

Gram-positive 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 antimicrobial susceptibilities for bacterial pathogens isolated from patients receiving care in Canadian hospitals. This paper focuses on Gram-positive pathogens.

Methods: In total, 25 897 Gram-positive pathogens were received and 22 132 underwent CLSI broth microdilution testing providing susceptibility data.

Results: 47.9%, 30.2%, 5.7% and 16.2% of isolates tested were from blood, respiratory, urine and wound specimens, respectively; 29.9%, 24.8%, 19.0%, 18.1% and 8.2% of isolates were from patients in medical wards, emergency rooms, intensive care units, hospital clinics and surgical wards. Patient demographics associated with the isolates were: 58.9% male/41.1% female; 13.5% patients aged ≤17 years, 48.5% 18–64 years and 38.0% ≥65 years. Of the 25 897 pathogens received, the most common were: *Staphylococcus aureus* [20.9% (MSSA 16.5%/MRSA 4.4%)], *Streptococcus pneumoniae* (5.2%) and *Enterococcus* spp. (*Enterococcus faecalis* and *Enterococcus faecium*) (5.0%). MRSA rates (MRSA as a % of all *S. aureus* tested) decreased significantly during 2007–15 from 26.0% to 19.3% ($P < 0.0001$); subsequently they increased significantly through study years 2016–23 (16.9%–24.1%; $P = 0.002$). VRE rates (VRE as a % of all *E. faecium* tested) ranged from 3.8% to 18.4%, with marked fluctuation year-to-year. Susceptibility rates for MRSA were highest with: 100% ceftobiprole, 99.9% linezolid, vancomycin and daptomycin, 99.8% dalbavancin and 99.4% tedizolid, while susceptibility rates for VRE were 98.4% daptomycin and 86.0% with linezolid.

Conclusions: The CANWARD surveillance study has provided 17 years of reference antimicrobial susceptibility testing data on Gram-positive pathogens.

Introduction

Infections caused by antimicrobial-resistant and MDR pathogens are increasing worldwide.^{1–3} Gram-positive pathogens of concern include MRSA, both community-associated (CA-MRSA) and healthcare-associated (HA-MRSA), VRE and penicillin-resistant *Streptococcus pneumoniae*.^{3–7} Treatment options for antimicrobial-resistant organisms can be severely limited as these pathogens frequently display an MDR phenotype.^{3,5,8}

Proposed solutions to the global problem of antimicrobial resistance include surveillance and antimicrobial stewardship programmes.^{2,9} In 2007, we initiated the CANWARD study, which is an ongoing, annual, national, Canadian Antimicrobial Resistance Alliance (CARA)/Health Canada partnered surveillance study.^{9,10} The purpose of CANWARD is to assess the pathogens causing infections in patients seeking care in tertiary-care medical centres across Canada, as well as their susceptibilities to commonly prescribed and newer antimicrobial agents.

In the current report, we summarize the Gram-positive pathogens causing infections and the *in vitro* activities of commonly used antimicrobial agents against these isolates collected from 2007 to 2023, inclusive, from patients seeking care in tertiary-care medical centres across Canada.

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 the 10 Canadian provinces submitted pathogens from patients attending emergency rooms, medical and surgical wards, intensive care units and hospital clinics.^{9,10} The sites were geographically distributed in a population-based fashion. From 2007 through 2023, inclusive, each study site was asked to submit clinically significant isolates as defined by their individual hospital criteria (consecutive, one per patient, per infection site) from inpatients and outpatients attending hospital clinics with respiratory, urine, wound and bloodstream infections. By year, each centre was asked to provide: 2007—200 respiratory, 50 wounds, 100 urinary, 30/month blood isolates; 2008—150 respiratory, 50 wounds, 100 urinary, 20/month blood isolates; 2009–10—100 respiratory, 50 wound, 50 urinary, 15/month (January–November) blood isolates; and 2011–23—100 respiratory, 25 wounds, 25 urinary, 10/month (January to October) blood isolates. 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 were 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 were published previously¹¹ and are 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 and haemolysis patterns) and antimicrobial susceptibility patterns.^{9,10} 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 MIC testing was performed.^{9,10} Isolate viability (including fastidious organisms such as *S. pneumoniae*) using these methods was >99%. Patient demographic information collected with the isolates included gender, age, hospital location and specimen source. From 2007–23, a total of 25 897 Gram-positive isolates: 3503 (2007), 2533 (2008), 2408 (2009), 2225 (2010), 1536 (2011), 1253 (2012), 1504 (2013), 1445 (2014), 1409 (2015), 1289 (2016), 1347 (2017), 1186 (2018), 1165 (2019), 779 (2020), 845 (2021), 777 (2022) and 693 (2023) were collected. The focus of this study was the 25 897 Gram-positive pathogens collected from CANWARD 2007 to 2023, inclusive. 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 broth microdilution in accordance with CLSI guidelines.¹² Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were

prepared and dilutions made as described by CLSI.¹² MICs were determined using 96-well custom-designed microtitre plates made in-house by our laboratory. Quality control followed CLSI guidelines.¹² MICs were interpreted according to CLSI breakpoints¹³ except for tigecycline, where FDA MIC breakpoints were used [*S. aureus* (MSSA and MRSA), ≤0.5 mg/L susceptible; *Enterococcus faecalis* (vancomycin susceptible) ≤0.25 mg/L susceptible] (<https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria>) and for ceftobiprole, where Health Canada MIC breakpoints were used [*S. aureus* (MSSA and MRSA), ≤4 mg/L susceptible; *S. pneumoniae*, ≤0.5 mg/L susceptible] (<https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=93212>). Of the 25 897 Gram-positive organisms collected by the CANWARD surveillance study from 2007 to 2023, 22 132 (85.5%) underwent susceptibility testing. Isolates selected for susceptibility testing included the top 20 Gram-positive (coagulase-negative staphylococci and viridans group streptococci were not tested) and Gram-negative pathogens. Development of a centralized database for the CANWARD study results was created by IHMA (Schaumburg, IL, USA).

Characterization of MRSA and VRE

Screening for methicillin resistance was performed by the CLSI-approved disk diffusion with cefoxitin,^{10,14} as well as by growth on MRSA Select chromogenic media (Bio-Rad Laboratories Ltd, Mississauga, Ontario, Canada). Potential MRSA isolates were confirmed by *mecA* PCR as previously described.¹⁴ All isolates of MRSA were typed using staphylococcal protein A (*spa*) DNA sequencing to assess whether the isolates were community-associated (CA) or healthcare-associated (HA).¹⁴ Isolates with a *spa* type associated with C(Canadian)MRSA7 or CMRSA10 were considered CA-MRSA. Isolates with a *spa* type associated with CMRSA1, CMRSA2, CMRSA4, CMRSA5, CMRSA3/6, CMRSA8 or CMRSA9 were considered HA-MRSA.¹⁴ Potential VRE isolates were confirmed by *vanA* and *vanB* PCR, as previously described.¹⁵

Statistical analysis

Annual proportions of MRSA isolates were assessed by the Cochran–Armitage test of trend using XLSTAT (v.2019). Statistical significance was defined as a *P* value of ≤0.05.

Results

Patient demographics and specimen types

A total of 25 897 isolates of Gram-positive bacteria were collected between 2007 and 2023. They were more commonly collected from males (15 255, 58.9%) than females (10 641, 41.1%); a biological sex identifier was not available for one isolate. Isolates were from blood (*n*=12 410; 47.9%), respiratory (*n*=7828; 30.2%), urinary (*n*=1461; 5.7%) and wound (*n*=4198; 16.2%) specimens. By age group, 3505 (13.5%), 12 545 (48.5%) and 9847 (38.0%) isolates were from patients ≤17 years, 18–64 years and ≥65 years, respectively. Regarding hospital location, 7925 (30.6%), 6630 (25.6%), 4816 (18.6%), 4428 (17.1%) and 2098 (8.1%) isolates were received from patients in medical wards, emergency rooms, intensive care units, clinics and surgical wards, respectively. The geographical locations of the referring centres were as follows: British Columbia/Alberta (16.7%), Manitoba/Saskatchewan (17.2%), from Ontario (27.5%), Quebec (25.4%) and New Brunswick/Nova Scotia (13.2%).

Most common organisms isolated

Though the focus of this paper is Gram-positive isolates, for completeness, 61 066 Gram-positive and Gram-negative isolates

Table 1. The 20 most common Gram-positive and Gram-negative bacterial^a pathogens isolated in Canadian hospital laboratories

Rank	Organism	No. of isolates	% of total isolates
1	<i>Staphylococcus aureus</i>	12 734	20.9
	(<i>Staphylococcus aureus</i> , MSSA)	10 037	16.5
	(<i>Staphylococcus aureus</i> , MRSA)	2 697	4.4
2	<i>Escherichia coli</i>	11 932	19.5
3	<i>Pseudomonas aeruginosa</i>	5 961	9.8
4	<i>Klebsiella pneumoniae</i>	3 973	6.5
5	<i>Streptococcus pneumoniae</i>	3 170	5.2
6	<i>Haemophilus influenzae</i>	2 351	3.8
7	<i>Enterococcus faecalis</i>	2 261	3.7
8	CoNS ^b / <i>Staphylococcus epidermidis</i>	2 129	3.5
9	<i>Enterobacter cloacae</i>	1 659	2.7
10	<i>Stenotrophomonas maltophilia</i>	1 210	2.0
11	<i>Klebsiella oxytoca</i>	1 060	1.7
12	<i>Serratia marcescens</i>	1 003	1.6
13	<i>Streptococcus agalactiae</i>	968	1.6
14	<i>Proteus mirabilis</i>	957	1.6
15	<i>Streptococcus pyogenes</i>	866	1.4
16	<i>Enterococcus faecium</i>	810	1.3
17	<i>Moraxella catarrhalis</i>	585	1.0
18	<i>Candida albicans</i>	563	0.9
19	Viridans group streptococci	531	0.9
20	<i>Klebsiella aerogenes</i>	437	0.7
Other ^c		5 906	9.7
Total		61 066	

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

^aList also contains *Candida* spp. collected as part of the CANWARD bloodstream infection objective. The *Candida* spp. collected specifically for the *Candida* objective are not included.¹¹

^bCoNS, coagulase-negative staphylococci.

^cOther: *Abiotrophia* spp., *Achromobacter* spp., *Acinetobacter* spp., *Aerococcus* spp., *Aeromonas* spp., *Aggregatibacter* spp., *Agrobacterium* spp., *Alcaligenes* spp., *Arcanobacterium* spp., *Bacillus* spp., *Bactobacillus* spp., *Bordetella* spp., *Branhamella* spp., *Brevibacillus* spp., *Brevibacterium* spp., *Burkholderia* spp., *Campylobacter* spp., *Candida* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Cedecea* spp., *Chryseobacterium* spp., *Citrobacter* spp., *Clostridium* spp., *Comamonas* spp., *Corynebacterium* spp., *Cronobacter* spp., *Cryptococcus* spp., *Cupriavidus* spp., *Cutibacterium* spp., *Delftia* spp., *Dermabacter* spp., *Diphtheroids*, *Eikenella* spp., *Elizabethkingia* spp., *Empedobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Ewingella* spp., *Flavobacterium* spp., *Gemella* spp., *Gordonia* spp., *Granulicatella* spp., *Haemophilus* spp., *Hafnia* spp., *Jeotgallibacter* spp., *Klebsiella* spp., *Kluyvera* spp., *Kocuria* spp., *Kytococcus* spp., *Lactobacillus* spp., *Lactococcus* spp., *Leclercia* spp., *Legionella* spp., *Leifsonia* spp., *Lelliottia* spp., *Leuconostoc* spp., *Listeria* spp., *Macroccoccus* spp., *Micrococcus* spp., *Moraxella* spp., *Morganella* spp., *Mycobacterium* spp., *Myroides* spp., *Neisseria* spp., *Nocardia* spp., *Ochrobactrum* spp., *Oligella* spp., *Paenibacillus* 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., *Rhodococcus* spp., *Roseomonas* spp., *Rothia* spp., *Saccharomyces* spp., *Salmonella* spp., *Serratia* spp., *Shigella* spp., *Sphingobacterium* spp., *Sphingomonas* spp., *Staphylococcus* spp., *Stenotrophomonas* spp., *Stomatococcus* spp., *Streptococcus* spp., *Trichosporon* spp., *Trueperella* spp., *Vibrio* spp., *Weissella* spp., *Yersinia* spp.

were isolated (Table 1). The 20 most common organisms isolated ($n = 55\,160$, 90.3% of isolates) from hospitals across Canada included 23 469 (42.5%) Gram-positive cocci and 31 128 (56.4%) Gram-negative bacilli. No significant changes occurred over the study period (2007–23) in the proportions of individual Gram-positive cocci causing infections (bacteraemia, respiratory, urinary or wound). For example, *S. pneumoniae* was consistently the first or second most common pathogen causing respiratory tract infections each year.

Of the 25 897 Gram-positive cocci isolated, the 10 most common species accounted for 92.7% ($n = 24\,018$) of isolates (Table 2). *Staphylococcus aureus* (both MSSA and MRSA), *S. pneumoniae*, *Enterococcus* spp. and *Streptococcus* spp. were the most

common Gram-positive organisms (Table 2). MRSA represented 21.2% of all *S. aureus* isolates obtained and tested from 2007 to 2023 (Table 2). VRE were 6.1% of all *Enterococcus* spp. and 23.0% of all *Enterococcus faecium* collected from 2007 to 2023.

Antimicrobial activity against Gram-positive cocci

The *in vitro* activity of various antimicrobials against MSSA, MRSA, including HA-MRSA and CA-MRSA, *Staphylococcus epidermidis*, *S. pneumoniae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *E. faecalis*, *E. faecium* and VRE is displayed in Table 3. For MSSA, limited resistance was observed with the exception of

Table 2. The 10 most common Gram-positive bacterial^a pathogens isolated in Canadian hospital laboratories

Rank	Organism	No. of isolates	% of total isolates
1	<i>Staphylococcus aureus</i>	12 734	49.2
	(<i>Staphylococcus aureus</i> , MSSA)	10037	38.8
	(<i>Staphylococcus aureus</i> , MRSA)	2697	10.4
2	<i>Streptococcus pneumoniae</i>	3170	12.2
3	<i>Enterococcus faecalis</i>	2261	8.7
4	CoNS ^b / <i>Staphylococcus epidermidis</i>	2129	8.2
5	<i>Streptococcus agalactiae</i>	968	3.7
6	<i>Streptococcus pyogenes</i>	866	3.4
7	<i>Enterococcus faecium</i>	810	3.1
8	Viridans group streptococci	531	2.1
9	<i>Staphylococcus hominis</i>	281	1.1
10	β-Haemolytic streptococci, Group G	268	1.0
Other ^c		1879	7.3
Total		25 897	

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.¹¹
^bCoNS, coagulase-negative staphylococci.
^cOther: *Abiotrophia* spp., *Aerococcus* spp., *Arcanobacterium* spp., *Bacillus* spp., *Bactobacillus* spp., *Brevibacillus* spp., *Brevibacterium* spp., *Clostridium* spp., *Corynebacterium* spp., *Cutibacterium* spp., *Dermabacter* spp., *Diphtheroids*, *Enterococcus* spp., *Gemella* spp., *Gordonia* spp., *Granulicatella* spp., *Jeotgalicoccus* spp., *Kocuria* spp., *Kytococcus* spp., *Lactobacillus* spp., *Lactococcus* spp., *Leifsonia* spp., *Leuconostoc* spp., *Listeria* spp., *Macrococcus* spp., *Micrococcus* spp., *Mycobacterium* spp., *Nocardia* spp., *Paenibacillus* spp., *Rhodococcus* spp., *Rothia* spp., *Staphylococcus* spp., *Stomatococcus* spp., *Streptococcus* spp., *Trueperella* spp., *Weissella* spp.

clarithromycin, the fluoroquinolones and clindamycin. Only 23 (0.3%) of the 10037 MSSA tested displayed vancomycin MICs of 2 mg/L. The most active agents tested against MRSA were ceftobiprole (100% susceptible), linezolid, vancomycin and daptomycin (99.9% susceptibility), dalbavancin (99.8%), tedizolid (99.4%) and tigecycline (98.2%), respectively. Resistance rates in MRSA were 76.9%–85.9% to fluoroquinolones, 80.4% to clarithromycin, 39.1% to clindamycin and 5.2% to trimethoprim-sulfamethoxazole. MRSA rates decreased significantly from 2007 (26.0%) to 2015 (19.3%) ($P<0.0001$); however, they increased significantly in study years 2016 (16.9%) to 2023 (24.1%) ($P=0.002$). Thirty-five of the 2697 (1.3%) MRSA tested displayed vancomycin MICs of 2 mg/L, while three (0.11%) isolates of MRSA had vancomycin MICs of 4 mg/L. The proportion of MRSA with vancomycin MICs of 2 mg/L per year from 2007 to 2023 ranged from 0% to 2.9% but did not change significantly over time ($P>0.05$).
Against *S. epidermidis* significant resistance was observed for clarithromycin, clindamycin, gentamicin, fluoroquinolones and

trimethoprim-sulfamethoxazole (Table 3). The most active agents tested against *S. epidermidis* were vancomycin, daptomycin, linezolid and tigecycline. Ceftobiprole, dalbavancin and tedizolid demonstrated excellent activity with MIC₉₀ of ≤ 2 mg/L, 0.06 mg/L and 0.25 mg/L, respectively. Three-hundred and seventy of the 1323 *S. epidermidis* (28.0%) displayed vancomycin MICs of 2 mg/L while 0.15% (two of 1323 isolates) displayed vancomycin MICs of 4 mg/L.
For *S. pneumoniae*, limited resistance was observed with the exception of clarithromycin (18.7%), clindamycin (7.1%), doxycycline (12.6%), penicillin (MIC₉₀ of 0.25 mg/L, with 4.6% resistance) and trimethoprim-sulfamethoxazole (9.1%). Isolates were 100% susceptible to vancomycin, while susceptibility was 99.97% to linezolid, 99.92% to ceftobiprole, 99.4% to ceftriaxone and 97.7% to amoxicillin/clavulanate (Table 3). Dalbavancin and tedizolid were very active against *S. pneumoniae*, with MIC₉₀ values of ≤ 0.03 mg/L and 0.25 mg/L, respectively. Phenotypic (susceptibility) testing with clarithromycin and clindamycin suggested that ~38% of isolates displayed altered target site resistance to macrolides, while ~62% of *S. pneumoniae* demonstrated efflux mediated resistance to macrolides.¹⁰ Both *S. pyogenes* and *S. agalactiae* were highly susceptible to most antimicrobials tested with the exception of clarithromycin, for which resistance was 9.8% and 33.4%, respectively.
For *E. faecalis* and *E. faecium*, resistance was 24.6% and 91.3% to ciprofloxacin and 33.3% and 84.8% to levofloxacin, respectively. *E. faecalis* isolates were 99.9% vancomycin-susceptible and 98.2% daptomycin-susceptible. *E. faecium* isolates were 76.9% vancomycin-susceptible and 99.5% daptomycin-susceptible-dose dependent (Table 3). *E. faecalis* susceptibilities were >90% for dalbavancin (99.8%), tedizolid (99.7%), tigecycline 96.0% and linezolid (92.6%). Linezolid susceptibility with *E. faecium* was 89.3%. Ceftobiprole was very active against *E. faecalis* (MIC₉₀, 0.5 mg/L) but not against *E. faecium* (MIC₉₀, >16 mg/L). Vancomycin-resistant *E. faecium* [23.0% (186/810)] were comprised of 95.2% *vanA*-positive and 4.3% *vanB*-positive isolates; one isolate (0.5%) was positive for both *vanA* and *vanD* genes. The most active agents tested against VRE were daptomycin (98.4% susceptible-dose dependent), and linezolid (86.0%).

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 intensive care units).^{9,10} A total of 61066 organisms were collected between 2007 and 2023, inclusive, of which 25 897 were Gram-positive organisms (Table 1).
The most potent antimicrobial agents (depending on the specific pathogen and based upon MIC data only) against Gram-positive bacterial pathogens were vancomycin, linezolid, ceftobiprole, dalbavancin, daptomycin, tedizolid and tigecycline (Table 2). As an *in vitro* susceptibility study, the evaluation of antimicrobial activity was based solely upon population MIC values even though potency, which depends upon an agent's pharmacokinetics along with *in vitro* susceptibility (i.e. pharmacodynamics), is a more clinically relevant measure.^{5,8}

Table 3. Antimicrobial susceptibility testing results for the most common Gram-positive cocci ($n = 22\,132$) isolated from patients attending Canadian hospitals 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>Staphylococcus aureus</i> , MSSA ^b (10 037)						
Cefazolin ^c	100			≤0.5	1	≤0.5 to >128
Ceftobiprole ^d	100			0.5	0.5	≤0.03–2
Ciprofloxacin	87.6	3.0	9.4	0.5	2	≤0.06 to >16
Clarithromycin	75.7	0.7	23.6	0.25	>32	≤0.03 to >32
Clindamycin	94.1	0.4	5.5	≤0.25	≤0.25	≤0.25 to >8
Dalbavancin	100			0.06	0.06	≤0.03–0.25
Daptomycin	99.97		0.03	0.25	0.5	≤0.03–2
Gentamicin	98.3	0.1	1.6	≤0.5	≤0.5	≤0.5–≤0.5
Levofloxacin	90.1	0.3	9.6	0.25	1	≤0.06 to >32
Linezolid	99.99		0.01	2	4	≤0.12–8
Moxifloxacin	90.6	0.8	8.6	≤0.06	0.25	≤0.06 to >16
Nitrofurantoin	99.88	0.02	0.10	16	16	≤0.5 to >512
Tedizolid	99.6	0.4		0.25	0.5	≤0.03–1
Tigecycline ^e	99.1		0.9	0.25	0.25	≤0.03–2
Trimethoprim–sulfamethoxazole	99.4		0.6	≤0.12	≤0.12	≤0.12 to >8
Vancomycin	100			1	1	≤0.25–2
<i>Staphylococcus aureus</i> , MRSA ^b (2697)						
Cefazolin ^c			100	64	>128	≤0.5 to >128
Ceftobiprole ^d	100			1	2	0.25–4
Ciprofloxacin	22.4	0.5	77.1	>16	>16	≤0.06 to >16
Clarithromycin	19.0	0.6	80.4	>32	>32	≤0.03 to >32
Clindamycin	60.8	0.1	39.1	≤0.25	>8	≤0.25 to >8
Dalbavancin	99.8		0.2	0.06	0.06	≤0.03–1
Daptomycin	99.9		0.1	0.25	0.5	0.06–4
Gentamicin	93.4	0.3	6.3	≤0.5	1	≤0.5 to >32
Levofloxacin	14.1		85.9	>32	>32	0.12 to >32
Linezolid	99.9		0.1	2	2	≤0.12 to >16
Moxifloxacin	19.1	4.0	76.9	8	>16	≤0.06 to >16
Nitrofurantoin	99.7	0.1	0.2	16	16	8–128
Tedizolid	99.4	0.4	0.2	0.25	0.5	0.06 to >16
Tigecycline ^e	98.2		1.8	0.25	0.5	≤0.03–2
Trimethoprim–sulfamethoxazole	94.8		5.2	≤0.12	0.25	≤0.12 to >8
Vancomycin	99.9	0.1		1	1	≤0.25–4
<i>Staphylococcus epidermidis</i> (1323)						
Cefazolin				1	32	≤0.5 to >128
Ceftobiprole ^d				1	2	≤0.3–8
Ciprofloxacin	48.1	1.6	50.3	4	>16	≤0.06 to >16
Clarithromycin	34.8	1.8	63.4	32	>32	≤0.03 to >32
Clindamycin	59.7	1.4	38.9	≤0.25	>8	≤0.25 to >8
Dalbavancin				≤0.03	0.06	≤0.03–1
Daptomycin	99.8		0.2	0.25	0.25	≤0.03–2
Gentamicin	62.3	5.4	32.3	≤0.5	>32	≤0.5 to >32
Levofloxacin	44.2	1.6	54.2	4	>32	0.12 to >32
Linezolid	100			0.5	1	≤0.12–4
Moxifloxacin	48.0	8.8	43.2	1	>16	≤0.06 to >16
Nitrofurantoin	99.7	0.3		8	16	≤0.5–64
Tedizolid				0.12	0.25	≤0.03–0.5
Tigecycline ^e	98.2		1.8	0.12	0.5	≤0.03–2
Trimethoprim–sulfamethoxazole	62.3		37.7	0.25	8	≤0.12 to >8

Continued

Table 3. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% susceptible	% intermediate	% resistant	MIC ₅₀	MIC ₉₀	MIC range
Vancomycin	100			1	2	≤0.12–4
<i>Streptococcus pneumoniae</i> (3170)						
Amoxicillin/clavulanate	97.7	1.3	1.0	≤0.06	0.12	≤0.06–16
Ceftobiprole ^d	99.92		0.1	≤0.03	0.06	≤0.03–1
Ceftriaxone ^f	99.4	0.4	0.2	≤0.12	≤0.12	≤0.12–4
Cefuroxime	91.9	1.2	6.9	≤0.25	0.5	≤0.25 to >16
Ciprofloxacin	97.1		2.9	1	2	≤0.06 to >16
Clarithromycin	78.3	3.0	18.7	≤0.03	4	≤0.03 to >32
Clindamycin	92.4	0.5	7.1	≤0.25	≤0.25	≤0.25 to >8
Dalbavancin				≤0.03	≤0.03	≤0.03–0.12
Doxycycline	86.3	1.1	12.6	≤0.25	2	≤0.25 to >16
Ertapenem	98.97	0.99	0.04	≤0.06	0.12	≤0.06–4
Levofloxacin	99.2	0.1	0.7	1	1	≤0.06–32
Linezolid	99.97		0.03	1	1	≤0.12–4
Meropenem	94.9	3.3	1.8	≤0.06	0.12	≤0.06–2
Moxifloxacin	99.2	0.4	0.4	0.12	0.25	≤0.06–8
Penicillin ^f	82.6	12.8	4.6	≤0.03	0.25	≤0.03 to >8
Tedizolid				0.12	0.25	≤0.03–0.5
Telithromycin				0.008	0.06	≤0.002–2
Tigecycline ^e	99.7		0.3	0.03	0.06	≤0.015–0.25
Trimethoprim–sulfamethoxazole	84.9	6.0	9.1	≤0.12	2	≤0.12 to >8
Vancomycin	100			≤0.25	≤0.25	≤0.25–1
<i>Streptococcus agalactiae</i> (968)						
Amoxicillin/clavulanate				≤0.06	0.12	≤0.06–0.25
Ceftobiprole ^d				≤0.03	0.06	≤0.03–0.06
Ceftriaxone	100			≤0.12	≤0.12	≤0.12–0.5
Cefuroxime				≤0.25	≤0.25	≤0.25–0.5
Ciprofloxacin				0.5	1	0.25 to >16
Clarithromycin	63.5	3.1	33.4	≤0.03	>32	≤0.03 to >32
Clindamycin	79.2	0.8	20.0	≤0.25	>8	≤0.25 to >8
Dalbavancin	100			≤0.03	≤0.03	≤0.03–≤0.03
Daptomycin	100			0.25	0.25	≤0.03–1
Doxycycline				8	16	≤0.25 to >16
Ertapenem	100			≤0.06	≤0.06	≤0.06–0.12
Levofloxacin	96.4		3.6	1	1	≤0.06 to >32
Linezolid	98.1		1.9	1	2	≤0.12–4
Meropenem	100			≤0.06	≤0.06	≤0.06–0.12
Moxifloxacin				0.12	0.25	≤0.06–16
Penicillin	100			0.06	0.12	≤0.03–0.12
Tedizolid	100			0.25	0.25	≤0.03–0.5
Telithromycin				0.015	0.06	≤0.002–1
Tigecycline ^e	99.9		0.1	0.06	0.06	≤0.015–1
Trimethoprim–sulfamethoxazole				≤0.12	0.25	≤0.12–1
Vancomycin	100			0.5	0.5	≤0.25–1
<i>Streptococcus pyogenes</i> (866)						
Amoxicillin/clavulanate				≤0.06	≤0.06	≤0.06–0.25
Ceftobiprole ^d				≤0.03	0.06	≤0.03–0.5
Ceftriaxone	100			≤0.12	≤0.12	≤0.12–0.5
Cefuroxime				≤0.25	≤0.25	≤0.25–1
Ciprofloxacin				0.5	1	≤0.06 to >16
Clarithromycin	88.6	1.6	9.8	≤0.03	0.5	≤0.03 to >32

Continued

Table 3. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% susceptible	% intermediate	% resistant	MIC ₅₀	MIC ₉₀	MIC range
Clindamycin	97.5	0.1	2.4	≤0.25	≤0.25	≤0.25 to >8
Dalbavancin	100			≤0.03	≤0.03	≤0.03–0.06
Daptomycin	100			0.06	0.12	≤0.03–0.25
Doxycycline				≤0.25	4	≤0.25 to >16
Ertapenem	100			≤0.06	≤0.06	≤0.06–1
Levofloxacin	99.8	0.1	0.1	0.5	1	≤0.06–16
Linezolid	99.4		0.6	1	2	≤0.12–4
Meropenem	100			≤0.06	≤0.06	≤0.06–0.25
Moxifloxacin				0.12	0.25	≤0.06–4
Penicillin	100			≤0.03	≤0.03	≤0.03–0.12
Tedizolid	100			0.12	0.25	≤0.03–0.5
Telithromycin				0.008	0.015	≤0.002–4
Tigecycline ^e	100			0.03	0.06	≤0.015–0.25
Trimethoprim–sulfamethoxazole				≤0.12	≤0.12	≤0.12 to >8
Vancomycin	100			0.5	0.5	≤0.25–1
<i>Enterococcus faecalis</i> (2261)						
Amoxicillin/clavulanate				0.5	1	≤0.06 to >32
Ceftobiprole ^d				0.5	2	≤0.03–16
Ciprofloxacin	64.6	10.8	24.6	1	>16	≤0.06 to >16
Clarithromycin				2	>32	≤0.03 to >32
Dalbavancin	99.8		0.2	0.06	0.06	≤0.03–1
Daptomycin	98.2	1.8		1	2	≤0.03–4
Ertapenem				16	16	0.25 to >32
Levofloxacin	65.7	1.0	33.3	2	>32	0.25 to >32
Linezolid	92.6	7.4		2	2	0.25–4
Meropenem				4	8	≤0.06 to >32
Moxifloxacin				0.25	16	≤0.06 to >16
Nitrofurantoin	99.3	0.3	0.4	8	16	≤0.5–256
Tedizolid	99.7		0.3	0.25	0.5	0.06–1
Tigecycline ^e	96.0		4.0	0.12	0.25	≤0.03–1
Vancomycin	100			1	2	≤0.25–2
<i>Enterococcus faecium</i> (810)						
Amoxicillin/clavulanate				>32	>32	≤0.06 to >32
Ceftobiprole ^d				>16	>16	0.25 to >16
Ciprofloxacin	7.1	1.6	91.3	>16	>16	0.25 to >16
Clarithromycin				>32	>32	≤0.03 to >32
Dalbavancin				0.12	>16	≤0.03 to >16
Daptomycin ^g	99.5		0.5	1	2	≤0.03–16
Ertapenem				>32	>32	0.5 to >32
Levofloxacin	13.3	1.9	84.8	>32	>32	1 to >32
Linezolid	89.3	9.7	1.0	2	4	≤0.12 to >16
Meropenem				>32	>32	0.25 to >64
Moxifloxacin				>16	>16	0.12 to >16
Nitrofurantoin	31.0	28.2	40.8	64	256	≤0.5 to >512
Tedizolid				0.25	0.5	0.12–4
Tigecycline ^e				0.12	0.25	≤0.03–2
Vancomycin	76.9	0.1	23.0	1	>32	≤0.25 to >32
<i>Vancomycin-resistant enterococci</i> (186) ^h						
Amoxicillin/clavulanate				>32	>32	4 to >32
Ciprofloxacin			100	>16	>16	16 to >16
Clarithromycin				>32	>32	0.06 to >32

Continued

Table 3. Continued

Organism (no. of isolates) Antimicrobial agent ^a	MIC interpretation			MIC (mg/L)		
	% susceptible	% intermediate	% resistant	MIC ₅₀	MIC ₉₀	MIC range
Daptomycin ^g	98.4		1.6	1	2	≤0.03–16
Ertapenem				>32	>32	32 to >32
Levofloxacin			100	>32	>32	32 to >32
Linezolid	86.0	11.3	2.7	2	4	0.5 to >16
Meropenem				>32	>32	32 to >64
Moxifloxacin				>16	>16	8 to >16
Nitrofurantoin	17.4	21.1	61.5	128	256	4 to >512
Tedizolid				0.25	0.5	0.12–4
Tigecycline ^e				0.12	0.25	≤0.03–0.5
Vancomycin			100	>32	>32	32 to >32

Clindamycin inducibility was not tested for staphylococci or streptococci.
^aOrganism-antimicrobial combinations for which intrinsic resistance is known have been excluded from the table.
^bMSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; HA, healthcare-associated; CA, community-associated.
^cSusceptibility and resistance to cefazolin based upon oxacillin susceptibility testing result.
^dHealth Canada approved breakpoints were used to interpret ceftobiprole MICs.
^eFDA approved breakpoints were used to interpret tigecycline MICs.
^fMICs interpreted by CLSI breakpoints for ceftriaxone (non-meningitis MIC breakpoints) and penicillin (oral penicillin V MIC breakpoints).
^gCLSI susceptible-dose dependent (SDD) breakpoints were used to interpret daptomycin MICs.
^hVancomycin-resistant enterococci were comprised of 177 *vanA* isolates, eight *vanB* isolates and one isolate with both *vanA* and *vanD* genes.

Consistent with other reports, we report that vancomycin was potent against MSSA and MRSA with only three isolates (0.11%) of MRSA displaying a vancomycin MIC of 4 mg/L and no vancomycin MIC creep.^{4,16–19} Vancomycin was less potent against *S. epidermidis* than against MSSA and MRSA, which is consistent with previous reports.^{4,19} In this study, as well as in previous reports, vancomycin remains very active against all *Streptococcus* spp.^{7,16,19} Vancomycin was also less potent against *E. faecium* with 23.0% of isolates demonstrating resistance. Consistent with reports in international studies,^{19,20} the predominant *vanA* genotype continues to be the most common form of VRE in Canada (~95% in this study).

Linezolid was active against MSSA, MRSA, MSSE, MRSE and *Streptococcus* spp., with 86.1%–100% of all isolates demonstrating susceptibility to linezolid. Linezolid’s continued high-level *in vitro* activity versus these isolates is consistent with the current literature.^{16,18–21} Linezolid was less active against *E. faecalis* and *E. faecium* with 7.4% and 9.7% of isolates demonstrating an intermediate MIC interpretation (and 1.0% resistance for *E. faecium*), respectively. The observed low rate of linezolid non-susceptibility in *E. faecalis* and *E. faecium* is consistent with previous reports.^{16,19,21} Tedizolid was active against MSSA, MRSA, MSSE, MRSE, *Streptococcus* spp. and *Enterococcus* spp., with 4–8-fold greater activity versus linezolid. Tedizolid’s 4–8-fold greater activity versus Gram-positive cocci compared to linezolid has been well described.^{16,21,22}

Daptomycin was active against MSSA, MRSA, methicillin-susceptible *S. epidermidis* (MSSE) and methicillin-resistant *S. epidermidis* (MRSE) with 95.1%–100% susceptibility. Daptomycin’s excellent activity against MSSA, MRSA, MSSE and MRSE has been previously documented.^{16,18–21} In addition, it has been reported

that daptomycin displays excellent activity (MIC₉₀ of 0.5 mg/L) and maintains bactericidal activity against MRSA with vancomycin MICs of 2 mg/L, many of which are heteroresistant VISAs (vancomycin-intermediate *S. aureus*).^{5,18} As has been previously reported, daptomycin was active against *Streptococcus* spp.¹⁹ Daptomycin was also very active against *E. faecalis*, *E. faecium* and VRE. Daptomycin-resistant *Enterococcus* spp. continue to be rare in Canada, consistent with previous reports from Canada and the USA.^{15,19,20} From our data, it is clear that daptomycin is a very active agent against all common Gram-positive organisms causing infections in Canadian hospitals.

Dalbavancin was active against MSSA, MRSA, MSSE and MRSE with ≥99.6% susceptibility. Dalbavancin’s excellent activity against Gram-positive pathogens has been previously documented.^{18,19,23–25} As has been previously reported, dalbavancin was active against *Streptococcus* spp.^{19,23–25} Dalbavancin was also very active against *E. faecalis*, but not VRE (*vanA E. faecium*).^{19,23,24} From our data, it is clear that dalbavancin is a very active agent against common Gram-positive organisms causing infections in Canadian hospitals.

Tigecycline was active against MSSA, MRSA, MSSE and MRSE, which has been previously documented.^{5,26} In addition, tigecycline was very active against *Streptococcus* spp. and also very active against *E. faecalis* and *E. faecium*, including VRE isolates. In Canada, tigecycline continues to be a very active agent against common Gram-positive organisms.

Ceftobiprole was active against MSSA, MRSA, MSSE, MRSE and *Streptococcus* spp. which has been previously documented.^{5,27–29} Unlike other cephalosporins, it was active against *E. faecalis* but not *E. faecium*.^{5,27,28} In Canada, ceftobiprole continues to be the only cephalosporin available for use which is active against MRSA

(100% susceptible using Health Canada breakpoints) as ceftaroline is not approved for usage.^{5,18,28,30}

The data generated by the CANWARD surveillance study have three important limitations. One, each participating medical centre commits to study criteria that encourage the submission of clinically significant specimens from patients with a presumed infectious disease, however, this interpretation cannot be rigorously controlled by the coordinating site. Two, the coordinating site does not have admission date data for each patient/clinical specimen, thus we are not able to provide an accurate description of community versus healthcare onset. Third, 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.

In conclusion, *S. aureus*, *Streptococcus* spp. and *Enterococcus* spp. are the most common Gram-positive bacterial pathogens in Canadian hospitals. MRSA rates decreased significantly during 2007–15 from 26.0% to 19.3% ($P < 0.0001$) and subsequently increased significantly through study years 2016–23 (16.9%–24.1%; $P = 0.002$). All isolates of MSSA were susceptible to ceftobiprole, dalbavancin and vancomycin. MRSA susceptibilities were highest with ceftobiprole, dalbavancin, daptomycin, linezolid, tedizolid and vancomycin. *S. pneumoniae* susceptibilities were highest to amoxicillin/clavulanate, ceftobiprole, ceftriaxone, linezolid, tigecycline and vancomycin. VRE rates ranged from 3.8% to 18.4%, with marked fluctuation year-to-year. Daptomycin and linezolid demonstrated the highest susceptibilities for VRE.

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Transparency declarations

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Disclaimer

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References

- 1 WHO 2024 Bacterial Priority Pathogens. Available at: <https://www.who.int/publications/i/item/9789240093461>.
- 2 GBD 2021 Antimicrobial resistance collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet* 2024; **404**: 1199–226. [https://doi.org/10.1016/S0140-6736\(24\)01867-1](https://doi.org/10.1016/S0140-6736(24)01867-1)
- 3 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399**: 629–55. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
- 4 Lynch JP, Zhanet GG. Escalation of antimicrobial resistance among MRSA part 1: focus on global spread. *Expert Rev Anti Infect Ther* 2023; **21**: 99–113. <https://doi.org/10.1080/14787210.2023.2154653>
- 5 Lynch JP III, Zhanet GG. Escalation of antimicrobial resistance among MRSA part 2: focus on infections and treatment. *Expert Rev Anti Infect Ther* 2023; **21**: 115–26. <https://doi.org/10.1080/14787210.2023.2154654>
- 6 Pfaller MA, Carvalhaes CG, Smith CJ *et al.* Bacterial and fungal pathogens isolated from patients with bloodstream infection: frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (2012–2017). *Diagn Microbiol Infect Dis* 2020; **97**: 115016. <https://doi.org/10.1016/j.diagmicrobio.2020.115016>
- 7 Deshpande LM, Huband MD, Charbon S *et al.* High rates of nonsusceptibility to common oral antibiotics in *Streptococcus pneumoniae* clinical isolates from the United States (2019–2021). *Open Forum Infect Dis* 2024; **11**: ofae470. <https://doi.org/10.1093/ofid/ofae470>
- 8 Rotstein C, Lynch JP III, Zhanet GG. Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in Canada: treatment update and the role of new IV antimicrobials. *Expert Rev Anti Infect Ther* 2023; **9**: 1–13. <https://doi.org/10.1080/14787210.2023.2268287>
- 9 Zhanet GG, Adam HJ; Canadian Antimicrobial Resistance Alliance (CARA) and CANWARD. Ten years of the CANWARD study (2007–16). *J Antimicrob Chemother* 2019; **74**(Suppl 4): iv2–4. <https://doi.org/10.1093/jac/dkz282>
- 10 Zhanet GG, Adam HJ, Baxter MR *et al.* 42 936 pathogens from Canadian hospitals: 10 years of results (2007–16) from the CANWARD surveillance study. *J Antimicrob Chemother* 2019; **74**(Suppl 4): iv5–21. <https://doi.org/10.1093/jac/dkz283>
- 11 Fuller J, Dingle TC, Bull A *et al.* Species distribution and antifungal susceptibility of invasive *Candida* isolates from Canadian hospitals: results of the CANWARD 2011–16 study. *J Antimicrob Chemother* 2019; **74**(Suppl 4): iv48–54. <https://doi.org/10.1093/jac/dkz287>
- 12 CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically–Twelfth Edition: M07. 2024.
- 13 CLSI. Performance Standards for Antimicrobial Susceptibility Testing–Thirty-Fourth Edition: M100. 2024.
- 14 Nichol KA, Adam HJ, Golding GR *et al.* Characterization of MRSA in Canada from 2007 to 2016. *J Antimicrob Chemother* 2019; **74**(Suppl 4): 55–63. <https://doi.org/10.1093/jac/dkz288>
- 15 Simner PJ, Adam H, Baxter M *et al.* Epidemiology of vancomycin-resistant enterococci in Canadian hospitals (CANWARD study, 2007 to 2013). *Antimicrob Agents Chemother* 2015; **59**: 4315–7. <https://doi.org/10.1128/AAC.00384-15>

- 16 Carvalhoes CG, Sader HS, Rhomberg PR et al. Activity of tedizolid and comparator agents against Gram-positive isolates causing skin and skin structure infections in pediatric patients in United States hospitals (2015–2019). *Ped Infect Dis J* 2022; **41**: 731–5. <https://doi.org/10.1097/INF.0000000000003597>
- 17 Paukner S, Mendes RE, Ryan Arends SJ et al. 7-Year (2015–21) longitudinal surveillance of lefamulin in vitro activity against bacterial pathogens collected worldwide from patients with respiratory tract infections including pneumonia and characterization of resistance mechanisms. *J Antimicrob Chemother* 2024; **79**: 360–9. <https://doi.org/10.1093/jac/dkad389>
- 18 Sader HS, Castanheira M, Duncan LR et al. Update on the in vitro activity of ceftaroline against *Staphylococcus aureus* from United States (US) medical centers stratified by infection type (2018–2020). *Diag Microbiol Infect Dis* 2023; **105**: 115820. <https://doi.org/10.1016/j.diagmicrobio.2022.115820>
- 19 Sader HS, Castanheira M, Huband M et al. Antimicrobial activity of dalbavancin against Gram-positive bacteria isolated from patients hospitalized with bloodstream infection in United States and European medical centers (2018–2020). *Eur J Clin Microbiol Infect Dis* 2022; **41**: 867–73. <https://doi.org/10.1007/s10096-022-04437-0>
- 20 Carvalhoes CG, Sader HS, Streit JM et al. Activity of oritavancin against Gram-positive pathogens causing bloodstream infections in the United States over 10 years: focus on drug-resistant enterococcal subsets (2010–2019). *Antimicrob Agents Chemother* 2022; **66**: e0166721. <https://doi.org/10.1128/AAC.01667-21>
- 21 Pfaller MA, Mendes RE, Streit JM et al. Tedizolid in vitro activity against Gram-positive clinical isolates causing bone and joint infections in hospitals in the USA, Europe, Latin America, and the Asia-Pacific region (2015–2019). *Diagn Microbiol Infect Dis* 2022; **104**: 115804. <https://doi.org/10.1016/j.diagmicrobio.2022.115804>
- 22 Zhanel GG, Love R, Adam H et al. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant Gram-positive pathogens. *Drugs* 2015; **75**: 253–70. <https://doi.org/10.1007/s40265-015-0352-7>
- 23 Zhanel GG, Calic D, Schweizer F et al. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; **70**: 859–86. <https://doi.org/10.2165/11534440-000000000-00000>
- 24 Karlowksy JA, Nichol K, Zhanel GG. Telavancin: mechanisms of action, in vitro activity, and mechanisms of resistance. *Clin Infect Dis* 2015; **61** Suppl 2: S58–68. <https://doi.org/10.1093/cid/civ534>
- 25 Zhanel G, Silverman M, Malhotra J et al. Real-life experience with IV dalbavancin in Canada; results from the CLEAR (Canadian LEadership on Antimicrobial Real-life usage) registry. *J Glob Antimicrob Resist* 2024; **38**: 154–7. <https://doi.org/10.1016/j.jgar.2024.06.002>
- 26 Zhanel GG, Cheung D, Adam H et al. Review of eravacycline, a novel fluorocycline antibacterial agent. *Drugs* 2016; **76**: 567–88. <https://doi.org/10.1007/s40265-016-0545-8>
- 27 Pfaller MA, Flamm RK, Duncan LR et al. Antimicrobial activity of ceftobiprole and comparator agents when tested against contemporary Gram-positive and -negative organisms collected from Europe (2015). *Diagn Microbiol Infect Dis* 2018; **91**: 77–84. <https://doi.org/10.1016/j.diagmicrobio.2017.12.020>
- 28 Zhanel GG, Lam A, Schweizer F et al. Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am J Clin Dermatol* 2008; **9**: 245–54. <https://doi.org/10.2165/00128071-200809040-00004>
- 29 Zhanel GG, Kosar J, Baxter M et al. How is ceftobiprole used in Canada: the CLEAR study final results. *Expert Rev Anti Infect Ther* 2024; **22**: 681–8. <https://doi.org/10.1080/14787210.2024.2374280>
- 30 Zhanel GG, Sniezek G, Schweizer F et al. Ceftaroline: a novel broad-spectrum cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*. *Drugs* 2009; **69**: 809–31. <https://doi.org/10.2165/00003495-200969070-00003>
- 31 Zhanel GG, Adam HJ. Seventeen years of the CANWARD study (2007–23). *J Antimicrob Chemother* 2025; **80**(Suppl 2): ii2–4. <https://doi.org/10.1093/jac/dkaf216>