.03**	**0.005**	**0.02**
No. of reporting hospitals	33	37	38

*CRA=Carbapenem-Resistant *Acinetobacter*

The incidence rate for CRA by region is shown in Table 4. There were no cases of CRA reported in the Eastern region between January 1st, 2010 and December 31st, 2012. The incidence rates for CRA in Western region remained low at 0.03 cases per 1,000 patient admissions although this represented a 2-fold increase from 2011 (0.01 cases per 1,000 patient admissions in 2011 vs. 0.03 cases per 1,000 patient admissions in 2012, $p < 0.052$).

In the Central region, the incidence rate of CRA decreased in 2011 to 0.004 cases per 1,000 patient admissions from 0.03 cases per 1,000 patient admissions in 2010 ($p < 0.0001$). Only one case of CRA was reported among 23 hospitals in the Central region. In 2012, seven cases of CRA were reported from 24 hospitals for a rate of 0.02 cases per 1,000 patient admissions.

Table 4. Number of CRA* cases and incidence rates per 1,000 patient admissions and 10,000 patient-days, by region, from January 1, 2010 to December 31, 2012 (n=22)

Region	2010	2011	2012
Western			
No. of cases	3	1	4
No. of total patient admissions	140,472	140,472	150,417
No. of total patient-days	1,148,779	1,207,701	1,237,910
Rate per 1,000 patient admissions	**0.02**	**0.01**	**0.03**
Rate per 10,000 patient-days	**0.03**	**0.01**	**0.03**
No. of reporting hospitals	7	7	7
Central			
No. of cases	6	1	7
No. of total patient admissions	228,347	285,634	347,129
No. of total patient-days	1,448,172	2,100,545	2,575,613
Rate per 1,000 patient admissions	**0.03**	**0.004**	**0.02**
Rate per 10,000 patient-days	**0.04**	**0.005**	**0.03**
No. of reporting hospitals	20	23	24
Eastern			
No. of cases	0	0	0
No. of total patient admissions	83,275	87,095	91,286
No. of total patient-days	763,075	817,475	836,710
Rate per 1,000 patient admissions	**0.00**	**0.00**	**0.00**
Rate per 10,000 patient-days	**0.00**	**0.00**	**0.00**
No. of reporting hospitals	6	7	7

*CRA=Carbapenem-Resistant *Acinetobacter*

Carbapenemase-producing Organisms

Table 5 provides the number and proportion of carbapenamase producers (CPO) cases reported nationally and by geographic region. A total of 154 CGNB were found to be carbapenamase producers. Of these, 145 were fully resistant to carbapenem, while the remaining nine CPO had intermediate resistance to carbapenem.

The last column illustrates the proportion of CRGNB isolates by region that were CPOs. The greatest proportion of CPO cases was identified in central Canada. Overall, more than a third (35.1%) of CRGNB was a CPO.

Table 5. Number and proportion of CPO* isolates by region, 2010-2012 (n=154)

Region	No. of hospitals	No. of isolates submitted	No. of CRGNB**	No. of CPO	Proportion of CPO among CRGNB isolates (%)
West	7 of 7	242	169	26	15.4
Central	11 of 24	354	265	127	47.9
East	3 of 7	7	5	1	20.0
Canada	21 of 38	603	439	154	35.1

*CPO=Carbapenemase-producing organism (CPO)
**CRGNB=Carbapenem resistant Gram negative bacilli

Figure 1 illustrates the regional distribution of CPO isolates by year. The greatest proportion of CPO isolates was identified in central Canada across all years.

Figure 1. Proportion of CPO isolates by region and year, 2010-2012 (n=154)

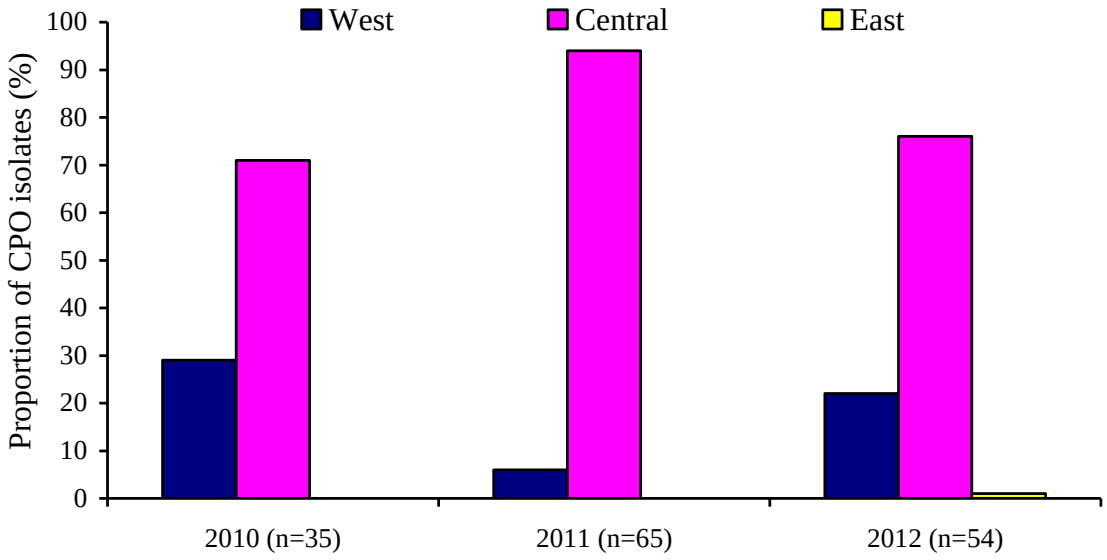


Table 6 provides the number of cases of CPO and the incidence rate by surveillance year. The incidence rate for CPO in 2012 was 0.09 cases per 1,000 patient admissions and 0.12 cases per 10,000 patient-days. The CPO incidence rate increased by 50% in 2011 to 0.12 cases per 1,000 cases from 0.08 cases in 2010 (p = 0.024). The rate decreased by 25% between 2011 and 2012, although this was not statistically significant (p = 0.091).

Table 6. Number of CPO* cases and incidence rates per 1,000 patient-admissions and 10,000 patient-days from January 1, 2010 to December 31, 2012 (n=154)

National	2010	2011	2012
No. of cases	35	65	54
No. of total patient admissions	452,094	520,134	588,832
No. of total patient-days	3,360,026	4,125,721	4,650,233
Rate per 1,000 patient admissions	**0.08**	**0.12**	**0.09**
Rate per 10,000 patient-days	**0.10**	**0.16**	**0.12**
No. of reporting hospitals	33	37	38

*CPO=Carbapenemase-producing organism

The number of cases of CPO and incidence rate by region is shown in Table 7 and Figure 2. The highest incidence rate was in the Central region for all surveillance years. The incidence rate was 0.12 cases per 1,000 patient admissions and 0.16 per 10,000 patient-days in 2012. The incidence rate in the Central region remains higher than the overall national rate for all surveillance years (0.09 cases per 1,000 patient admissions in 2012). The incidence in the Western region was lower than the Central region for all surveillance years. In 2012, the incidence rate in the Western region was 0.08 cases per 1,000 patient admissions compared to 0.12 cases in the Central region. An increase in the 2011 national rate is likely driven by the increased rate in the Central region due to an outbreak in two hospitals.

CPO remains rare in the Eastern region. Only one case was reported in 2012. There were no cases reported in 2010 and 2011. The incidence rate in 2012 was 0.01 cases per 1,000 patient admissions.

Table 7. Number of CPO* cases and incidence rates per 1,000 patient admissions and 10,000 patient-days, by region, from January 1, 2010 to December 31, 2012 (n=154)

Region	2010	2011	2012
Western			
No. of cases	10	4	12
No. of total patient admissions	140,472	140,472	150,417
No. of total patient-days	1,148,779	1,207,701	1,237,910
Rate per 1,000 patient admissions	**0.07**	**0.03**	**0.08**
Rate per 10,000 patient-days	**0.09**	**0.03**	**0.10**
No. of reporting hospitals	7	7	7
Central			
No. of cases	25	61	41
No. of total patient admissions	228,347	285,634	347,129
No. of total patient-days	1,448,172	2,100,545	2,575,613
Rate per 1,000 patient admissions	**0.11**	**0.21**	**0.12**
Rate per 10,000 patient-days	**0.17**	**0.29**	**0.16**
No. of reporting hospitals	20	23	24
Eastern			
No. of cases	0	0	1
No. of total patient admissions	83,275	87,095	91,286
No. of total patient-days	763,075	817,475	836,710
Rate per 1,000 patient admissions	**0.00**	**0.00**	**0.01**
Rate per 10,000 patient-days	**0.00**	**0.00**	**0.01**
No. of reporting hospitals	6	7	7

*CPO=Carbapenemase-producing organism

Figure 2. CPO incidence rates by region per 10,000 patient-days, 2010-2012 (n=154)

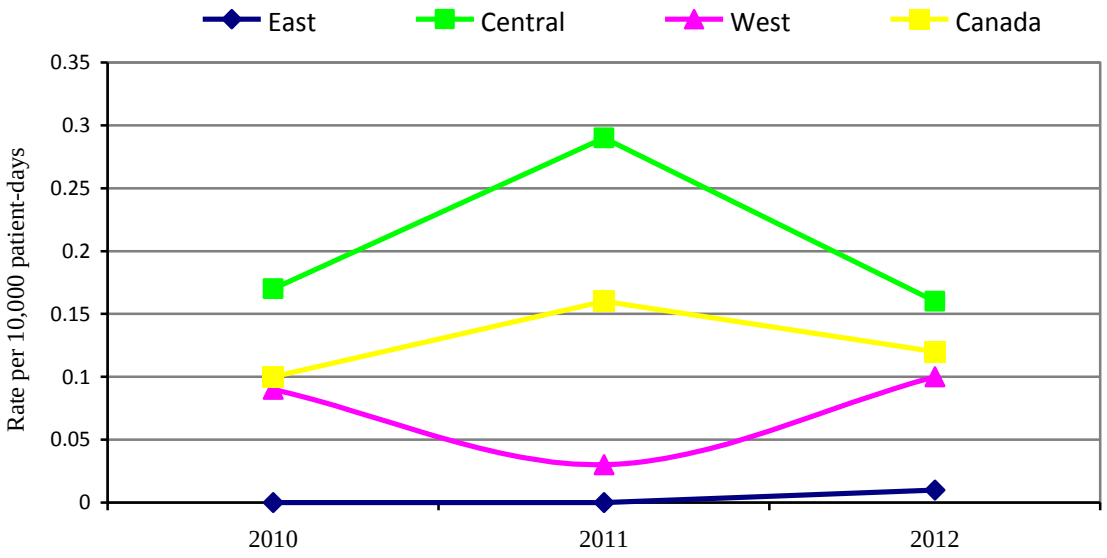


Table 8 shows the proportion of positive isolates among all isolates submitted by bed size. Intermediate size hospitals (200 to 500 beds) represent nearly half of the reporting hospitals (n=10) however large hospitals (>500 beds) submitted the most isolates and had the highest proportion of positive isolates among all isolates submitted (21.1%).

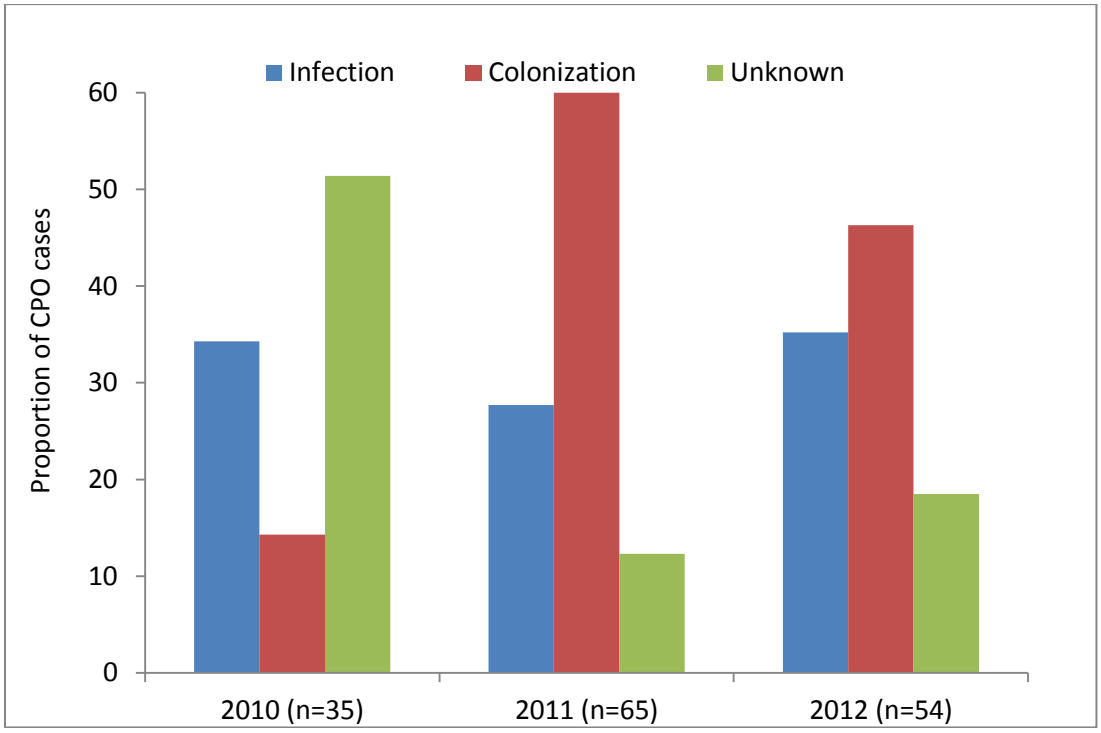
Typically, larger hospitals provide care to complex patients who are characterized as higher risk (e.g. individuals with chronic conditions such as renal failure and cancer as well as patients with longer hospital stay). They also provide specialized services such as burn units, transplant units, trauma centers, specialized cardiac surgery etc. Additionally, larger hospitals often act as referral centres for smaller hospitals. Therefore, these larger hospitals are more likely to have a greater number of CRGNB and CPO cases.

Table 8. Number and incidence rate of CPO isolates by bed size, 2010-2012 (n=154)

Bed size	No. of hospitals	No. of isolates submitted	No. of CPO	Overall Incidence rate of CPO per 10,000 pt days
< 200 beds	3	16	0	0.00
200 - 500 beds	10	121	27	0.05
501+ beds	8	466	127	0.22
Total	**21**	**603**	**154**	**0.13**

Among the 154 CPO cases, 49 (31.8%) were infected, 69 (44.8%) were colonized and classification status was unknown for 36 cases (23.4%). Figure 3 shows the distribution of cases by classification status and year.

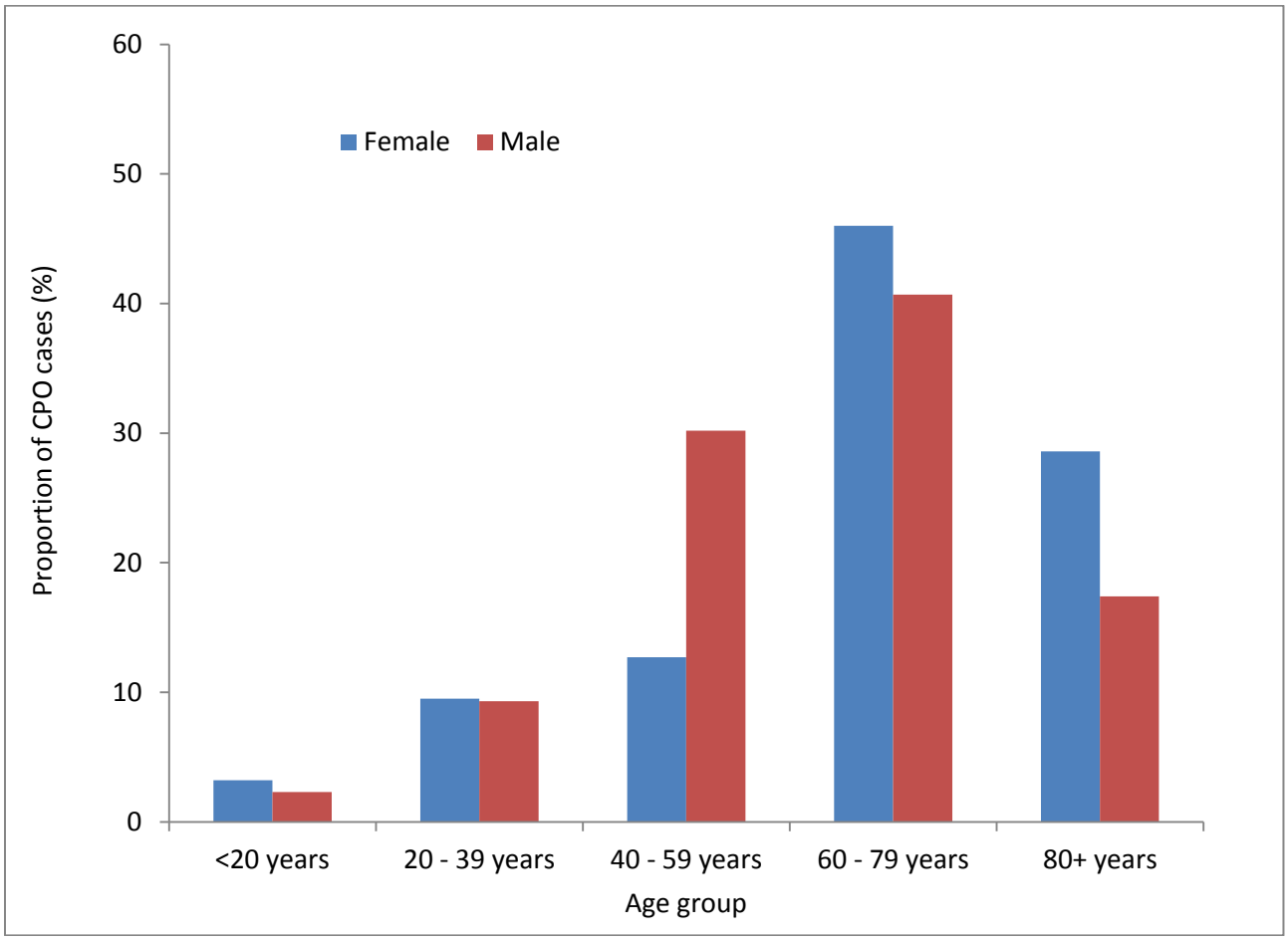
Figure 3. Proportion of CPO cases by classification status and year, 2010-2012 (n=154)



Patient demographics

From 2010 to 2012, data on gender were available for 149 CPO cases. The majority of those cases were male (n=86, 57.7%). Age data were available for 152 cases and the median age was 70.5 years (range 3 months to 98 years). Figure 4 illustrates that a significantly higher proportion of male cases (p =0.012) were observed among those 40 to 59 years while a significantly higher proportion of female cases (p =0.037) were observed among those 60 years and older.

Figure 4. Proportion of CPO cases by age group and sex, 2010-2012 (n=149)



The majority of CPO cases (92.1%, n=139) were hospitalized at the time of specimen collection while the remainder (7.9%, n=12) were seen in outpatient areas such as emergency departments. Evidence of nosocomial (patient to patient) transmission within the facility was reported for 42.6% of CPO cases (46/108).

Patient risk factors

Data on underlying medical conditions were available for 115 CPO cases (74.7%). Eighty-nine per cent of CPO cases (n=102) reported an underlying medical condition. The most commonly reported underlying medical conditions were heart disease and active cancer (Table 9).

Table 9. Underlying medical conditions among CPO cases, 2010-2012 (n=115)

Underlying medical condition	Number	Proportion (%)
Any condition	102	88.7
Heart disease	49	48.0
Cancer (active)	39	38.2
Diabetes	27	26.5
Lung disease (e.g. asthma, COPD)	27	26.5
Kidney disease	21	20.6
Liver disease	10	9.8
Other immunosuppression	6	5.9
Solid organ transplantation	6	5.9
Other	40	39.2

*Note: Cases may report more than one underlying medical condition. Proportion is determined by the number of each underlying medical condition divided by the total CPO cases (n=115)

Data on international travel were available for 114 CPO cases (74.0%). Only twenty-three cases (20.2%) reported international travel within the 12 months prior to diagnosis (Table 10). Six cases reported travel to India, four cases traveled to Europe (Italy, Croatia and Greece), three cases traveled to the Middle East (Israel, Egypt and Lebanon) and one case traveled to the United States. Other countries included Algeria, Ecuador, and China while the location of travel was unknown for six cases. Of the 23 cases that traveled internationally, 16 cases reported that they sought medical care while on international travel. Fifteen cases required inpatient medical care and the type of care was unknown for one case. No cases were active members of the Canadian Armed Forces.

Table 10. CPO cases who reported international travel 12 months prior to diagnosis (n=24)

Country	Carbapenemase	Organism	No. of cases	Medical attention received abroad (Y/N)
India	NDM-1	*Providencia rettgeri, K. pneumoniae, E.coli,* Enterobacter sp.	4	Yes (4)
	NDM-7	*E.coli*	1	Yes
	OXA-181	*K.pneumoniae*	1	No
Italy	KPC-3	*K.pneumoniae*	1	Yes
Croatia	VIM-1	Enterobacter sp.	1	Yes
Greece	OXA-23	*A. baumannii*	1	Yes
	KPC-2+VIM-1	*K.pneumoniae*	1	Unknown
Israel	KPC-3	*K.pneumoniae*	1	Yes
Egypt	OXA-48	*A. baumannii*	1	Yes
Lebanon	OXA-23	*A. baumannii*	1	Yes
USA	KPC-3	Enterobacter sp.	1	Yes
Algeria	OXA-23	*A. baumannii*	1	Yes
Ecuador	KPC-2+VIM-1	*K.pneumoniae*	1	Unknown
China	OXA-23	*A. baumannii*	1	Yes
Unknown	KPC-3	*Kluyvera sp, 2 K.pneumoniae,* 2 Enterobacter sp.	5	Yes (2), Unknown (2)
	OXA-181	*K.pneumoniae*	1	Unknown

Patient treatment

Of the 49 infected CPO cases, 39 (79.6%) were treated with antimicrobials. Table11 lists the antimicrobials prescribed to CPO infected cases within two weeks of their diagnosis. The most commonly prescribed antimicrobials were *B*-lactam inhibitors followed by carbapenems.

Table 11. Antimicrobial treatment for CPO infected cases, 2010-2012 (n=39)

Antimicrobial treatment	Number	Proportion (%)
Treated	39	79.6
B-lactam inhibitors	10	25.6
Carbapenem	6	15.4
Aminoglycoside	2	5.1
Cephalosporin	2	5.1
Tigecycline	1	2.6
Colistin	1	2.6
Unknown	17	43.6

Patient outcomes

Data on CPO cases in requiring intensive care unit (ICU) admission were available for 127 cases (82.5%). Of those, no cases were admitted to the ICU due to complications associated with CPO. Twenty-nine cases (22.8%) were already admitted to the ICU at the time of diagnosis. Thirty-day outcome data were available for 120 cases (77.9%). Table 12 shows that of those cases, 104 cases (86.7%) survived and either remained in hospital, were discharged or transferred while 16 cases (13.3%) died. Death was attributable to CPO in three cases while CPO was unrelated to death in 10 cases and in 3 cases it was not possible to determine if CPO was related to death.

Table 12. 30-day outcome for CPO cases, 2010-2012 (n=120)

30-day Outcome	Number	Proportion (%)
Patient survived	104	86.7
Remains in hospital	57	47.5
Discharged or transferred	44	36.7
Unknown	3	2.5
Patient died	16	13.3
CPO primary cause of death	2	1.7
CPO contributed to death	1	0.8
CPO unrelated to death	10	8.3
Unable to determine	3	2.5

Characterization of Carbapenemase-Producing Organisms

Table 13 describes the distribution of CPO isolates by pathogen and type of carbapenemase. *K. pneumoniae* and *Enterobacter* sp are the two most common CPOs in Canada which is attributable to the high proportion of KPC-type carbapenemases isolated from both of these species. Note that a *Klebsiella pneumonia*e isolate produced KPC and VIM, and an *Acinetobacter sp*. isolate produced OXA-23, OXA-58 and IMP-26 thus accounting for 157 carbapenemases.

Table 13. Number of CPO isolates by pathogen and type of carbapenemase, 2010-2012 (n=157)

	Type of carbapenemase						
Pathogen	**KPC**	**NDM**	**OXA-23**	**VIM**	**OXA-48**	**Other**	**Total positive isolates**
Klebsiella pneumoniae	54	11	0	1	5	0	71
Enterobacter sp.	23	1	0	2	0	1	27
Acinetobacter sp.	0	0	15	0	0	3	18
Serratia sp.	12	0	0	0	0	5	17
Escherichia coli	6	4	0	0	2	2	14
Citrobacter sp.	4	0	0	0	0	0	4
Klebsiella oxytoca	2	0	0	0	0	0	2
Kluyvera sp.	1	0	0	0	0	0	1
Morganella morganii	0	1	0	0	0	0	1
Pantoea sp.	1	0	0	0	0	0	1
Providencia rettgeri	0	1	0	0	0	0	1

*Other carbapenemase includes: GES, IMP, NMC, OXA-24, SME, 0XA-58

Table 14 shows the number of CPO isolates by site and classification. The most common site of infection was urine while the most common site of colonization was stool.

Table 14. Number of CPO isolates by site and classification, 2010-2012 (n=154)

Site	Infection	Colonization	Unknown	Total	Proportion of all CPO isolates (%)
Urine	18	14	14	46	29.9
Stool	0	30	3	33	21.4
Sputum	6	4	8	18	11.7
Skin/soft tissue/wound	9	0	0	9	5.8
Blood	8	0	2	10	6.5
Surgical site	6	3	1	10	6.5
Other	4	18	6	28	18.2
Total	**51**	**69**	**34**	**154**	**100**

Figure 5 illustrates the proportion of isolates harbouring carbapenemases between 2010 and 2012. In all three years $bla_{\text{KPC-type}}$ (*Klebsiella pneumoniae* carbapenamase, KPC) were observed in the highest proportion followed by $bla_{\text{NDM-1}}$ (New Delhi Metallo-beta-lactamase, NDM-1). Note that a *Klebsiella pneumoniae* isolate produced KPC and VIM, and an *Acinetobacter sp*. isolate produced OXA-23, OXA-58 and IMP-26 thus accounting for 157 carbapenemases.

Figure 5. Propotion of CPO isolates by type of carbapenemase and year, 2010-2012 (n-=157)

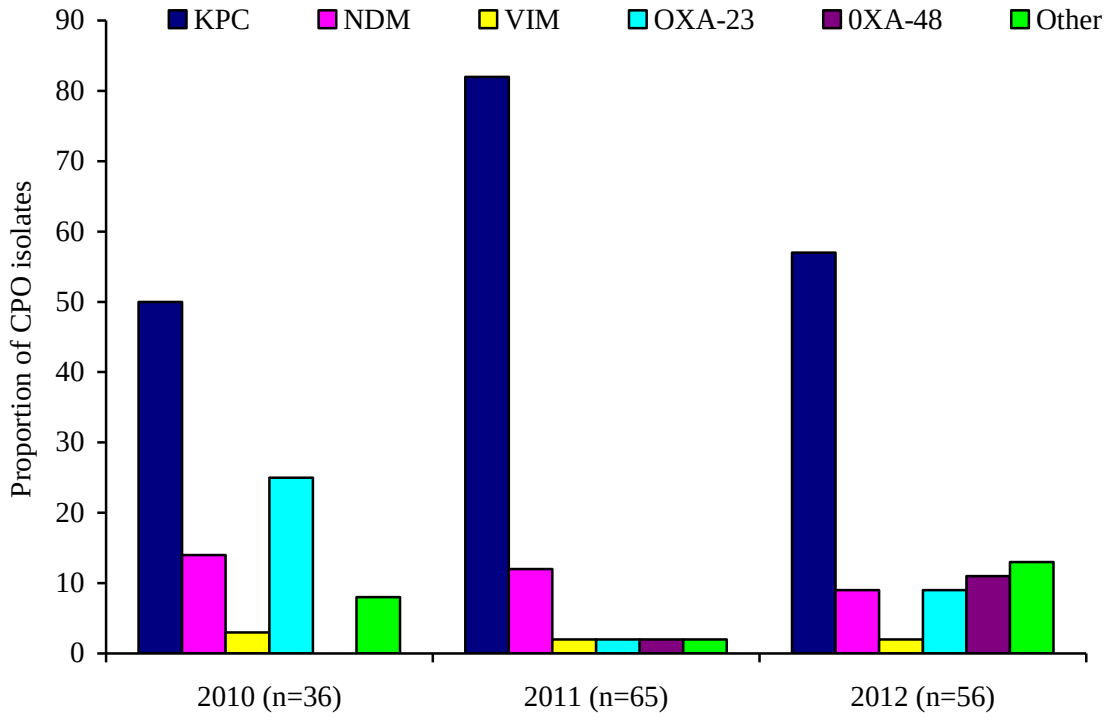
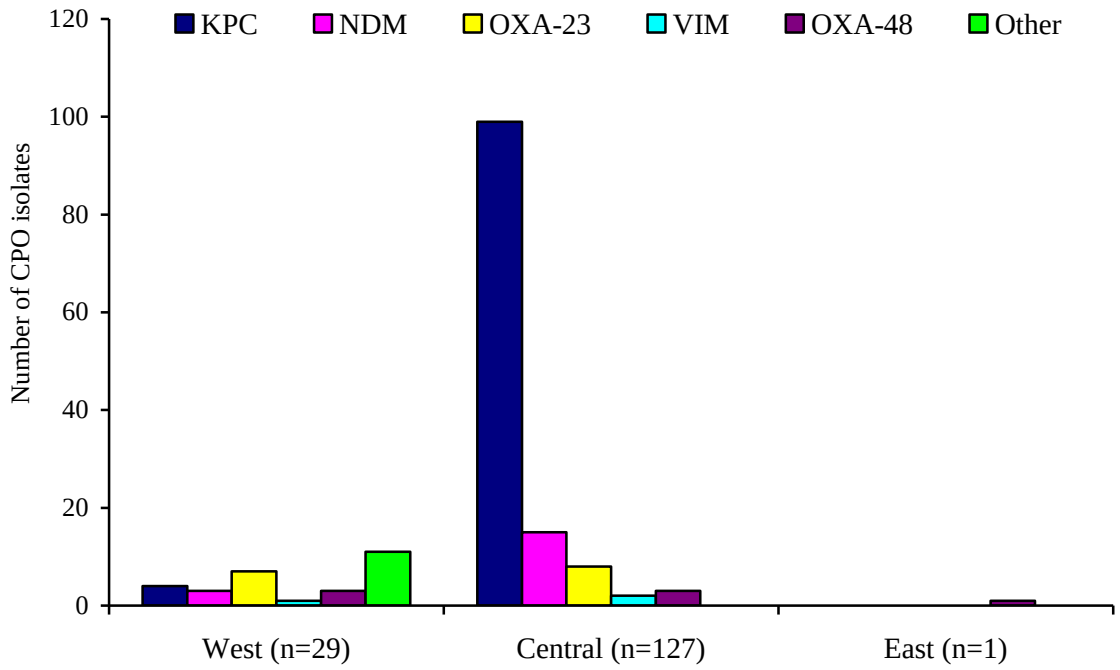


Figure 6 illustrates the regional distribution of isolates by type of carbapenemase. The greatest number of CPO isolates cases were identified in central Canada across all years. This is likely due to a KPC outbreak reported by one hospital in the central region. Note that a *Klebsiella pneumoniae* isolate produced KPC and VIM, and an *Acinetobacter sp*. isolate produced OXA-23, OXA-58 and IMP-26 thus accounting for 157 carbapenemases.

Figure 6. Number of CPO isolates by region and type of carbapenemase, 2010-2012 (n=157)



Antimicrobial susceptibility testing of Carbapenemase-Producing Organisms

From 2010 to 2012, there was a significant decrease in isolates harbouring bla_{KPC} that were resistant to ciprofloxacin ($p<0.0001$), amikacin ($p<0.0001$), tobramycin (0.0214) and trimethoprim/sulfamethoxazole ($p<0.0001$). Additionally, multiple drug resistant (MDR) observed in bla_{KPC} producers significantly decreased ($p<0.0001$) over the three years from 100.0% in 2010 to 84.4% in 2012. These observations are due to a clonal outbreak of *K.pneumoniae* observed in 2011 which had similar susceptibility data.

Limitations

Several limitations should be considered when interpreting the data presented in this report. First, surveillance data understates the magnitude of CPO and subsequently does not represent the total number of CPO cases in Canada. Surveillance data can only tell us about patients who have been tested and diagnosed with CPO and not those who remain untested and undiagnosed.

Second, participating hospitals may not be representative of all Canadian hospitals. Hospitals which submit CPO data to the Agency are large, tertiary acute care centres located in major cities. CPO data from small hospitals and those in rural and northern areas are underreported.

Third, CLSI breakpoints for carbapenems have been lowered since the start of this surveillance, where susceptible is now <0.5, <1 and <1 mg/L for ertapenem, meropenen and imipenem, respectively, allowing for detection of carbapenemases with low MICs of carbapenems such as KPC and OXA-48.

Fourth, it was not possible to correlate data regarding antibiotic prescribing practices and implementation of infection prevention and control measures with the occurrence of CPO, as the Agency does not collect information on these practices.

Finally, healthcare-associated infection surveillance methodologies are not standardized across countries. For this reason, caution must be used when comparing rates between countries without knowing the details of their surveillance strategies. Currently no data regarding the percentage of isolates resistant to carbapenems are reported to the Agency. As such, no comparisons to international data using this indicator are made in this report.

Discussion

The surveillance data in this report show that carbapenemase-producing organisms (CPO) remain relatively uncommon in most acute-care hospitals in Canada, especially in the eastern region. Carbapenemase producers are mainly identified among *Klebsiella pneumoniae* and the majority of CPO cases (92.1%, n=139) were hospitalized at the time of specimen collection. In addition, 42.6% of CPO cases were the result of nosocomial transmission in one CNISP hospital in 2011.

Canadian surveillance data presented in this report show that CPO rates have remained stable over the three years since the Agency began conducting surveillance. However, an increase in the national rate was observed in 2011 but was largely driven by a KPC outbreak in the central region. Several other countries such as Belgium[5], France[6] and the United States[7] have reported an increase in carbapenemase-producing enterobactereciae (CPE). They have suggested that the apparent increase may be due to the spreading of these microorganisms or may reflect the application of more effective detection methods by hospitals and laboratories.

Recent surveillance data from three surveillance systems in the United States[7]; the National Healthcare Safety Network (NHSN), the National Nosocomial Infection Surveillance Program (NNIS) and the Emerging Infections Program (EIP) align with Canadian trends. They report that carbapenem-resistant enterobacteriaceae (CRE) is relatively uncommon in most acute-care hospitals in the United States, that regional variation in the distribution of cases has been observed as well as a higher proportion of cases among larger, teaching hospitals and the majority of cases are associated with recent healthcare exposure. It is important to note that the United States reports CRE data while Canadian data focuses on Gram-negative bacilli which produce carbapenemases.

As described, regional differences in CPO rates are observed across Canada. A major contributor to this variation is a KPC outbreak reported in the central region. Regional variation of rates has also been reported by the United States[7,8] and among European countries.[9,10] Factors which may influence the regional emergence and spread of carbapenemases include local antimicrobial usage patterns, different policies or implementation of infection control measures, the role of interfacility transfers as well as differences in screening practices and detection methods across hospitals and laboratories. Importation of carbapenemases from other countries as a consequence of travel and medical tourism may also play an important role in the regional distribution of cases as hospitals in larger, urban cities may serve patients who are more likely to have travelled internationally.

In many cases, the spread of carbapenemase-producing organisms results from hospitalization abroad. Therefore cases without importation links may represent local acquisition. Our surveillance findings indicate a significant proportion of non-travel associated CPO positive patients as only 20% of cases reported foreign travel within the year prior to diagnosis. Of those few actually sought medical care while abroad. In addition, outbreaks where CPO has been isolated from patients with no history of foreign travel have also been reported by Canadian

hospitals.[3,11-12] These findings are concerning as they imply the local establishment and spread of carbapenemase-producing organisms in Canada. Furthermore, France[6] and the United States[13] have also reported local acquisition and suggest that these organisms may be spreading through the transfer of colonized patients between healthcare facilities within the country.

Carbapenems represent the last line of antibiotics that are still effective for treating many gram-negative infections. The increasing trends in carbapenem resistance and carbapenemase producers reported by other countries is concerning as it may only be a matter of time before we observe similar increasing trends in Canadian acute-care facilities and because, in response, the Agency has developed a document to provide infection prevention and control guidance for healthcare workers in the management of patients colonized or infected with carbapenem-resistant Gram negative bacilli, including carbapenemase-producing organisms. The document can be found at http://www.phac-aspc.gc.ca/nois-sinp/guide/ipcm-mpci/ipcm-mpci-eng.php.[1]

In conclusion, the burden of CPO among Canadian acute-care hospitals remains low, yet the global dissemination of gram-negative bacilli that have acquired carbapenemase genes is a growing public health concern. Moreover, the significant proportion of non-travel associated CPO positive patients suggests the local establishment and spread of carbapenemase-producing organisms in Canada. Thus, the continued surveillance of carbapenemase-producing organisms will enable the Agency to continue to monitor the spread and burden of CPO in Canadian acute-care hospitals.

Appendix 1. Data Sources

The following are members of the Canadian Nosocomial Infection Surveillance Program who submitted CRGNB data to the Public Health Agency of Canada:

Natalie Bridger, Health Sciences Centre, St. John's, Newfoundland and Labrador
Elizabeth Bryce, Vancouver General Hospital, Vancouver, British Columbia
John Conly, Foothills Medical Centre, Calgary, Alberta
Andre Dascal, SMBD-Jewish General Hospital, Montreal, Quebec
Janice Deheer, Kelowna General Hospital, Kelowna, British Columbia
John Embil, Health Sciences Centre, Winnipeg, Manitoba
Joanne Embree, Health Sciences Centre, Winnipeg, Manitoba
Gerard Evans, Kingston General Hospital, Kingston, Ontario
Sarah Forgie, Stollery Children's Hospital, Edmonton, Alberta
Charles Frenette, McGill University Health Centre, Montreal, Quebec
Gregory German, Queen Elizabeth Hospital, Charlottetown, Prince Edward Island
David Haldane, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia
Deanna Hembroff, University Hospital Northern BC, Prince George, British Columbia
Elizabeth Henderson, Peter Lougheed Centre, Calgary, Alberta
Michael John, London Health Sciences Centre, London, Ontario
Lynn Johnston, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia
Kevin Katz, North York General Hospital, Toronto, Ontario
Pamela Kibsey, Royal Jubilee Hospital, Victoria, British Columbia
Magdalena Kuhn, South East Regional Health Authority, Moncton, New Brunswick
Joanne Langley, IWK Health Centre, Halifax, Nova Scotia
Camille Lemieux, University Health Network, Toronto, Ontario
Nicole Le Saux, Children's Hospital of Eastern Ontario, Ottawa, Ontario
Mark Loeb, Hamilton Health Sciences Corporation, Hamilton, Ontario
Susan Richardson, Hospital for Sick Children, Toronto, Ontario
Allison McGeer, Mount Sinai Hospital, Toronto, Ontario
Dominik Mertz, Hamilton Health Sciences Corporation, Hamilton, Ontario
Mark Miller, SMBD-Jewish General Hospital, Montreal, Quebec
Dorothy Moore, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec
Caroline Quach, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec
Suzanne Pelletier, Health Sciences North, Sudbury, Ontario
Virginia Roth, The Ottawa Hospital, Ottawa, Ontario
Andrew Simor, Sunnybrook Health Sciences Centre, Toronto, Ontario
Stephanie Smith, University of Alberta Hospital, Edmonton, Alberta
Kathryn Suh, The Ottawa Hospital, Ottawa, Ontario
Geoffrey Taylor, University of Alberta Hospital, Edmonton, Alberta
Eva Thomas, Children's and Women's Health Center, Vancouver, British Columbia
Nathalie Turgeon, Hôtel-Dieu de Québec du CHUQ, Quebec

Mary Vearncombe, Sunnybrook Health Sciences Centre, Toronto, Ontario
Joseph Vayalumkal, Alberta Children's Hospital, Calgary, Alberta
Karl Weiss, Maisonneuve-Rosemont Hospital, Montreal, Quebec
Alice Wong, Royal University Hospital, Saskatoon, Saskatchewan

We acknowledge the contribution of the Infection Control Practitioners and laboratories at each participating hospital.

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