

Gram-negative pathogens from Canadian hospitals: 17 years of results from the CANWARD study (2007–23)

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Objectives: CANWARD is a Canadian Antimicrobial Resistance Alliance (CARA)/Health Canada partnered national surveillance study established in 2007 to annually assess the *in vitro* activities of commonly tested and recently approved antimicrobial agents for bacterial pathogens isolated from patients receiving care in Canadian hospitals.

Methods: In total, 34 155 Gram-negative pathogens were tested using the CLSI reference broth microdilution method.

Results: In total, 39.4%, 37.1%, 17.7% and 5.8% of isolates tested were from respiratory, blood, urine and wound specimens, respectively; 31.1%, 23.9%, 19.0%, 18.5% and 7.5% of isolates were from patients in medical wards, emergency rooms, ICUs, hospital clinics and surgical wards. In total, 51.8% of isolates were from male patients; and 10.1%, 40.7% and 49.2% of isolates were from patients aged ≤17, 18–64 and ≥65 years. The most common Gram-negative pathogens received were: *Escherichia coli* (34.9%), *Pseudomonas aeruginosa* (17.5%) and *Klebsiella pneumoniae* (11.6%). An ESBL-producing phenotype was identified in 8.4% of *E. coli* and 5.6% of *K. pneumoniae* isolates. Percent susceptible values for *E. coli* included: 100% for meropenem/vaborbactam and imipenem/relebactam; >99% for ceftazidime/avibactam, meropenem and ceftolozane/tazobactam; 95.6% for piperacillin/tazobactam; and 73.9% for ciprofloxacin. Percent susceptible values for *K. pneumoniae* included: >99% for meropenem/vaborbactam, imipenem/relebactam, ceftazidime/avibactam and meropenem; 97.4% for ceftolozane/tazobactam; 91.9% for piperacillin/tazobactam; and 87.0% for ciprofloxacin. Percent susceptible values for *P. aeruginosa* included: 96.6% for ceftolozane/tazobactam; 92.6% for ceftazidime/avibactam; 92.0% for imipenem/relebactam; 79.9% for piperacillin/tazobactam; ceftazidime 78.1%; 78.0% for meropenem; and 68.6% for ciprofloxacin.

Conclusions: The CANWARD surveillance study has provided 17 years of reference antimicrobial susceptibility testing data.

Introduction

Infections caused by antimicrobial-resistant bacterial pathogens are of worldwide concern.^{1–3} Important Gram-negative pathogens, including ESBL-producing Enterobacterales, and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*, are increasing in prevalence globally.^{4–7} Treatment

options for antimicrobial-resistant organisms can be limited particularly if isolates demonstrate an MDR or XDR phenotype.^{4–7}

Proposed solutions to the global problem of antimicrobial resistance include surveillance, antimicrobial stewardship programs and new agent development.^{2,3} In 2007, we initiated CANWARD, an ongoing, annual, national, Canadian Antimicrobial Resistance Alliance (CARA)/Health Canada partnered surveillance study. CANWARD

serves to assess bacterial pathogens causing infections in patients seeking care in tertiary care medical centres across Canada as well as their *in vitro* susceptibility to commonly tested and recently approved antimicrobial agents.^{8,9} In the current report, we summarize our data for Gram-negative pathogens causing infections in Canadian patients from 2007 to 2023, inclusive, and the *in vitro* susceptibilities (MIC₅₀ and MIC₉₀) of those isolates. It should be stated that since many newer β -lactam/ β -lactamase inhibitor combination agents such as ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam as well as the siderophore cephalosporin cefiderocol are not yet Health Canada approved, or have only very recently obtained Health Canada approval, only limited testing has been performed with these agents. Additionally, we do not report on investigational non-FDA approved β -lactam/ β -lactamase inhibitor combination agents.^{10–13}

Materials and methods

Bacterial isolates

As part of the CANWARD study, tertiary-care medical centres (12 centres in 2007, 10 in 2008, 15 in 2009, 14 in 2010, 15 in 2011, 12 in 2012, 15 in 2013, 13 in 2014, 13 in 2015, 13 in 2016, 14 in 2017, 12 in 2018, 13 in 2019, 10 in 2020, 10 in 2021, 9 in 2022 and 8 in 2023) representing 8 of 10 provinces in Canada submitted pathogens isolated from patients attending emergency rooms, medical and surgical wards, ICUs and hospital clinics.^{8,9} The sites were geographically distributed in a population-based fashion. From 2007 to 2023, each study site was asked to submit clinically significant isolates from bloodstream, respiratory, wound and urinary tract infections as defined by their individual hospital criteria (consecutive, one per patient, per infection site) from inpatients and outpatients attending their hospital. By year, each centre was asked to provide: 2007–200 respiratory, 50 wound and 100 urine isolates, and 30 bloodstream isolates/month; 2008–150 respiratory, 50 wound and 100 urine isolates, and 20 bloodstream isolates/month; 2009–10–100 respiratory, 50 wound and 50 urine isolates, and 15 bloodstream isolates/month (January–November); and 2011–23–100 respiratory, 25 wound and 25 urine isolates, and 10 bloodstream isolates/month (January to October). Surveillance swabs, eye, ear, nose and throat swabs were excluded. Anaerobic bacteria and fungi were also excluded from the primary CANWARD objectives, except for yeast from bloodstream infections. Yeast from bloodstream infections was included in two components of CANWARD: (i) the assessment of the epidemiology of causative agents of bloodstream infections in Canadian hospitalized patients and (ii) the *Candida*-specific objective in which antifungal susceptibility testing was performed (data was published previously¹⁴ and is not presented in this manuscript). Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics (e.g. Gram stain, colonial morphology, haemolysis patterns) and antimicrobial susceptibility patterns.^{8,9} Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media and stocked in skim milk at -80°C until antimicrobial susceptibility testing was performed.^{8,9} Isolate viability using these methods was >99%. Patient demographics collected with the isolates included biological sex, age, hospital location and specimen source. From 2007 to 2023, annual total numbers of Gram-negative isolates collected were 4215 in 2007, 2750 in 2008, 2965 in 2009, 2735 in 2010, 2249 in 2011, 1549 in 2012, 2007 in 2013, 1727 in 2014, 1797 in 2015, 1836 in 2016, 2071 in 2017, 1763 in 2018, 1904 in 2019, 1452 in 2020, 1486 in 2021, 1450 in 2022 and 1213 in 2023 (1, 2). The focus of this report was the 34 155 Gram-negative pathogens collected by CANWARD from 2007 to 2023. The decline in isolates per year from 2007 to 2011 is mostly related

to a decrease in the number of isolates requested from each participating institution and not extensive changes to the annual collection protocol.

The CANWARD study receives annual approval by the University of Manitoba Research Ethics Board (H2009:059).

Antimicrobial susceptibility testing

Following two subcultures from frozen stock, the *in vitro* activity of antimicrobial agents was determined by the reference broth microdilution method in accordance with CLSI guidelines.¹⁵ Antimicrobial agents were either obtained as laboratory-grade powders from their respective manufacturers or purchased from Sigma-Aldrich Canada (Oakville, ON, Canada). Stock solutions were prepared and dilutions made as described by CLSI.¹⁵ MICs were determined using 96-well custom-designed microtitre plates made in-house by our laboratory. Quality control followed CLSI guidelines.¹⁵ MICs were interpreted according to CLSI breakpoints¹⁶ except for tigecycline where FDA MIC breakpoints (<https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria>) were used and for ceftobiprole, where MICs were interpreted according to breakpoints established by Health Canada: Enterobacteriaceae, ≤ 1 mg/L susceptible, 2 mg/L intermediate and ≥ 4 mg/L resistant. Isolates selected for antimicrobial susceptibility testing included the top 20 pathogens and a variety of less common Gram-negative bacilli. Development of a centralized database for the CANWARD study results was created by IHMA (Schaumburg, IL, USA).

Identification of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates

Potential ESBL-producing isolates of *Escherichia coli* and *Klebsiella pneumoniae* were screened for by first identifying isolates with a ceftriaxone and/or ceftazidime MIC of ≥ 1 mg/L and then confirming ESBL production using the CLSI double disc diffusion method, as previously described.^{9,17}

Results

Patient demographics and specimen types

A total of 34 155 Gram-negative isolates were collected between 2007 and 2023; 17 684 (51.8%) of the isolates were from males and 16 468 (48.2%) were from females (biological sex was not indicated for three isolates). By specimen source, 39.4% ($n = 13\,440$) of isolates were from respiratory sources, 37.1% ($n = 12\,688$) were from blood, 17.7% ($n = 6037$) were from urine and 5.8% ($n = 1990$) were from wounds. By patient age group, 3459 (10.1%), 13 898 (40.7%) and 16 795 (49.2%) isolates were from patients aged ≤ 17 years, 18–64 years and ≥ 65 years, respectively (patient age was not indicated for three isolates). In regard to hospital location, 10 635 (31.1%), 8153 (23.9%), 6476 (19.0%), 6323 (18.5%) and 2565 (7.5%) isolates were from patients in medical wards, emergency rooms, ICUs, clinics and surgical wards, respectively (hospital location not indicated for three isolates).

The geographical locations of the referring centres were as follows: 5457 (16.0%) from British Columbia/Alberta, 5707 (16.7%) from Manitoba/Saskatchewan, 9661 (28.3%) from Ontario, 8972 (26.2%) from Quebec and 4358 (12.8%) from New Brunswick/Nova Scotia.

Most common organisms isolated

In total, 61 066 Gram-positive and Gram-negative isolates were isolated by CANWARD from 2007 to 2023. The 20 most common organisms isolated ($n = 55160$, 90.3% of isolates) included

31 128 (56.4%) Gram-negative bacilli and 23 469 (42.5%) Gram-positive cocci. No significant changes occurred over the study period (2007–23) in the proportions of individual Gram-negative bacilli and Gram-positive cocci causing infections (bacteraemia, respiratory, urinary or wound). For example, *E. coli* was consistently the most common pathogen causing urinary tract infections each year.

Of all 34 155 Gram-negative bacilli isolated by CANWARD from 2007 to 2023, the 10 most common accounted 89.9% ($n = 30\,691$) of isolates (Table 1). *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *Haemophilus influenzae* and *Enterobacter cloacae* were the most common Gram-negative organisms (Table 1).

Antimicrobial activity against Gram-negative bacilli

The *in vitro* activity of various antimicrobials against frequently isolated Gram-negative bacilli is displayed in Table 2. For *E. coli*,

Table 1. The 10 most frequent Gram-negative bacterial^a pathogens isolated from common patient specimens in Canadian hospital laboratories from 2007 to 2023

Rank	Organism	No. of isolates	% of total isolates
1	<i>Escherichia coli</i>	11 932	34.9
2	<i>Pseudomonas aeruginosa</i>	5961	17.5
3	<i>Klebsiella pneumoniae</i>	3973	11.6
4	<i>Haemophilus influenzae</i>	2351	6.9
5	<i>Enterobacter cloacae</i>	1659	4.9
6	<i>Stenotrophomonas maltophilia</i>	1210	3.5
7	<i>Klebsiella oxytoca</i>	1060	3.1
8	<i>Serratia marcescens</i>	1003	2.9
9	<i>Proteus mirabilis</i>	957	2.8
10	<i>Moraxella catarrhalis</i>	585	1.7
Other ^b		3464	10.1
Total		34 155	

Organisms isolated from blood, respiratory, urine and wound specimens.

^aList also contains *Candida* spp. collected as part of the CANWARD blood-stream infection objective. The *Candida* spp. collected specifically for the *Candida* objective are not included.¹⁴

^bOther: *Achromobacter* spp., *Acinetobacter* spp., *Aeromonas* spp., *Aggregatibacter* spp., *Agrobacterium* spp., *Alcaligenes* spp., *Bordetella* spp., *Branhamella* spp., *Burkholderia* spp., *Campylobacter* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Cedecea* spp., *Chryseobacterium* spp., *Citrobacter* spp., *Comamonas* spp., *Cronobacter* spp., *Cupriavidus* spp., *Delftia* spp., *Eikenella* spp., *Elizabethkingia* spp., *Empedobacter* spp., *Enterobacter* spp., *Escherichia* spp., *Ewingella* spp., *Flavobacterium* spp., *Haemophilus* spp., *Hafnia* spp., *Klebsiella* spp., *Kluyvera* spp., *Ledercia* spp., *Legionella* spp., *Lelliottia* spp., *Moraxella* spp., *Morganella* spp., *Myroides* spp., *Neisseria* spp., *Ochrobactrum* spp., *Oligella* spp., *Pantoea* spp., *Paracoccus* spp., *Pasteurella* spp., *Phenylobacterium* spp., *Pluralibacter* spp., *Proteus* spp., *Providencia* spp., *Pseudocitrobacter* spp., *Pseudomonas* spp., *Psychrobacter* spp., *Rahnella* spp., *Ralstonia* spp., *Raoultella* spp., *Rhizobium* spp., *Roseomonas* spp., *Salmonella* spp., *Serratia* spp., *Shigella* spp., *Sphingobacterium* spp., *Sphingomonas* spp., *Stenotrophomonas* spp., *Vibrio* spp. and *Yersinia* spp.

percent resistant values were >20% for trimethoprim/sulfamethoxazole, ciprofloxacin and levofloxacin. The most active agents against *E. coli* (percent susceptible values >99%) were ceftazidime/avibactam, ceftolozane/tazobactam, ertapenem, imipenem/relebactam, meropenem, meropenem/vaborbactam, plazomicin and tigecycline. For *K. pneumoniae*, percent susceptible values were >99% for ceftazidime/avibactam, imipenem/relebactam, meropenem and plazomicin.

Percent susceptible values against ESBL-producing *E. coli* were 99.9% for meropenem, 99.6% for ertapenem, 95.6% for piperacillin/tazobactam and <50% for fluoroquinolones and trimethoprim/sulfamethoxazole (Table 2). Percent susceptible values against ESBL-producing *K. pneumoniae* were 95.5% for meropenem, 89.9% for ertapenem, 52.0% for piperacillin/tazobactam and <50% for fluoroquinolones and trimethoprim/sulfamethoxazole.

For *E. cloacae*, >99% of isolates were susceptible to ceftazidime/avibactam, plazomicin and meropenem (Table 2). All isolates of *P. mirabilis* isolates were susceptible to ceftazidime/avibactam and meropenem. For *K. oxytoca*, >99% of isolates were susceptible to ceftazidime/avibactam, ertapenem, imipenem/relebactam, meropenem and plazomicin. For *Serratia marcescens*, >99% of isolates were susceptible to ceftazidime/avibactam and meropenem. For *Klebsiella aerogenes*, >99% of isolates were susceptible to amikacin, ceftazidime/avibactam, gentamicin, meropenem and plazomicin. For *Citrobacter freundii*, >99% of isolates were susceptible to ceftazidime/avibactam, meropenem and plazomicin.

Ceftolozane-tazobactam, which in Canada is primarily used to treat infections caused by MDR *P. aeruginosa* was the most active (96.6% susceptible) agent tested against *P. aeruginosa* while percent susceptible values were <80% for cefepime, ceftazidime, fluoroquinolones, meropenem and piperacillin/tazobactam (Table 2). Percent susceptible values were >97% for all agents tested against *H. influenzae* except for ampicillin (80.0%), clarithromycin (87.7%) and trimethoprim/sulfamethoxazole (77.9%). Greater than 97% of *Stenotrophomonas maltophilia* isolates were susceptible to trimethoprim/sulfamethoxazole. For *Acinetobacter baumannii*, percent susceptible values were >95% for amikacin and imipenem/relebactam, while only 1.9% of strains were resistant to colistin (Table 2).

Discussion

The CANWARD study is the only national, ongoing, prospective, CARA/Health Canada partnered surveillance study assessing antimicrobial activity against pathogens received from patients accessing care in Canadian hospitals (hospital clinics, emergency rooms, medical and surgical wards, and ICUs).^{8,9} A total of 61 066 organisms were collected between 2007 and 2023, inclusive, of which 34 155 were Gram-negative organisms (Table 1). As an *in vitro* susceptibility study, the evaluation of antimicrobial activity was based solely upon population MIC values and the interpretation of those values as susceptible, intermediate or resistant by established criteria.¹⁶ Agent potency, which depends upon an agent's pharmacokinetics, along with *in vitro* susceptibility (i.e. pharmacodynamics) and dosing also require consideration as clinically relevant measures when viewing MIC values and their interpretation.^{5,6}

Table 2. Antimicrobial susceptibility testing results for the most common Gram-negative bacilli isolated from common patient specimens in Canadian hospital laboratories from 2007 to 2023

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% Susceptible	% Intermediate	% Resistant	MIC ₅₀	MIC ₉₀	MIC range
<i>Escherichia coli</i> (11 932)						
Amikacin	95.0	3.9	1.1	≤2	4	≤2->64
Amoxicillin/clavulanate	79.8	13.2	7.0	4	16	≤0.06->32
Cefazolin	67.6	12.0	20.4	2	128	≤0.5->128
Cefepime	92.5	2.7	4.8	≤1	≤1	≤1->32
Cefoxitin	90.9	5.1	4.0	4	8	≤0.06->32
Ceftazidime	91.1	1.4	7.5	≤0.5	4	≤0.5->32
Ceftazidime/avibactam	99.9		0.1	≤0.25	≤0.25	≤0.25->16
Ceftobiprole ^b	91.2	0.2	8.6	≤1	≤1	≤1->16
Ceftolozane/tazobactam	99.1	0.2	0.7	0.25	0.5	≤0.12->64
Ceftriaxone	89.4	0.3	10.3	≤1	4	≤1->64
Ciprofloxacin	73.9	1.7	24.4	≤0.06	>16	≤0.06->16
Colistin		99.6	0.4	0.25	0.5	≤0.06->16
Ertapenem	99.6	0.2	0.2	≤0.06	≤0.06	≤0.06->32
Fosfomycin	98.8	0.8	0.4	≤1	4	≤1->512
Gentamicin	90.0	0.5	9.5	≤0.5	4	≤0.5->32
Imipenem/relebactam	100			0.25	0.25	≤0.03-0.5
Levofloxacin	76.7	1.6	21.7	≤0.06	16	≤0.06->32
Meropenem	99.9		0.1	≤0.12	≤0.12	≤0.12->32
Meropenem/vaborbactam	100			≤0.06	≤0.06	≤0.06-0.5
Moxifloxacin				≤0.06	>16	≤0.06->16
Nitrofurantoin	97.1	1.8	1.1	16	32	≤0.5->512
Piperacillin/tazobactam	95.6	1.6	2.8	2	4	≤1->512
Plazomicin	99.3	0.6	0.1	0.5	1	≤0.03->64
Tigecycline ^c	99.9	0.1		0.25	0.5	≤0.03-4
Trimethoprim/sulfamethoxazole	72.7		27.3	≤0.12	>8	≤0.12->8
<i>Escherichia coli</i> , ESBL-positive (1007)						
Amikacin	76.1	17.8	6.1	≤2	8	≤2-64
Amoxicillin/clavulanate	45.3	35.8	18.9	16	32	1->32
Cefazolin		0.1	99.9	>128	>128	4->128
Cefepime	21.0	27.6	51.4	16	>32	≤1->32
Cefoxitin	77.1	14.3	8.6	8	16	0.5->32
Ceftazidime	25.4	11.7	62.9	16	>32	≤0.5->32
Ceftazidime/avibactam	99.6		0.4	≤0.25	0.5	≤0.25->16
Ceftobiprole ^b	2.0	1.3	96.7	>16	>16	≤1->16
Ceftolozane/tazobactam	96.0	1.1	2.9	0.5	1	≤0.12->64
Ceftriaxone	1.2	0.9	97.9	>64	>64	≤1->64
Ciprofloxacin	12.7	1.3	86.0	>16	>16	≤0.06->16
Colistin		99.7	0.3	0.5	1	≤0.06-8
Ertapenem	97.5	1.0	1.5	≤0.06	0.12	≤0.06->32
Fosfomycin	96.7	1.9	1.4	≤1	4	≤1->512
Gentamicin	64.3	1.0	34.7	1	>32	≤0.5->32
Imipenem/relebactam	100			0.25	0.25	0.06-0.5
Levofloxacin	11.6	1.3	87.1	16	32	≤0.06->32
Meropenem	99.5		0.5	≤0.12	≤0.12	≤0.12->32
Meropenem/vaborbactam	100			≤0.06	≤0.06	≤0.06-0.5
Moxifloxacin				16	>16	≤0.06->16
Nitrofurantoin	92.3	4.5	3.2	16	32	≤1-512
Piperacillin/tazobactam	83.6	9.0	7.4	4	16	≤1->512
Plazomicin	99.5	0.3	0.2	0.5	1	≤0.12-32

Continued

Table 2. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% Susceptible	% Intermediate	% Resistant	MIC ₅₀	MIC ₉₀	MIC range
Tigecycline ^c	99.9	0.1		0.5	1	0.12–4
Trimethoprim/sulfamethoxazole	34.1		65.9	>8	>8	≤0.12–>8
<i>Pseudomonas aeruginosa</i> (5961)						
Amikacin	92.0	3.4	4.6	4	16	≤2–>64
Cefepime	79.4	12.6	8.0	4	16	≤1–>32
Ceftazidime	78.1	7.0	14.9	4	32	≤0.5–>32
Ceftazidime/avibactam	92.6		7.4	2	8	≤0.25–>16
Ceftobiprole				4	16	≤1–>16
Ceftolozane/tazobactam	96.6	1.7	1.7	0.5	2	≤0.12–>64
Ciprofloxacin	68.6	9.0	22.4	0.25	4	≤0.06–>16
Colistin		96.3	3.7	1	2	≤0.06–>16
Fosfomycin				64	256	≤1–>512
Imipenem/relebactam	92.0	4.9	3.1	0.5	2	≤0.03–>32
Levofloxacin	52.9	10.6	36.5	1	16	≤0.06–>32
Meropenem	78.0	6.9	15.1	0.5	8	≤0.12–>32
Meropenem/vaborbactam				0.5	8	≤0.06–>32
Moxifloxacin				2	>16	≤0.06–>16
Nitrofurantoin				>512	>512	≤0.5–>512
Piperacillin/tazobactam	79.9	5.9	14.2	4	128	≤1–>512
Plazomicin				4	16	≤0.12–>64
<i>Klebsiella pneumoniae</i> (3973)						
Amikacin	98.8	0.5	0.7	≤2	≤2	≤2–>64
Amoxicillin/clavulanate	91.2	4.5	4.3	2	8	≤0.06–>32
Cefazolin	81.7	6.1	12.2	1	8	≤0.5–>128
Cefepime	94.4	1.4	4.2	≤1	≤1	≤1–>32
Cefoxitin	90.5	4.2	5.3	4	8	0.12–>32
Ceftazidime	93.7	0.5	5.8	≤0.5	1	≤0.5–>32
Ceftazidime/avibactam	99.8		0.2	≤0.25	0.5	≤0.25–>16
Ceftobiprole ^b	93.2	0.5	6.3	≤1	≤1	≤1–>16
Ceftolozane/tazobactam	97.4	0.4	2.2	0.25	1	≤0.12–>64
Ceftriaxone	93.0	0.4	6.6	≤1	≤1	≤1–>64
Ciprofloxacin	87.0	3.7	9.3	≤0.06	0.5	≤0.06–>16
Colistin		97.8	2.2	0.5	1	≤0.06–>16
Fosfomycin				≤0.06	≤0.06	≤0.06–>32
Ertapenem	89.0	3.8	7.2	32	128	≤1–>512
Gentamicin	96.2	0.2	3.6	≤0.5	≤0.5	≤0.5–>32
Imipenem/relebactam	99.3	0.6	0.1	0.25	0.5	0.06–>32
Levofloxacin	87.5	4.4	8.1	≤0.06	1	≤0.06–>32
Meropenem	99.5	0.1	0.4	≤0.12	≤0.12	≤0.12–>32
Meropenem/vaborbactam	99.6		0.4	≤0.06	≤0.06	≤0.06–>32
Moxifloxacin				0.12	1	≤0.06–>16
Nitrofurantoin	40.5	36.2	23.3	64	128	≤1–>512
Piperacillin/tazobactam	91.9	4.2	3.9	2	8	≤1–>512
Plazomicin	99.8	0.1	0.1	0.25	0.5	≤0.12–>64
Tigecycline ^c	95.7	3.5	0.8	1	2	0.06–>16
Trimethoprim/sulfamethoxazole	88.8		11.2	≤0.12	>8	≤0.12–>8
<i>Klebsiella pneumoniae</i> , ESBL-positive (221)						
Amikacin	84.0	7.7	8.3	≤2	8	≤2–>64
Amoxicillin/clavulanate	27.9	34.4	37.7	16	>32	2–>32
Cefazolin			100	>128	>128	8–>128
Cefepime	17.1	18.0	64.9	32	>32	≤1–>32

Continued

Table 2. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% Susceptible	% Intermediate	% Resistant	MIC ₅₀	MIC ₉₀	MIC range
Cefoxitin	69.1	12.0	18.9	8	>32	2->32
Ceftazidime	17.3	4.7	78.0	>32	>32	≤0.5->32
Ceftazidime/avibactam	99.5		0.5	0.5	1	≤0.25-16
Ceftobiprole ^b	5.5	2.2	92.3	>16	>16	≤1->16
Ceftolozane/tazobactam	75.8	4.4	19.8	1	32	≤0.12->64
Ceftriaxone	5.0	2.7	92.3	>64	>64	≤1->64
Ciprofloxacin	16.3	11.8	71.9	4	>16	≤0.06->16
Colistin		95.9	4.1	0.5	1	0.25->16
Fosfomycin	89.9	2.7	7.4	0.12	1	0.06->32
Ertapenem	80.0	10.0	10.0	32	128	2-256
Gentamicin	56.1	0.5	43.4	≤0.5	>32	≤0.5->32
Imipenem/relebactam	98.5	1.5		0.25	0.5	0.06-2
Levofloxacin	24.1	6.9	69.0	4	>32	≤0.06->32
Meropenem	95.5	0.9	3.6	≤0.12	≤0.12	≤0.12->32
Meropenem/vaborbactam	100			≤0.06	≤0.06	≤0.06
Moxifloxacin				4	>16	≤0.06->16
Nitrofurantoin	20.3	34.1	45.6	64	256	8->512
Piperacillin/tazobactam	52.0	15.9	32.1	8	>512	≤1->512
Plazomicin	98.5	0.7	0.8	0.25	0.5	≤0.12->64
Tigecycline ^c	88.2	9.1	2.7	1	4	0.5-16
Trimethoprim/sulfamethoxazole	15.4		84.6	>8	>8	≤0.12->8
<i>Haemophilus influenzae</i> (2351)						
Amoxicillin/clavulanate	97.3	2.4	0.3	0.5	2	≤0.06->32
Ampicillin	80.0	1.7	18.3	≤0.25	16	≤0.25->128
Cefepime	100			≤0.25	≤0.25	≤0.25-2
Ceftazidime/avibactam				≤0.03	0.06	≤0.03->1
Ceftobiprole				≤0.06	0.12	≤0.06-2
Ceftolozane/tazobactam	98.5		1.5	≤0.12	0.25	≤0.12-4
Ceftriaxone	99.9		0.1	≤0.06	≤0.06	≤0.06->4
Cefuroxime	97.9	1.7	0.4	1	2	≤0.25->16
Ciprofloxacin	100			≤0.015	≤0.015	≤0.015->0.5
Clarithromycin	87.7	10.1	2.2	4	16	≤0.03->32
Doxycycline				0.5	1	≤0.25-16
Ertapenem	99.7		0.3	≤0.03	0.12	≤0.03->4
Imipenem/relebactam	99.5		0.5	1	2	≤0.06->8
Levofloxacin	100			≤0.015	0.03	≤0.015->0.5
Meropenem	99.8		0.2	≤0.06	0.12	≤0.06-2
Moxifloxacin	100			≤0.015	0.03	≤0.015->0.5
Piperacillin/tazobactam	99.7		0.3	≤1	≤1	≤1-2
Trimethoprim/sulfamethoxazole	77.9	4.9	17.2	≤0.12	8	≤0.12->8
<i>Enterobacter cloacae</i> (1659)						
Amikacin	98.7	0.7	0.6	≤2	≤2	≤2->64
Cefepime	93.0	5.0	2.0	≤1	2	≤1->32
Ceftazidime	75.9	1.1	23.0	≤0.5	>32	≤0.5->32
Ceftazidime/avibactam	99.5		0.5	≤0.25	1	≤0.25->16
Ceftobiprole ^b	85.1	3.4	11.5	≤1	4	≤1->16
Ceftolozane/tazobactam	81.8	4.5	13.7	0.5	8	≤0.12->64
Ceftriaxone	71.6	2.1	26.3	≤1	>64	≤1->64
Ciprofloxacin	92.6	1.1	6.3	≤0.06	0.12	≤0.06->16
Colistin		81.2	18.8	0.5	>16	≤0.06->16
Fosfomycin				≤0.06	0.5	≤0.06->32

Continued

Table 2. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% Susceptible	% Intermediate	% Resistant	MIC ₅₀	MIC ₉₀	MIC range
Ertapenem	76.9	6.4	16.7	32	512	≤1-→512
Gentamicin	96.9	0.4	2.7	≤0.5	≤0.5	≤0.5-→32
Imipenem/relebactam	98.8	0.9	0.3	0.25	0.5	0.06-→32
Levofloxacin	92.9	1.2	5.9	≤0.06	0.5	≤0.06-32
Meropenem	99.5	0.3	0.2	≤0.12	≤0.12	≤0.12-→32
Moxifloxacin				≤0.06	0.5	≤0.06-→16
Nitrofurantoin	36.3	42.5	21.2	64	128	≤1-→512
Piperacillin/tazobactam	79.1	4.1	16.8	2	64	≤1-→512
Plazomicin	99.6	0.2	0.2	0.5	0.5	≤0.12-64
Tigecycline ^c	95.3	3.1	1.6	0.5	1	0.12-16
Trimethoprim/sulfamethoxazole	91.8		8.2	≤0.12	1	≤0.12-→8
<i>Proteus mirabilis</i> (957)						
Amikacin	89.6	7.8	2.6	4	8	≤2-32
Amoxicillin/clavulanate	94.9	1.9	3.2	1	4	0.5-→32
Cefazolin	3.3	58.0	38.7	4	16	1-→128
Cefepime	99.3	0.1	0.6	≤1	≤1	≤1-→32
Cefoxitin	95.8	2.6	1.6	4	8	≤0.06-→32
Ceftazidime	98.5	0.4	1.1	≤0.5	≤0.5	≤0.5-→32
Ceftazidime/avibactam	100			≤0.25	≤0.25	≤0.25-4
Ceftobiprole				≤1	≤1	≤1-→16
Ceftolozane/tazobactam	99.2	0.5	0.3	0.5	1	≤0.12-8
Ceftriaxone	97.6	0.7	1.7	≤1	≤1	≤1-→64
Ciprofloxacin	82.4	1.3	16.3	≤0.06	2	≤0.06-→16
Ertapenem	99.5	0.3	0.2	≤0.06	≤0.06	≤0.06-4
Fosfomycin				4	128	≤1-→512
Gentamicin	92.8	1.1	6.1	1	2	≤0.5-→32
Imipenem/relebactam	10.0	25.4	64.6	4	4	0.12-16
Levofloxacin	79.3	3.1	17.6	0.12	2	≤0.06-→32
Meropenem	100			≤0.12	≤0.12	≤0.12-1
Moxifloxacin				0.5	16	≤0.06-→16
Piperacillin/tazobactam	99.6	0.2	0.2	≤1	≤1	≤0.12-64
Plazomicin	41.5	48.3	10.2	4	8	0.25-32
Trimethoprim/sulfamethoxazole	82.3		17.7	≤0.12	>8	≤0.12-→8
<i>Klebsiella oxytoca</i> (1060)						
Amikacin	98.6	1.1	0.3	≤2	≤2	≤2-→64
Amoxicillin/clavulanate	87.7	5.0	7.3	4	16	0.5-→32
Cefazolin	21.2	19.6	59.2	8	>128	≤0.5-→128
Cefepime	97.1	1.6	1.3	≤1	≤1	≤1-→32
Cefoxitin	94.9	3.2	1.9	2	8	0.5-→32
Ceftazidime	97.6	0.3	2.1	≤0.5	1	≤0.5-→32
Ceftazidime/avibactam	99.9		0.1	≤0.25	0.5	≤0.25-16
Ceftobiprole ^b	85.7	2.1	12.2	≤1	16	≤1-→16
Ceftolozane/tazobactam	98.4	1.3	0.3	0.25	1	≤0.12-64
Ceftriaxone	89.9	1.3	8.8	≤1	2	≤1-→64
Ciprofloxacin	96.1	0.8	3.1	≤0.06	≤0.06	≤0.06-→16
Colistin		98.1	1.9	0.5	1	≤0.06-→16
Ertapenem	99.7	0.1	0.2	≤0.06	≤0.06	≤0.06-32
Fosfomycin				16	128	2-→512
Gentamicin	97.6	0.1	2.3	≤0.5	1	≤0.5-→32
Imipenem/relebactam	100			0.25	0.5	≤0.03-1
Levofloxacin	94.9	1.8	3.3	≤0.06	0.25	≤0.06-→32

Continued

Table 2. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% Susceptible	% Intermediate	% Resistant	MIC ₅₀	MIC ₉₀	MIC range
Meropenem	99.9	0.1		≤0.12	≤0.12	≤0.12–2
Moxifloxacin				≤0.06	0.25	≤0.06–>16
Nitrofurantoin	85.1	12.2	2.7	32	64	≤1–>512
Piperacillin/tazobactam	88.3	0.8	10.9	2	64	≤1–>512
Plazomicin	100			0.5	1	≤0.12–2
Tigecycline ^c	98.7	1.1	0.2	0.5	1	0.06–8
Trimethoprim/sulfamethoxazole	94.6		5.4	≤0.12	0.25	≤0.12–>8
<i>Stenotrophomonas maltophilia</i> (1210)						
Ceftazidime				>32	>32	≤0.5–>32
Ciprofloxacin				4	16	≤0.06–>16
Colistin				8	>16	0.12–>16
Levofloxacin	66.8	12.9	20.3	2	8	≤0.06–>32
Moxifloxacin				1	4	≤0.06–>16
Tigecycline				2	4	0.12–>16
Trimethoprim/sulfamethoxazole	97.9		2.1	0.25	1	≤0.12–>8
<i>Serratia marcescens</i> (1003)						
Amikacin	96.1	2.3	1.6	≤2	4	≤2–>64
Cefepime	98.8	0.8	0.4	≤1	≤1	≤1–>32
Ceftazidime	98.5	0.4	1.1	≤0.5	1	≤0.5–>32
Ceftazidime/avibactam	99.1		0.9	≤0.25	1	≤0.25–>16
Ceftobiprole				≤1	≤1	≤1–>16
Ceftolozane/tazobactam	96.5	1.4	2.1	1	2	≤0.12–64
Ceftriaxone	92.0	2.5	5.5	≤1	≤1	≤1–>64
Ciprofloxacin	82.3	3.6	14.1	≤0.06	1	≤0.06–>16
Ertapenem	98.0	1.0	1.0	≤0.06	0.12	≤0.06–>32
Fosfomycin				16	32	≤1–64
Gentamicin	96.1	0.9	3.0	≤0.5	1	≤0.5–>32
Imipenem/relebactam	76.7	21.6	1.7	1	2	0.25–>32
Levofloxacin	82.2	5.5	12.3	0.12	2	≤0.06–16
Meropenem	99.5	0.3	0.2	≤0.12	≤0.12	≤0.12–8
Moxifloxacin				0.25	2	≤0.06–>16
Nitrofurantoin		0.7	99.3	256	>512	64–>512
Piperacillin/tazobactam	94.8	2.1	3.1	2	4	≤1–256
Plazomicin	97.1	2.1	0.8	1	2	≤0.12–8
Tigecycline ^c	81.7	15.6	2.7	2	4	0.06–>16
Trimethoprim/sulfamethoxazole	96.0		4.0	0.5	1	≤0.12–>8
<i>Klebsiella aerogenes</i> (437)						
Amikacin	99.4	0.6		≤2	≤2	≤2–8
Cefepime	98.0	0.7	1.3	≤1	≤1	≤1–>32
Ceftazidime	73.3	2.3	24.4	≤0.5	>32	≤0.5–>32
Ceftazidime/avibactam	99.1		0.9	≤0.25	0.5	≤0.25–16
Ceftobiprole ^b	98.5		1.5	≤1	≤1	≤1–>16
Ceftolozane/tazobactam	85.9	8.4	5.7	0.5	4	≤0.12–64
Ceftriaxone	72.1	0.9	27.0	≤1	32	≤1–>64
Ciprofloxacin	92.8	2.3	4.9	≤0.06	0.25	≤0.06–>16
Colistin		98.0	2.0	0.5	1	0.12–>16
Ertapenem	93.2	4.4	2.4	0.12	0.5	≤0.06–>32
Fosfomycin				32	64	8–64
Gentamicin	99.8		0.2	≤0.5	≤0.5	≤0.5–32
Imipenem/relebactam	97.3	1.6	1.1	0.25	1	0.06–16
Levofloxacin	92.2	1.1	6.7	≤0.06	0.5	≤0.06–16

Continued

Table 2. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% Susceptible	% Intermediate	% Resistant	MIC ₅₀	MIC ₉₀	MIC range
Meropenem	99.3	0.2	0.5	≤0.12	≤0.12	≤0.12->32
Moxifloxacin				0.12	1	≤0.06-16
Nitrofurantoin	18.1	51.0	30.9	64	128	8->512
Piperacillin/tazobactam	73.4	9.6	17.0	4	32	≤1-512
Plazomicin	100			0.5	1	≤0.12-2
Tigecycline ^c	96.3	2.8	0.9	1	2	0.06-8
Trimethoprim/sulfamethoxazole	98.1		1.9	≤0.12	0.5	≤0.12->8
<i>Citrobacter freundii</i> (260)						
Amikacin	97.3	2.7		≤2	≤2	≤2-8
Cefepime	95.3	3.4	1.3	≤1	≤1	≤1->32
Ceftazidime	79.2	0.9	19.9	≤0.5	>32	≤0.5->32
Ceftazidime/avibactam	99.5		0.5	≤0.25	1	≤0.25-16
Ceftobiprole ^b	87.9	3.3	8.8	≤1	2	≤1->16
Ceftolozane/tazobactam	83.7	4.1	12.2	0.25	8	≤0.12->64
Ceftriaxone	77.7	1.5	20.8	≤1	64	≤1->64
Ciprofloxacin	86.5	2.3	11.2	≤0.06	1	≤0.06->16
Colistin		99.1	0.9	0.5	0.5	0.12-8
Ertapenem	96.2	2.1	1.7	≤0.03	0.25	≤0.03-32
Fosfomycin				≤1	2	≤1-2
Gentamicin	90.3	0.4	9.3	≤0.5	2	≤0.5->32
Imipenem/relebactam	98.9	1.1		0.25	0.5	0.12-2
Levofloxacin	88.4	2.3	9.3	≤0.06	1	≤0.06->32
Meropenem	99.6	0.4		≤0.12	≤0.12	≤0.12-2
Moxifloxacin				0.12	4	≤0.06->16
Nitrofurantoin	93.4	4.0	2.6	16	32	4->512
Piperacillin/tazobactam	80.3	4.6	15.1	2	64	≤1->512
Plazomicin	100			0.5	1	≤0.12-2
Tigecycline ^c	95.4	4.2	0.4	0.5	1	0.25-8
Trimethoprim/sulfamethoxazole	82.6		17.4	≤0.12	>8	≤0.12->8
<i>Acinetobacter baumannii</i> (274)						
Amikacin	95.6		4.4	≤2	4	≤2->64
Cefepime	83.7	6.1	10.2	4	32	≤1->32
Ceftazidime	78.0	10.8	11.2	8	32	≤0.5->32
Ceftazidime/avibactam				8	>16	≤0.25->16
Ceftolozane/tazobactam				1	8	≤0.12->64
Ceftriaxone	41.6	47.8	10.6	16	64	≤1->64
Ciprofloxacin	92.3	1.5	6.2	0.25	1	≤0.06-32
Colistin		98.1	1.9	1	2	0.25->16
Gentamicin	92.4	1.8	5.8	≤0.5	2	≤0.5->32
Imipenem/relebactam	95.4		4.6	0.25	0.5	0.06->32
Levofloxacin	92.2		7.8	0.12	1	≤0.06->16
Meropenem	94.2	1.8	4.0	0.5	2	≤0.12->32
Moxifloxacin				≤0.06	0.5	≤0.06->16
Piperacillin/tazobactam	79.2	10.2	10.6	4	128	≤1->512
Plazomicin				1	4	0.25->64
Tigecycline				0.5	1	0.12->16
Trimethoprim/sulfamethoxazole	91.6		8.4	≤0.12	2	≤0.12->8

^aOrganism-antimicrobial combinations for which intrinsic resistance is known¹⁶ have been excluded from the table.

^bHealth Canada approved breakpoints were used to interpret ceftobiprole MICs.

^cFDA approved breakpoints were used to interpret tigecycline MICs.

The most active agents against the Gram-negative bacilli tested by the CANWARD study were the newer β -lactam/ β -lactamase inhibitor combination agents (ceftazidime/avibactam, imipenem/relebactam, meropenem/vaborbactam) and plazomicin as well as the established agents amikacin, cefepime, ceftobiprole, ceftolozane/tazobactam, ertapenem (excluding *P. aeruginosa*), meropenem and tigecycline (excluding *P. aeruginosa*) (Table 2). Percent susceptible values approaching 100% for the newer β -lactam/ β -lactamase inhibitor combination agents versus Gram-negative bacilli, including various resistance phenotypes as well as *P. aeruginosa* has been previously documented.^{10,11,17–23}

In this study, amikacin was very active against *E. coli* (including ESBL-producing isolates) and other Enterobacterales (Table 2). Against *P. aeruginosa* and *A. baumannii*, amikacin was one of the most active agents tested. The excellent *in vitro* activity of amikacin and other aminoglycosides against both Enterobacterales and non-fermenters isolated from patients in hospitals, including those in ICUs, is well established. The reduced usage (selective pressure) of aminoglycosides in favour of other less toxic antimicrobial classes (e.g. β -lactams, fluoroquinolones) over the last three decades has resulted in the maintenance of aminoglycoside activity in the setting of increasing fluoroquinolone resistance.^{18,19} Thus, amikacin represents a potential option for the treatment of infections caused by Gram-negative bacilli resistant to other less toxic agents. Plazomicin, a new aminoglycoside was active against *E. coli* (including 99.5% of ESBL-producing isolates) and other Enterobacterales tested (Table 2) including gentamicin-resistant isolates (data not shown). As previously documented, this agent holds promise for the treatment of ESBL, carbapenem-resistant and MDR Enterobacterales.^{19,20}

In this study, we report that cefepime, ertapenem, meropenem and piperacillin/tazobactam were very active against Enterobacterales. However, only ertapenem and meropenem maintained their activity against ESBL-producing isolates due to the presence of multiple β -lactamases in these isolates. Against *P. aeruginosa*, resistance rates for piperacillin/tazobactam, meropenem and cefepime were less than ~15%. Previous investigators have reported the ongoing activity of these agents against Gram-negative bacilli isolated from hospitalized patients.^{21–23} Ceftolozane-tazobactam is a broad-spectrum cephalosporin with activity against Enterobacterales, including ESBL-producing isolates (Table 2). In this study, we report that ceftolozane-tazobactam was the most active agent tested against *P. aeruginosa* (96.6% susceptibility). We and others have reported that ceftolozane-tazobactam demonstrated excellent *in vitro* activity against resistant Enterobacterales as well as MDR and XDR *P. aeruginosa* isolates.^{24–26} Ceftobiprole is a broad-spectrum cephalosporin with activity versus both Gram-negative and Gram-positive organisms.^{27–29} In this study, we report that its activity against Enterobacterales is greater than ceftriaxone (Table 2) but was inactive against ESBL-producing isolates, which was expected. Ceftobiprole's activity against *P. aeruginosa* is similar to cefepime and ceftazidime (Table 2).

Tigecycline demonstrated excellent *in vitro* activity versus *E. coli* (including ESBL-producing isolates) and was also active against other Enterobacterales including *K. pneumoniae*, *E. cloacae*, *S. marcescens* and *K. oxytoca* (Table 2). These data are

consistent with recent studies showing the excellent *in vitro* activity of tigecycline versus Gram-negative bacilli, including MDR isolates.^{19,24} Tigecycline displayed good activity against *S. maltophilia* and *A. baumannii*, organisms frequently resistant to other antimicrobial classes (Table 2).³⁰ Fosfomycin was highly active *in vitro* against *E. coli* (98.8% susceptible), including ESBL-producing isolates (96.7% susceptible). Fosfomycin's activity versus *E. coli* was consistent with earlier reports.^{31,32}

There are limitations associated with the CANWARD surveillance study including that we cannot be certain that all isolates from clinical specimens represented active infection. In the CANWARD surveillance study, participating medical centres committed to study criteria that encouraged the submission of clinically significant specimens from patients with a presumed infectious disease; however, this interpretation cannot be rigorously controlled by the coordinating site. Another limitation is that we do not have admission date data for each patient/clinical specimen, thus we are not able to provide a more accurate description of community versus healthcare onset. Finally, an important limitation is that antimicrobial susceptibility testing was not performed for all commercially available antimicrobial agents due to the lack of space on the custom-designed susceptibility panels utilized. It is recognized that data on antimicrobials such as cefotaxime, imipenem, tobramycin and others would be beneficial as different hospital formularies stock these and other antimicrobials not tested in this study.

In conclusion, *E. coli*, *P. aeruginosa*, *Klebsiella* spp., *H. influenzae*, *E. cloacae* and *S. maltophilia* represent the most common Gram-negative bacterial pathogens isolated by laboratories in Canadian hospitals. ESBL-producing *E. coli* and *K. pneumoniae* increased significantly over the study period, while carbapenem-resistant *E. coli* and *K. pneumoniae* remained at less than 1% for the entire study period. Percent susceptible values for *E. coli* isolates were highest for meropenem/vaborbactam and imipenem/relebactam, 100%; ceftazidime/avibactam, tigecycline and meropenem, 99.9%; ertapenem, 99.6%; ceftolozane/tazobactam, 99.1%; and piperacillin/tazobactam, 95.6%. Percent susceptible values for *P. aeruginosa* isolates were highest for ceftolozane/tazobactam, 96.6%; ceftazidime/avibactam, 92.6%; and amikacin and imipenem/relebactam, 92.0%.

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CANWARD data can also be found at www.can-r.ca, the official website of the Canadian Antimicrobial Resistance Alliance (CARA).

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Transparency declarations

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Disclaimer

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