

# CANWARD 2013: Antimicrobial Resistance in Pathogens Isolated from Canadian Hospital Clinics, Emergency Rooms, Medical/Surgical Wards and Intensive Care Units

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## REVISED ABSTRACT

**Objectives:** The CANWARD study assesses the pathogens causing infections in patients affiliated with Canadian hospitals and evaluates the prevalence of antimicrobial resistance in these isolates.

**Methods:** 15 tertiary-care centres across Canada submitted pathogens causing infections from patients attending clinics (C), emergency rooms (ER), medical and surgical wards (W) and intensive care units (ICU) in 2013. Susceptibility testing was performed by CLSI microdilution methods.

**Results:** A total of 3,511 isolates were collected: 41.2%, 38.8%, 10.5%, and 9.5% from blood, respiratory, urine and wound/IV site specimens, respectively. Isolates were from patients on W 37.6%, ER 22.9%, ICU 21.7%, and C 17.8%. The most common pathogens were: *E. coli* 18.7%, *S. aureus* (MSSA) 18.0%, *P. aeruginosa* 11.0%, *K. pneumoniae* 6.6%, *S. pneumoniae* 5.4% and *H. influenzae* 4.9%. Resistance rates (RR) for *E. coli* were: 0% for tigecycline (TGC), 0.2% meropenem (MER), 0.3% ertapenem (ERT) 1.1% piperacillin/tazobactam (PTZ), 9.8% gentamicin (GEN), 12.2% ceftriaxone (CTR), 24.9% ciprofloxacin (CIP) and 27.9% trimethoprim/sulfamethoxazole (SXT). For *P. aeruginosa*, RR were 3.4% colistin (COL), 6.7% GEN, 7.3% PTZ, 11.1% CIP, and 11.9% MER. RR for MRSA were: 0% vancomycin (VAN), linezolid (LZD), and daptomycin (DAP), 2.5% SXT, 32.7% clindamycin, 74.2% clarithromycin, and 78.0% CIP. Overall, the prevalence of MRSA was 20.1%.

**Conclusions:** In Canada, resistance rates for *E. coli* remain lowest for MER, ERT, TGC and PTZ, while for *P. aeruginosa*, rates are lowest with COL, PTZ, and GEN. No resistance was observed in MRSA with VAN, LZD, or DAP.

## BACKGROUND

Infections caused by antimicrobial resistant pathogens are a serious issue in Canada, and many parts of the world. Resistant pathogens include methicillin-resistant *Staphylococcus aureus* (community and healthcare-associated), vancomycin resistant enterococci (VRE), *Escherichia coli* and *Klebsiella* species resistant to extended-spectrum  $\beta$ -lactams, penicillin-resistant *Streptococcus pneumoniae*, and carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*. Treatment options for these infections are often limited as these pathogens are frequently multidrug-resistant (MDR).

## OBJECTIVES

The CANWARD study is a national, ongoing, population-based surveillance study. CANWARD, a study initiated in 2007, has three primary objectives:

- To determine the pathogens associated with respiratory, urinary, bacteremic, and wound/IV site infections in patients affiliated with Canadian hospitals.
- To determine the prevalence of antimicrobial resistance in pathogens associated with respiratory, urinary, bacteremic, and wound/IV site infections in patients affiliated with Canadian hospitals.
- To assess the activity of antimicrobials against respiratory, urinary, bacteremic, and wound/IV site pathogens in patients affiliated with Canadian hospitals.

## MATERIALS & METHODS

**Participating Sites:** Fifteen sentinel hospital sites in major population centres in 8 of the 10 provinces in Canada were recruited. These sites were geographically distributed in a population based fashion.

**Bacterial Isolates:** Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. From January through October 2013, each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory (100), urine (25), wound (25), and bloodstream (10/month x 10 months) infections. The medical centres submitted "clinically significant" isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. 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 minimum inhibitory concentration (MIC) testing was carried out. Characterization of MRSA isolates (*spa* typing) and putative VRE isolates (*van* PCR analysis) was performed at the National Microbiology Laboratory. In 2013, a total of 3,511 isolates were collected for the primary objectives of CANWARD.

**Antimicrobial Susceptibility Testing:** Following 2 subcultures from frozen stock, the *in vitro* activity of antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (M7-A9, 2012). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (M100-S23, 2013). Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (M7-A9, 2012). The MICs of the antimicrobial agents for the isolates were determined using 96-well custom designed microtitre plates. These plates contained doubling antimicrobial dilutions in 100 $\mu$ L/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10<sup>5</sup> CFU/mL then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms including *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

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Table 1. Top Pathogens Isolated in Canadian Hospitals in 2013

Rank	Organism	n	% of Total
1	<i>Escherichia coli</i>	655	18.7
2	<i>Staphylococcus aureus</i> , MSSA	632	18.0
3	<i>Pseudomonas aeruginosa</i>	386	11.0
4	<i>Klebsiella pneumoniae</i>	230	6.6
5	<i>Streptococcus pneumoniae</i>	188	5.4
6	<i>Haemophilus influenzae</i>	173	4.9
7	<i>Staphylococcus aureus</i> , MRSA	159	4.5
8	<i>Enterococcus faecalis</i>	104	3.0
9	CNS / <i>Staphylococcus epidermidis</i>	96	2.7
10	<i>Enterobacter cloacae</i>	85	2.4
11	<i>Stenotrophomonas maltophilia</i>	67	1.9
12	<i>Streptococcus agalactiae</i>	63	1.8
13	<i>Proteus mirabilis</i>	61	1.7
14	<i>Klebsiella oxytoca</i>	52	1.5
15	<i>Streptococcus pyogenes</i>	51	1.5
16	<i>Serratia marcescens</i>	50	1.4
17	<i>Enterococcus faecium</i>	47	1.3
18	<i>Moraxella catarrhalis</i>	35	1.0
19	<i>Candida albicans</i>	31	0.9
20	<i>Haemophilus parainfluenzae</i>	28	0.8
	Other	318	9.1
		<b>3,511</b>	

Figure 1. Patient Demographics by Hospital Location, Specimen Source, Gender, and Age Group (% of Total)

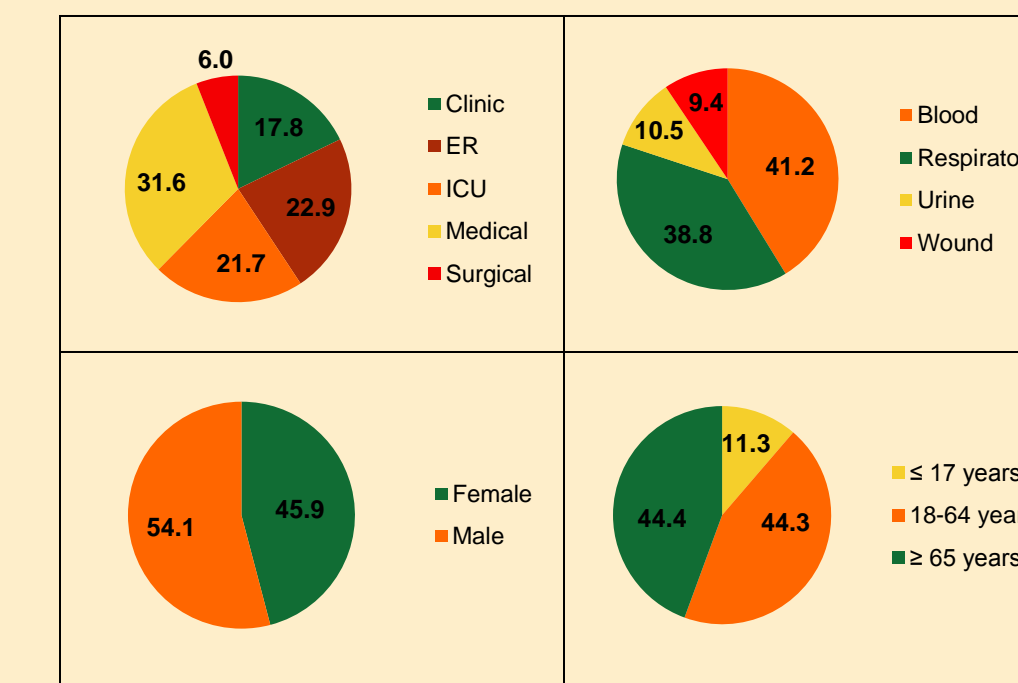
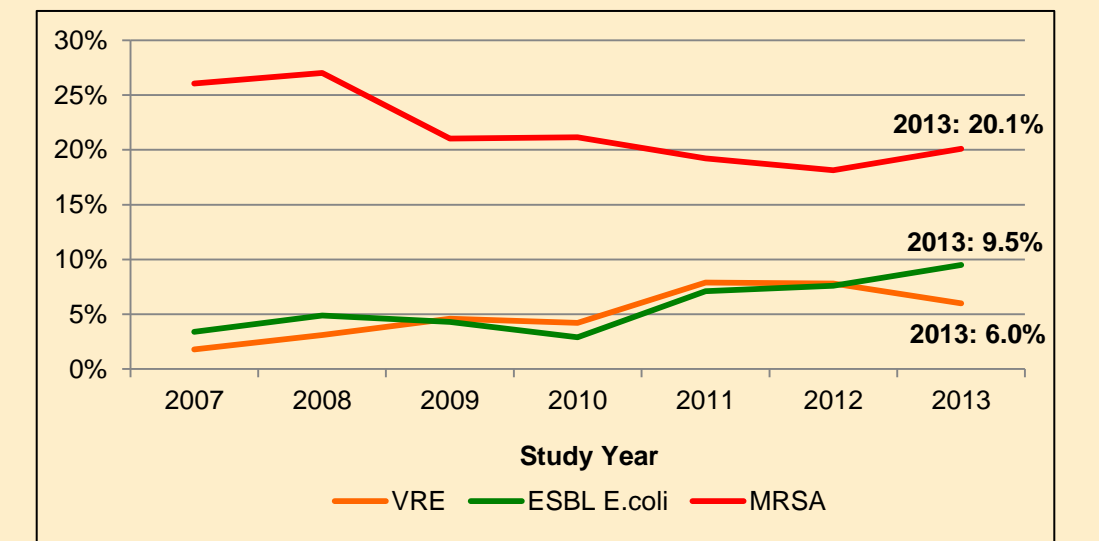


Figure 2. Prevalence (%) of MRSA, VRE and ESBL *E. coli* in CANWARD 2013



HA-MRSA: 57.2% (91/159); CA-MRSA: 35.8% (57/159)  
VRE: 6.0% (9/151 [9 vanA])

### *Staphylococcus aureus*, MSSA (n=630)

Antimicrobial Agent	Susceptibility					
	% S	% I	% R	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
Ciprofloxacin	85.7	4.3	10.0	0.5	2	≤ 0.06 > 16
Clarithromycin	76.3	1.3	22.4	0.12	> 32	≤ 0.03 > 32
Clindamycin	95.1	0.2	4.8	≤ 0.12	≤ 0.12	≤ 0.12 > 8
Daptomycin	100			0.25	0.25	0.06 1
Gentamicin	98.1	0.2	1.7	≤ 0.5	≤ 0.5	≤ 0.5 > 32
Linezolid	100			2	2	0.5 4
Moxifloxacin	90.5	1.4	8.1	≤ 0.06	0.25	≤ 0.06 > 16
Tigecycline *	99.5			0.25	0.25	0.06 1
Trimethoprim Sulfa	99.7		0.3	≤ 0.12	≤ 0.12	≤ 0.12 > 8
Vancomycin	100			0.5	1	≤ 0.12 2

\* FDA breakpoints used for tigecycline

### *Staphylococcus aureus*, MRSA (n=159)

Antimicrobial Agent	Susceptibility					
	% S	% I	% R	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
Ciprofloxacin	21.4	0.6	78.0	> 16	> 16	0.25 > 16
Clarithromycin	23.3	2.5	74.2	> 32	> 32	≤ 0.03 > 32
Clindamycin	67.3		32.7	≤ 0.12	> 8	≤ 0.12 > 8
Daptomycin	100			0.25	0.25	0.12 0.5
Gentamicin	93.1	1.9	5.0	≤ 0.5	1	≤ 0.5 > 32
Linezolid	100			2	2	1 4
Moxifloxacin	22.6	6.9	70.4	4	> 16	≤ 0.06 > 16
Tigecycline *	98.1			0.25	0.25	0.12 1
Trimethoprim Sulfa	97.5		2.5	≤ 0.12	≤ 0.12	≤ 0.12 > 8
Vancomycin	100			0.5	1	0.5 1

\* FDA breakpoints used for tigecycline

Tables 2-6. Antimicrobial Activities Against Common Gram Negative and Gram Positive Pathogens

### *Escherichia coli* (n=655)

Antimicrobial Agent	Susceptibility					
	% S	% I	% R	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
Amikacin	100			≤ 1	2	≤ 1 16
Amoxicillin Clav	81.4	12.1	6.6	4	16	0.5 > 32
Cefazolin	72.1	7.3	20.6	2	> 128	≤ 0.5 > 128
Cefepime	97.9	0.8	1.4	≤ 0.25	1	≤ 0.25 > 64
Cefoxitin	93.0	2.3	4.7	4	8	1 > 32
Ceftazidime	90.7	0.9	8.4	≤ 0.25	4	≤ 0.25 > 32
Ceftriaxone	87.8		12.2	≤ 0.25	16	≤ 0.25 > 64
Ciprofloxacin	75.1		24.9	≤ 0.06	> 16	≤ 0.06 > 16
Colistin	No breakpoints defined			0.25	0.5	0.12 > 16
Doripenem	99.8		0.2	≤ 0.03	≤ 0.03	≤ 0.03 16
Ertapenem	99.4	0.3	0.3	≤ 0.03	≤ 0.03	≤ 0.03 > 32
Gentamicin	89.8	0.5	9.8	≤ 0.5	8	≤ 0.5 > 32
Meropenem	99.8		0.2	≤ 0.03	≤ 0.03	32
Moxifloxacin	No breakpoints defined			≤ 0.06	16	≤ 0.06 > 16
Piperacillin Tazo	97.7	1.2	1.1	≤ 1	4	≤ 1 > 512
Tigecycline *	99.8	0.2		0.25	0.5	0.12 4
Trimethoprim Sulfa	72.1		27.9	≤ 0.12	> 8	≤ 0.12 > 8

\* FDA breakpoints used for tigecycline

### *Pseudomonas aeruginosa* (n=386)

Antimicrobial Agent	Susceptibility					
	% S	% I	% R	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
Amikacin	96.6	1.3	2.1	2	8	≤ 1 > 64
Cefepime	86.5	9.1	4.4	2	8	≤ 0.25 > 64
Ceftazidime	82.1	4.9	13.0	2	32	≤ 0.25 > 32
Ceftriaxone	No breakpoints defined			16	> 64	≤ 0.25 > 64
Ciprofloxacin	80.6	8.3	11.1	0.12	4	≤ 0.06 > 16
Colistin	94.8	1.8	3.4	1	2	0.12 > 16
Doripenem	85.5	4.4	10.1	0.5	8	≤ 0.03 > 32
Gentamicin	91.2	2.1	6.7	1	4	≤ 0.5 > 32
Meropenem	81.3	6.7	11.9	0.5	8	≤ 0.03 > 32
Piperacillin Tazo	85.0	7.8	7.3	4	32	≤ 1 > 512

### *Streptococcus pneumoniae* (n=182)

Antimicrobial Agent	Susceptibility					
	% S	% I	% R	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
Amoxicillin Clav <sup>a</sup>	96.7	2.7	0.5	≤ 0.06	0.12	≤ 0.06 8
Ceftriaxone	98.9	1.1		≤ 0.12	0.25	≤ 0.12 2
Cefuroxime <sup>b</sup>	94.0	1.1	4.9	≤ 0.25	≤ 0.25	≤ 0.25 16
Ciprofloxacin	96.7		3.3	1	2	0.12 > 16
Clarithromycin	73.1	3.3	23.6	≤ 0.03	4	≤ 0.03 > 32
Clindamycin	92.9	1.1	6.0	≤ 0.12	≤ 0.12	≤ 0.12 > 64
Doripenem	100			≤ 0.03	≤ 0.03	≤ 0.03 1
Doxycycline	84.1	1.6	14.3	≤ 0.25	2	≤ 0.25 16
Ertapenem	97.3	2.7		≤ 0.06	0.12	≤ 0.06 2
Levofloxacin	97.2		2.8	1	1	≤ 0.06 16
Linezolid	100			1	2	≤ 0.12 2
Meropenem	94.0	3.8	2.2	≤ 0.06	≤ 0.06	≤ 0.06 1
Moxifloxacin	97.8	1.7	0.6	0.12	0.25	≤ 0.06 4
Penicillin <sup>c</sup>	84.6	11.0	4.4	≤ 0.03	0.25	≤ 0.03 4
Teithromycin	100			0.008	0.12	≤ 0.002 0.5
Tigecycline *	100			≤ 0.015	0.03	≤ 0.015 0.03
Trimethoprim Sulfa	84.0	6.1	9.9	0.25	2	≤ 0.12 > 8
Vancomycin	100			0.25	0.25	≤ 0.12 0.5

<sup>a</sup> CLSI non-meeting breakpoints used; <sup>b</sup> cefuroxime oral breakpoints used; <sup>c</sup> penicillin V breakpoints used; \* FDA breakpoints used for tigecycline

## CONCLUSIONS

- Of the 3,511 pathogens obtained, the most common were: *E. coli* 18.7%, *S. aureus* (MSSA) 18.0%, *P. aeruginosa* 11.0%, *K. pneumoniae* 6.6%, and *S. pneumoniae* 5.4%.
- For *E. coli*, susceptibility was greatest to amikacin 100%, tigecycline 99.8%, meropenem 99.8%, and piperacillin-tazobactam 97.7%.
- For *P. aeruginosa*, susceptibility was greatest to amikacin 96.6%, colistin 94.8%, gentamicin 91.2%, and cefepime 86.5%.
- All MRSA isolates remained 100% susceptible to vancomycin, linezolid and daptomycin.
- Statistical analysis revealed that rates of ESBL-producing *E. coli* have increased significantly from 3.4% in 2007 to 9.5% in 2013.