

Trickle-Down Antimicrobial Stewardship: Reduction in Long-Term Care Resistance Rates Following Implementation of a Prospective Audit-and-Feedback Intervention in the Adjacent Acute Care Hospital

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ABSTRACT

Background: The Sunnybrook Health Sciences Center Bayview Campus is a shared site, home to a 627-bed acute care hospital and a 475-bed long-term-care (LTC) facility. A multidisciplinary antimicrobial stewardship (AMS) intervention was implemented in the acute care facility in October 2009. No specific intervention was initiated in LTC. This study explores the impact of the acute care intervention on the burden of resistance in the adjoining LTC facility in the 7 years following program implementation.

Methods: Patient level data for clinical isolates of aerobic gram negative bacteria, *Staphylococcus aureus*, and *Enterococcus spp.* was obtained over a 14 year time period. Changes in the trend (Δ slope) and level of resistance between the pre-intervention period (October 2002 – September 2009) and post-intervention period (October 2009 – September 2016) were assessed using interrupted time-series analyses with segmented regression. The primary outcome was the number of bacterial isolates exhibiting resistance to at least one therapeutically active antibiotic agent per month standardized to 10,000 patient days for all species collectively and all gram-negative species (GNs).

Results: A statistically significant reduction in resistance rate trend was found for all species collectively (Δ slope = -0.097 resistant isolates/month, $p=0.001$) and all GNs (Δ slope = -0.082 resistant isolates/month, $p=0.001$). A significant reduction in the level of resistance was found for all species beginning at post-intervention month 18 (-3.24 resistant isolates/month $p=0.023$) and at post-intervention month 30 for all GNs (-2.83 resistant isolates, $p=0.046$).

Conclusions: Time series modelling revealed that implementation of the acute care AMS program was associated with significant improvements in the adjoining LTC facility's antibiotic resistance rates, suggesting a trickle-down effect.

BACKGROUND

Antimicrobial Stewardship programs (ASPs) are coordinated interventions designed to promote the appropriate use of antimicrobials, optimize patient outcomes, reduce microbial resistance, and decrease the spread of infections caused by multidrug-resistant organisms.

In October 2009, our institution launched a multidisciplinary prospective audit-and-feedback (PAF) ASP in the acute care facility. Rates of antimicrobial use and antimicrobial resistance among acute care patients have significantly improved in the 7 years following program implementation.

The acute care facility shares personnel and educational resources with the geographically adjacent long-term care facility (LTCF). Although the LTCF lacks a formal ASP, the potential exists for antimicrobial prescribing in the LTCF to be positively influenced by policy and practice at the adjoining acute care facility, resulting in reduced rates of antimicrobial resistance in the LTCF by way of a "trickle down" effect.

OBJECTIVE

To explore the impact of our institution's acute care PAF AMS intervention on the burden of resistance in the adjoining LTCF in the 7 years following program implementation in acute care

METHODS

Study Design

Retrospective interrupted time series over 14 years (pre-intervention period October 2002 – September 2009; post-intervention period October 2009 – September 2016)

Study Setting & Population

Sunnybrook Health Sciences Center (SHSC) Bayview Campus is a shared site, home to a 627-bed acute care academic teaching hospital and a 475-bed LTCF, and is located Toronto, Ontario, Canada

Adult patients with positive clinical isolates admitted to the Bayview Campus LTCF during the study period were eligible for inclusion

Positive clinical isolate was defined as a positive culture collected to assist with the diagnosis of infection (i.e. screening cultures were excluded)

Patient-level data for positive clinical isolates of aerobic gram negative bacteria, *Staphylococcus aureus*, and *Enterococcus spp.* were extracted from the SHSC Microbiology Database

Primary outcome

Burden of antibiotic resistance expressed as the number of antibiotic resistant bacterial isolates per 10000 patient days (PD) per month for all bacteria, gram negative (GN) isolates, *Enterobacteriaceae*, and gram positive (GP) isolates

Statistical Analyses

Segmented regression was used to identify changes in resistance rate trends between the pre- and post-intervention period (Δ in time series slopes), and estimate the time lapse at which changes in the level of resistance occurred (Δ level)

RESULTS

Table 1. Patient and isolate characteristics for the entire study period, the pre-intervention period, and post-intervention period. Values represent counts unless otherwise indicated.

	Total	Pre-Intervention	Post-Intervention	P-value ¹
Patients	2753	1295	1458	
Male (%)	79%	81%	77%	0.0121
Median age (years)	88 years	86 years	90 years	<0.001
Positive cultures ²	4878	2344	2534	
Patient days	25,515,74	1,295,596	1,255,978	

Table 2. Microbiology for the entire study period, the pre-intervention period, and post-intervention period. Values represent counts (N) and counts standardized to 10000 patient days (N/10000 PD).

	Total		Pre-Intervention		Post-Intervention		P-value ³
	N	N/10000 PD	N	N/10000 PD	N	N/10000 PD	
Gram Negative Bacilli	3862	15.1	1718	13.3	2144	17.1	NS
<i>Enterobacteriaceae</i>	3450	13.5	1487	11.5	1963	15.6	NS
<i>Escherichia coli</i>	1796	7.0	730	5.6	1066	8.5	NS
<i>Klebsiella spp.</i>	611	2.4	236	1.8	375	3.0	NS
<i>Proteus spp.</i>	625	2.5	310	2.4	315	2.5	NS
Other <i>Enterobacteriaceae</i> ⁴	418	1.6	211	1.6	207	1.7	NS
Non-lactose fermenters ⁵	412	1.6	231	1.8	181	1.4	NS
Gram Positive Cocci	1016	4.0	626	4.8	390	3.1	NS
<i>Staphylococcus aureus</i>	993	3.9	621	4.8	372	3.0	NS
<i>Enterococcus spp.</i>	23	0.1	5	0.0	18	0.1	N/A

¹Pre vs Post comparison Chi Square or Mann Whitney Test; ²Positive cultures collected to assist with infection diagnosis; ³Pre vs Post comparison of standardized counts by Chi Square Test; ⁴*Citrobacter spp.*, *Enterobacter spp.*, *Morganella spp.*, *Providencia spp.*, *Serratia spp.*; ⁵*Acinetobacter spp.*, *Pseudomonas spp.*; NS no statistically significant difference ($P>0.05$); N/A test not applicable due to cell counts <1

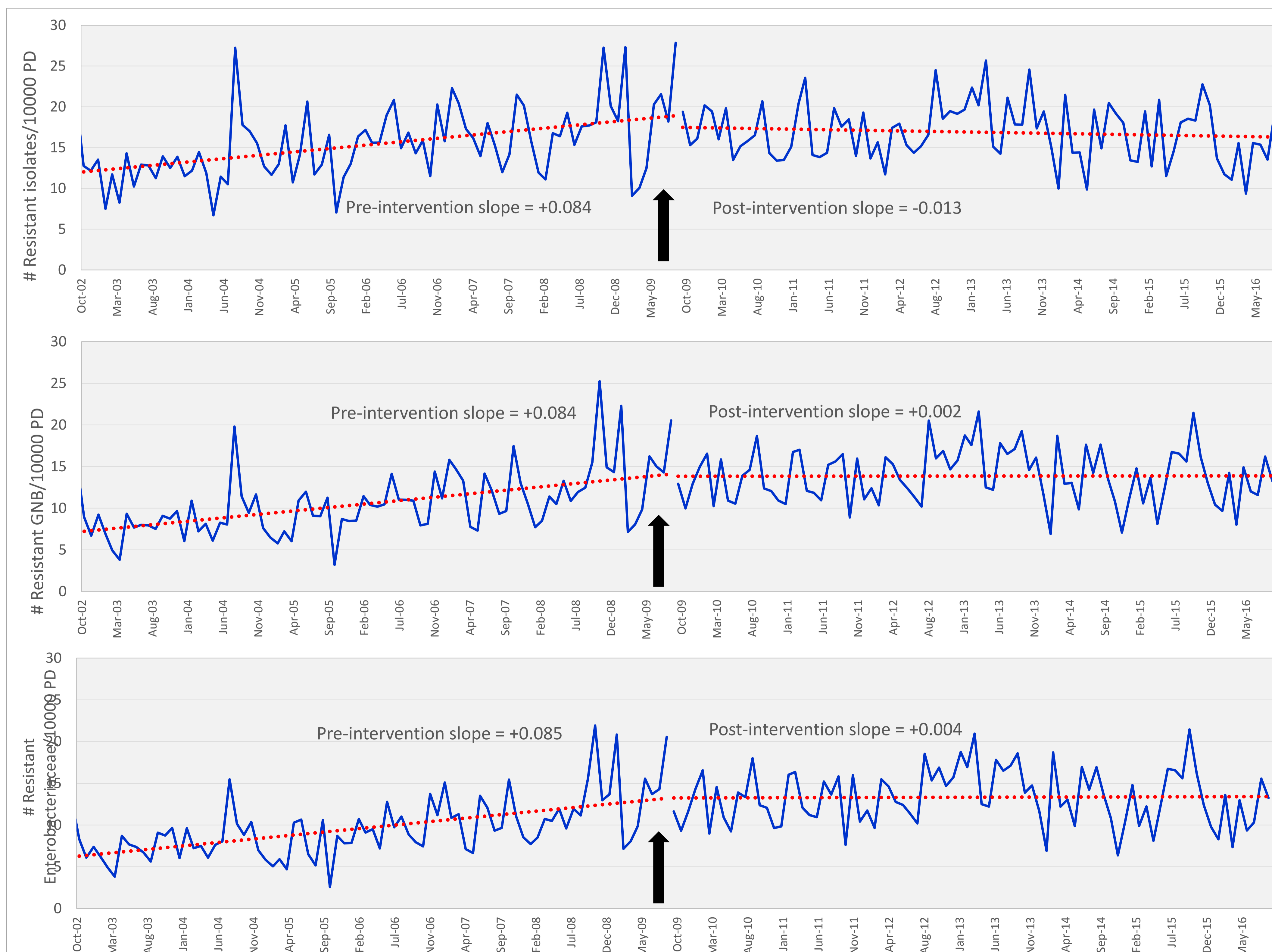


Figure 1. Monthly burden of antibiotic resistance measured as the number of resistant isolates exhibiting resistance to at least one therapeutically active antibiotic agent standardized to 10000 patient days for all bacteria (top panel), Gram Negative isolates (middle panel), and Enterobacteriaceae (bottom panel) at Sunnybrook Health Sciences Centre Long Term Care Facility over the 14 year study period. The pre-to-post-intervention period change in slope reveals that implementation of the acute care Prospective Audit and Feedback Antimicrobial Stewardship Program (bolded arrow) was associated with significant improvements in the trajectory of resistance in the adjoining Long Term Care Facility.

DISCUSSION

Implementation of the acute care PAF ASP was associated with significant improvements in the trend and level of resistance among (a) all species collectively, (b) GN species, and Enterobacteriaceae in the LTCF (Figure 1)

- All species resistance (Figure 1, top panel) was driven by changes in GN isolates
 - Δ slope = \downarrow 0.097 resistant isolates/10000 PD per month ($p=0.001$)
 - Δ level detected at post-intervention month 18 (-3.24 resistant isolates/month $p=0.023$)
- GN species resistance (Figure 1, middle panel) was driven by changes in *Enterobacteriaceae*
 - Δ slope = \downarrow 0.082 resistant isolates/10000 PD per month ($p=0.001$)
 - Δ level detected at post-intervention month 30 (-2.83 resistant isolates/month $p=0.046$)
- Enterobacteriaceae resistance (Figure 1, bottom panel)
 - Δ slope = \downarrow 0.081 resistant isolates/10000 PD per month ($p=0.001$)
 - Δ level detected at post-intervention month 36 (-3.07 resistant isolates/month $p=0.036$)

No statistically significant trends in GP resistance were detected (pre- and post-intervention slopes = zero); suggesting (a) no consistent statistically significant changes in month-to-month GP resistance rates, and (b) no trend change associated with implementation of the acute care PAF ASP. The lack of effect may be attributed to clonal resistance in the predominant GP species (*S. aureus*), which is impacted primarily by infection prevention and control initiatives (not antibiotic consumption).

Strengths

- This is the first study to analyze trends in antimicrobial resistance at a LTCF (a) as a primary outcome, and (b) over a prolonged period of time
- This is the first study to evaluate the indirect impact of an ASP implemented in a geographically adjacent facility which shares resources and personnel with the study facility
- This study employed an interrupted time series design constructed using Cochrane reviews criteria, which provides the strongest quasi-experimental design to estimate intervention effects in nonrandomized settings

Limitations

- Retrospective, single centre, observational design limits causal inference

Next steps

- Correlating trends in antimicrobial resistance with rates of antibiotic consumption in the LTCF
- Incorporating seasonality, length of stay, and the number of positive isolates into the time series analysis

CONCLUSION

Time series modelling revealed that implementation of the acute care PAF AMS program was associated with significant improvements in the adjoining LTCF antibiotic resistance rates, suggesting a trickle-down effect

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