C-112

# Trends in Antimicrobial Resistance in Canada Over Seven Years: Not All Bad News?


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## ABSTRACT (REVISED)


**Background:** Changes in antimicrobial resistance over time are important because they help inform decisions on antimicrobial stewardship and help identify potential future needs in new antimicrobial discovery/development. We describe trends observed in antimicrobial resistance in key pathogens in Canada over the past 7 years from the CANWARD surveillance program.

**Methods:** CANWARD is a national surveillance study assessing antimicrobial resistance from clinically relevant isolates in Canadian hospitals. Fifteen tertiary-care centers from across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. A total of 7718, 5282, 5375, 4868, 3557, 2808 and 3511 isolates were collected between 2007 and 2013, respectively. Isolates were tested for resistance to 18 different antimicrobials using microbroth dilution and interpreted according to CLSI 2013 criteria. A multiple regression model considering possible changes in demographic variables which included age, gender, specimen source and hospital ward (inpatient, outpatient or ICU) was used to ensure changes over time were independent of changes in other variables.

**Results:** Observed trends are summarized in the table below. Only antimicrobials where a significant trend was observed are noted.

**Conclusions:** In Canada, resistance to several key antimicrobials have decreased over the past seven years for *P. aeruginosa*, *S. aureus* and MRSA in Canada. Resistance to ciprofloxacin and ceftriaxone have increased in *E. coli*. Efforts to reduce increasing resistance should focus on *E. coli* and *K. pneumoniae* while maintaining vigilance for the emergence of other relevant antibiotic-resistant pathogens.


## INTRODUCTION

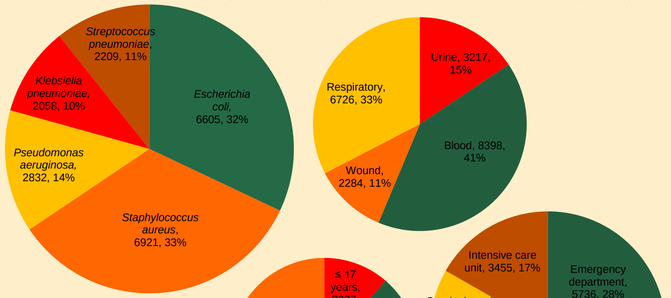
Antimicrobial resistance patterns change over time and longitudinal surveillance studies provide insight into these trends. We sought to describe the important trends in antimicrobial resistance in key pathogens across Canada to provide useful information to clinicians, policy makers and industry to assist in optimizing antimicrobial therapy, formulary choices and drug development.

## MATERIALS & METHODS

Isolates were collected as part of the CANWARD study occurring between January 2007 and December 2013. Up to 18 Canadian centers in 8 provinces contributed clinically relevant isolates. To ensure sufficient statistical power for the analysis, only isolates where >1000 organisms were submitted during the whole study period and for which >100 isolates per year were available for analysis were considered. These included: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus pneumoniae,* and *Staphylococcus aureus.* Susceptibility testing to key antimicrobials for each species was done using broth microdilution in accordance with the CLSI M07-A9 document (1). Susceptibility breakpoints were done in accordance with the CLSI M100-S23 (2) document. For the purpose of statistical analysis, isolates were defined to be either susceptible or non-susceptible. Variables included year of study, age group, gender, hospital location and specimen type. A second degree factorial multivariate logistic regression analysis using available demographic variables was used to isolate the effect of time on susceptibility from changes in demographic variables that may have occurred in the dataset as well as second degree interactions among the variables. Statistical analysis was performed using JMP 11 software by SAS (Cary, NC, USA).

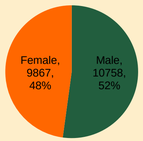
## RESULTS

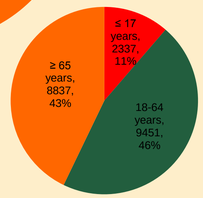
FIGURE 1: Distribution of isolates (n = 20,625), age of patients, patient location specimen type and gender.









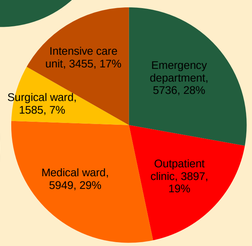




TABLE 1: Organism-antimicrobial combinations showing trends for **non-susceptibility** in the 7 year study. The change in total proportion of resistant isolates may not appear significant due to interactions between variables. These are nevertheless significant when controlled for these interactions. These variables are clearly explained in the Methods.

| Organism | Antibiotic or genotype | Proportion non-susceptible or positive (2007) | Proportion non-susceptible or positive (2013) | P value |
|---|---|---|---|---|
| *Escherichia coli* | AmpC hyperproducer | 0.3% | 3.1% | <0.01 |
| | Amoxicillin-clavulanate | 9.5% | 28.6% | <0.01 |
| | Ceftriaxone | 5.8% | 12.2% | <0.01 |
| | Ceftazidime | 5%[1] | 9.3% | <0.01 |
| | Ciprofloxacin | 20.7% | 24.8% | 0.02 |
| *Klebsiella pneumoniae* | Ceftriaxone | 5.3% | 7.7% | 0.03 |
| | Ceftazidime | 3.2%[1] | 8.5% | <0.01 |
| | Meropenem | 0% | 1.3% | <0.01 |
| | Ertapenem | 0% | 1.7% | <0.01 |
| *Streptococcus pneumoniae* | Levofloxacin | 0.6% | 2.8% | <0.01 |
| | Clindamycin | 8.5% | 7.1% | 0.02 |
| | Clarithromycin | 9% | 10.6% | <0.01 |

[1]Data available from 2008-2013 only.

TABLE 2: Organism-antimicrobial combinations showing trends for **non-susceptibility** in the 7 year study. The change in total proportion of resistant isolates may not appear significant due to interactions between variables. These are nevertheless significant when controlled for these interactions. These variables are clearly explained in the Methods.

| Organism | Antibiotic or genotype | Proportion non-susceptible or positive (2007) | Proportion non-susceptible or positive (2013) | P value |
|---|---|---|---|---|
| *Escherichia coli* | Cefazolin | 32.6% | 17.9% | 0.01 |
| *Pseudomonas aeruginosa* | Piperacillin-tazo | 15.2% | 15.0% | <0.01 |
| | Cefepime | 32.6% | 13.5% | <0.01 |
| | Amikacin | 14.4% | 3.4% | <0.01 |
| | Gentamicin | 39.7% | 8.8% | <0.01 |
| *Streptococcus pneumoniae* | Penicillin (oral breakpoints) | 20.8% | 15.4% | <0.01 |
| *Staphylococcus aureus* | MRSA | 26.1% | 20.1% | <0.01 |
| | Ciprofloxacin | 35.4% | 27.5% | <0.01 |
| | Co-trimoxazole | 3.7% | 0.8% | <0.01 |
| | Clindamycin | 22.8% | 10.5% | <0.01 |

TABLE 3: Organism-antimicrobial combinations showing **no significant trends** in resistance in the 7 year study.

| Organism | Antibiotic |
|---|---|
| *Escherichia coli* | Gentamicin<br>Co-trimoxazole<br>Piperacillin-tazobactam<br>Ertapenem<br>Meropenem |
| *Klebsiella pneumoniae* | Amoxicillin-clavulanate<br>Cefazolin<br>Gentamicin<br>Ciprofloxacin<br>Co-trimoxazole<br>Piperacillin-tazobactam |
| *Pseudomonas aeruginosa* | Tobramycin<br>Ceftazidime[1]<br>Meropenem<br>Ciprofloxacin |
| *Streptococcus pneumoniae* | Ceftriaxone<br>Cefuroxime<br>Co-trimoxazole<br>Vancomycin |
| *Staphylococcus aureus* | Vancomycin<br>Daptomycin<br>Linezolid<br>Clarithromycin |

[1]Data available from 2008-2013 only.

## CONCLUSIONS

We have observed an increase in resistance phenotypes for *E. coli* and *K. pneumoniae*. In particular *E. coli* has demonstrated an alarming trend towards increasing resistance to several key antimicrobials. This observation has been made globally, and is partially related to the expansion of ESBL and AmpC producing strains globally (3).

We observed increasing resistance to levofloxacin, clarithromycin and clindamycin in *S. pneumoniae*. These trends have been modest and may reflect the emergence of multi-drug-resistant 19A and other serotypes reported by us and others (4).

We observed a significant reduction in resistance phenotypes for *P. aeruginosa* to several key antibiotics. Although the explanation is not known, a reduction in the prevalence of strains expressing the MexX-MexY-OprM efflux system, which has specificity for cefepime, ciprofloxacin and aminoglycosides (5), may explain the observation.

We observed a significant reduction in the proportion of ciprofloxacin-, clindamycin- and co-trimoxazole-resistant *S. aureus* over the 7 year study. Given the concurrent significant reduction in MRSA proportions, the trends are likely explained by a reduction in the prevalence of MRSA, which has been observed by others and may be related to clonal replacement of MRSA by MSSA strains (6).

## ACKNOWLEDGMENTS


We acknowledge the contributions of the directors and technologists of the contributing site microbiology laboratories.

Funding for the CANWARD study was provided in part by the University of Manitoba, Health Sciences Centre (Winnipeg, Manitoba, Canada) and the National Microbiology Laboratory (Winnipeg, Manitoba, Canada).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54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington DC, September 6-9, 2014