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# Canadian *Staphylococcus aureus* Isolates Show Vancomycin MIC Creep Over Time

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## ABSTRACT

**Objective:** We analysed the vancomycin MIC of MRSA and methicillin-susceptible *S. aureus* (MSSA) isolates from across Canada obtained from large national surveillance studies in 2005/6 (CAN-ICU) and 2008 (CAN-WARD) to determine if vancomycin MICs increased between these two time periods.

**Methods:** The CAN-ICU study included pathogens from sentinel Canadian intensive care units (ICUs) collected between July 2005 and June 2006 while the CAN-WARD 2008 study characterized pathogens isolated from sentinel Canadian Hospitals (all wards) in 2008. Antimicrobial susceptibility to vancomycin and cefoxitin was determined using the CLSI microbroth dilution method for all *S. aureus* isolates. Differences between vancomycin MICs in MRSA and MSSA between the two study periods were analysed using the Mann-Whitney U test or Chi-Square test where appropriate.

**Results:** 1,873 *Staphylococcus aureus* isolates were studied, 866 in the CAN-ICU study and 1007 in the CANWARD study. Of these, 463 (24.7%) were MRSA; 192 (22.2%) from the CANICU study and 272 (27.0%) from the CANWARD study. The Mann-Whitney U test showed that a statistically significant increase in MIC to vancomycin was observed between the two study periods for MSSA but not MRSA. The proportion of isolates with MIC ≥ 1 mg/L increased from 72.0% to 84.2% (p<0.0001) and the proportion of isolates with MIC ≥ 2 mg/L increased from 0.6 to 1.3% (p = 0.057).

**Conclusions:** A statistically significant increase in vancomycin MIC in MSSA has occurred in Canada between 2005/6 and 2008. No increase was observed for MRSA. The increase was largely caused by a reduction in isolates with MIC < 1 mg/L to vancomycin. Increased vancomycin MIC has been shown to adversely affect patient outcomes and duration of hospitalization and should be closely monitored in Canada and abroad.

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## INTRODUCTION

Vancomycin creep has been observed in the United States and the United Kingdom and *Staphylococcus aureus* strains with increased MICs to vancomycin have been shown to be associated with poorer outcomes and increased cost of hospitalization and treatment compared to more susceptible strains (1,2). The factors involved in the development of reduced susceptibility to vancomycin and subsequent "glycopeptide MIC creep" are not entirely elucidated, but recognition of the phenomenon is important since it may be a precursor to hVISA (heterogenous vancomycin intermediate *Staphylococcus aureus*) and VISA (3).

Surveillance for vancomycin MIC creep is not routine in Canadian laboratories and most laboratories rely either on automated MIC determination (e.g. Vitek™ or MicroScan™) or prior to 2009, disk diffusion testing for determination of vancomycin susceptibility; neither of which are considered reference methods for the acurate determination of MICs in *S. aureus*. The purpose of this study was to determine if any increase in vancomycin MIC has occured over three years in two large national surveillance studies in Canada using the reference CLSI microbroth diluton method.

## MATERIALS AND METHODS

Isolates from 2008 were obtained as part of the CANWARD study which took place from January to December 2008. Ten tertiary care hospital laboratories from 8 provinces across Canada participated. Isolates were from inpatient medical and surgical wards, intensitve care units, emergency departments and outpatient clinics. Isolates from 2005/6 were collected from June 2005 to July 2006 as part of the CAN-ICU study. ICUs from 12 tertiary care hospitals in 8 provinces accross Canada participated. Minimum inhibitory concentration for vancomycin and cefoxitin were determined using the CLSI microbroth dilution method according to CLSI documents M07-A7 and M100-S16 (or S18). Isolates with cefoxitin MIC ≥ 8 mg/L were confirmed to be MRSA using *mec*A PCR.

Data were analysed using a variety of statistcal methods. The overall change in vancomycin MIC was evaluated using the Mann-Whitney U test in order to take into consideration the skewed distribution of MICs and the use of doubling dilutions. Differences in prevalence of isolates with a specific MIC was assessed using the Chi-square test. In order to assess whether any differences observed were due to sampling only from intensive care units in the CAN-ICU study, a seperate analysis where only intensive care unit isolates from the CANWARD study were compared to the CAN-ICU isolates was also performed. Statistical analysis was undertaken using JMP software version 8.0 by SAS.

## RESULTS

TABLE 1: MIC distributions for *S. aureus*, MRSA and MSSA between the two study periods. Significant changes occured only for MSSA and constituted a reduction in the proportion of isolates with an MIC of 0.5 mg/L and a concomitant increase in isolates with an MIC of 1 mg/L. No significant increase in isolates with MIC ≥ 2 mg/L was noted.

| Vancomycin MIC (mg/L) | 2005/6 (%) | 2008 (%) | P value |
|---|---|---|---|
| *S. aureus* | (n =866) | (n=1007) | |
| 0.25 | 11 (1.3) | 5 (0.5) | 0.12 |
| 0.5 | 231 (26.7) | 154 (15.3) | <0.0001 |
| 1.0 | 619 (71.5) | 835 (82.9) | <0.0001 |
| 2.0 | 5 (0.6) | 12 (1.2) | 0.16 |
| 4.0 | 0 (0) | 1 (0.1) | n/a |
| ≥ 1 | 624 (72.0) | 847 (84.2) | <0.0001 |
| ≥2 | 5 (0.6) | 13 (1.3) | 0.057 |
| MSSA | 2005/6 (%) | 2008 (%) | |
| | (n=674) | (n=735) | |
| 0.25 | 6 (0.9) | 5 (0.7) | 0.65 |
| 0.5 | 213 (31.6) | 118 (16.5) | <0.0001 |
| 1.0 | 453 (67.2) | 608 (82.7) | <0.0001 |
| 2.0 | 2 (0.3) | 4 (0.5) | 0.5 |
| MRSA | 2005/6 (%) | 2008 (%) | |
| | (n=192) | (n=272) | |
| 0.25 | 5 (2.6) | 0 (0) | n/a |
| 0.5 | 18 (9.4) | 36 (13.3) | 0.2 |
| 1.0 | 166 (86.5) | 227 (83.5) | 0.38 |
| 2.0 | 3 (1.6) | 8 (2.8) | 0.34 |
| 4.0 | 0 (0) | 1 (0.4) | n/a |

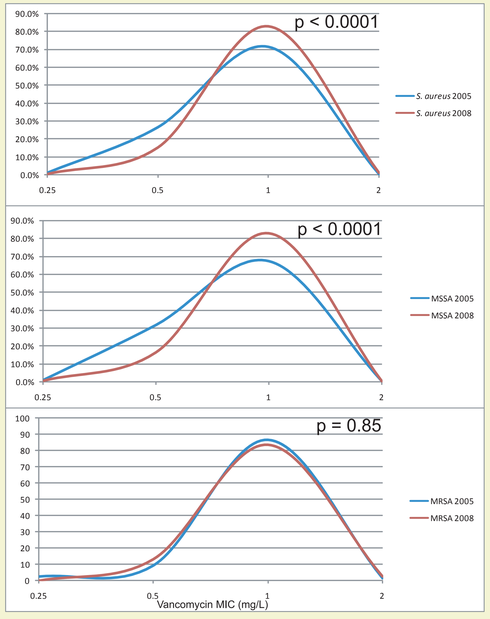


FIGURE 1: Vancomycin MIC distributions for *S. aureus* (A), MSSA (B) and MRSA (C) between the two study periods. A significant change was observed by the Mann Whitney U test for all *S. aureus* (p < 0.0001) and for MSSA (p < 0.0001) but not for MRSA (p = 0.85) Significance was maintained for all *S. aureus* (p = 0.0005) and MSSA (p = 0.0002) when only ICU isolates from CANWARD 2008 were considered.

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## CONCLUSIONS

MICs for vancomycin in *S. aureus* increased between 2005/6 and 2008 in this study of Canadian isolates. When stratified by methicillin resistance, the increase in MIC was only seen in methicillin-sensitive strains and was significant even when only intensive care unit isolates were considered. The observation of vancomycin creep in MSSA with stable MICs in MRSA has been described in other studies (4).

The most significant change in MIC distribution for all *S. aureus* and for MSSA between 2005/6 and 2008 was a reduction in isolates with an MIC of 0.5 mg/L and a concomitant increase in isolates with an MIC of 1 mg/L. No significant changes occured in prevalence of isolates with an MIC of 2 mg/L.

Although vancomycin MICs of 2 mg/L in *S. aureus* have been shown to correlate with worse outcomes, no such observation has been made for isolates with MICs of 1 mg/L. Therefore, the increase in prevalence of strains with MICs of 1 mg/L is of uncertain clinical significance.

The prevalence of *S. aureus* isolates with MICs ≥ 2mg/L more than doubled from 0.6% to 1.3% between the two study periods, an increase that approached statistical significance and may have clinical significance.

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