Clinical Burden of Antimicrobial Resistance Following Implementation of an Antimicrobial Stewardship Team Prospective Audit and Feedback Initiative at a Tertiary Care Centre: A Controlled Interrupted Time Series Over 14 Years

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Pharmaceutical Science
University of Toronto

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Abstract

**Background:** Reducing antimicrobial resistance (AMR) is a major incentive for institutional antimicrobial stewardship programs (ASPs). However, there remains a paucity of high-quality data evaluating the impact of these programs on nosocomial AMR. The Sunnybrook Health Sciences Centre (SHSC) Bayview Campus is a shared site, home to a 627-bed acute care hospital and a 530-bed long-term-care facility (LTCF). A prospective audit-and-feedback (PAF) ASP was implemented in the acute care facility in October 2009. No specific intervention was initiated in LTCF, but there was potential for antimicrobial prescribing in the LTCF to be positively influenced by policy and practice at the adjoining acute care facility. This research evaluated the impact of the SHSC PAF-ASP on the burden of antibiotic-resistant organisms (ARO) and multidrug-resistant organisms (MDRO) and on inpatient antimicrobial use (AMU) in the 7 years following program implementation. **Methods:** Patient-level microbiologic and AMU data were retrospectively obtained over a 14-year study period (October 2002–September 2016). Interrupted time series Poisson regression models were used to detect PAF-ASP associated changes in the incidence and trend of hospital-acquired (HA-) ARO, HA-MDRO, and targeted
(TGD) AMU and infer program impact. Changes in community-acquired (CA-) and long-term-care facility-acquired (LTCF-) ARO and MDRO were assessed for comparison. **Results:** PAF-ASP implementation was associated with improvements in HA-ARO incidence (9.3% reduction/post-intervention period, p<0.0278), HA-MDRO incidence (12.6% reduction/post-intervention period, p=0.1319), and the trends of both outcomes. Improvement in TGD AMU, increases in CA-ARO and CA-MDRO incidence, and attenuated effects on LTCF-ARO and LTCF-MDRO incidence were also found. **Conclusions:** Implementation of the acute care PAF-ASP was associated with improvements in acute care AMR and AMU. The lack of improvement in corresponding CA-AMR outcomes and limited improvement in corresponding LTCF AMR outcomes strengthen the causal inference of the acute care PAF-ASP curbing the development of acute care AMR.
Acknowledgments

This thesis is dedicated to my late grandfather, Nonno Amadeo, who passed away in May 2018. Although he immigrated to Canada with little formal education, he valued learning highly. He always said there was “no such thing as too much school”, and he made education a priority for his children and grandchildren. It is because of his ethic and hard work that I was able to pursue post-secondary education and complete this doctoral dissertation. Of course, my other grandparents, Nanna Virginia, Nonno Nick and Nonna Francesca shared his ethic and dedication, and this thesis is dedicated to them as well.

I wish to express my sincere gratitude and appreciation to my supervisor, Dr. Sandra (Sandy) Walker for the opportunity to work on this important project and for all her guidance, support, and encouragement over the past three years. I also cannot thank her enough for the opportunity to develop my clinical and research skills as a Pharmacy Research Fellow at Sunnybrook—this training has been a unique and enriching learning experience and a milestone in my pharmacy career! I would also like to thank Scott Walker for fostering a passion for research during my PharmD training and for his continued help and support in the years that followed. The Walkers embody the type of clinician, teacher, researcher, and pharmacy leader I aspire to be, and it has been an honour and privilege to have had them as mentors.

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Finally, I wish to express my love for my parents, little sisters, and fiancé: Loretta Peragine, Steve Peragine, Diana Peragine, Stephanie Peragine, and Bryan Cox. Thank you for your constant support and encouragement—this thesis would not have been possible without you!
# Table of Contents

Acknowledgments............................................................................................................................... iv

List of Tables ........................................................................................................................................ x

List of Figures ......................................................................................................................................... xii

List of Appendices ............................................................................................................................... xiii

List of Abbreviations ........................................................................................................................... xiv

Chapter 1 Introduction .......................................................................................................................... 1

1 Introduction......................................................................................................................................... 2

Chapter 2 Literature Review ..................................................................................................................... 3

2 Literature Review ............................................................................................................................... 4

2.1 Preface.............................................................................................................................................. 4

2.2 Antimicrobial Resistance ............................................................................................................... 4

2.3 Causes of the Antimicrobial Resistance Problem ......................................................................... 7

2.4 World Health Assembly Response to the Global Resistance Crisis ........................................... 13

2.5 Antimicrobial Stewardship Programs (ASPs) ........................................................................... 15

2.6 Antimicrobial Stewardship at Sunnybrook Health Science Centre ............................................ 19

2.7 Evidence for the Impact of Antimicrobial Stewardship Interventions on Relevant Outcomes .... 24

Chapter 3 Thesis Research Rationale .................................................................................................. 28

3 Thesis Research Rationale ................................................................................................................ 29

3.1 Preface.............................................................................................................................................. 29

3.2 Description of Research Problem ................................................................................................. 29

3.3 Overarching Research Objective ................................................................................................. 31

3.4 Overarching Research Question .................................................................................................. 33

3.5 Specific Research Objectives and Hypotheses ............................................................................ 33
3.5.1 Evaluate the Impact of the Sunnybrook Health Sciences Centre Acute Care Antimicrobial Stewardship Program on the Burden of Resistance in the Acute Care Facility ................................................................. 33

3.5.2 Evaluate the Impact of the Sunnybrook Health Sciences Centre Acute Care Antimicrobial Stewardship Program on Rates of Antibiotic Consumption in the Acute Care Facility ................................................................. 34

3.5.3 Explore and Characterize Trends in Resistance in the Affiliated Long-term Care Facility in Relation to Implementation of an Acute Care Antimicrobial Stewardship Program .............................................................................. 34

Chapter 4 Impact of the Sunnybrook Health Sciences Centre Acute Care Prospective Audit-and-Feedback Antimicrobial Stewardship Program on the Burden of Resistance in the Acute Care Facility .................................................................................................................. 35

4 Impact of the Sunnybrook Health Sciences Centre Acute Care Prospective Audit-and-Feedback Antimicrobial Stewardship Program on the Burden of Resistance in the Acute Care Facility .................................................................................................................. 36

4.1 Preface ......................................................................................... 36

4.2 Background ..................................................................................... 36

4.3 Objective and Hypothesis .............................................................. 37

4.4 Methods ........................................................................................ 38

4.4.1 Study Design ............................................................................... 38

4.4.2 Study Setting and Population ........................................................ 38

4.4.3 Outcomes ..................................................................................... 39

4.4.4 Data Collection and Preparation ..................................................... 41

4.4.5 Statistical Analyses ....................................................................... 42

4.5 Results ........................................................................................... 50

4.5.1 Descriptive Statistics – Base Case ............................................... 50

4.5.2 Primary Outcome: Hospital-Acquired Antibiotic Resistant Organisms – Base-Case and Sensitivity Analyses Results ................................................................. 55

4.5.3 Secondary Outcome: Hospital-Acquired Multidrug-Resistant Organisms – Base-Case and Sensitivity Analyses Results ................................................................. 57

4.5.4 Control Outcomes – Base-Case and Sensitivity Analyses Results ................................................................. 59
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6 Discussion</td>
<td>63</td>
</tr>
<tr>
<td>4.7 Conclusion</td>
<td>68</td>
</tr>
<tr>
<td>Chapter 5 Impact of the Sunnybrook Health Sciences Centre Acute Care Prospective Audit-and-Feedback Antimicrobial Stewardship Program on Antibiotic Consumption in the Acute Care Facility</td>
<td>69</td>
</tr>
<tr>
<td>5 Impact of the Sunnybrook Health Sciences Centre Acute Care Prospective Audit-and-Feedback Antimicrobial Stewardship Program on Rates of Antibiotic Consumption in the Acute Care Facility</td>
<td>70</td>
</tr>
<tr>
<td>5.1 Preface</td>
<td>70</td>
</tr>
<tr>
<td>5.2 Background</td>
<td>70</td>
</tr>
<tr>
<td>5.3 Objective and Hypothesis</td>
<td>71</td>
</tr>
<tr>
<td>5.4 Methods</td>
<td>72</td>
</tr>
<tr>
<td>5.4.1 Study Design</td>
<td>72</td>
</tr>
<tr>
<td>5.4.2 Study Setting and Population</td>
<td>72</td>
</tr>
<tr>
<td>5.4.3 Outcomes</td>
<td>73</td>
</tr>
<tr>
<td>5.4.4 Data Collection and Preparation</td>
<td>74</td>
</tr>
<tr>
<td>5.4.5 Statistical Analyses</td>
<td>75</td>
</tr>
<tr>
<td>5.5 Results</td>
<td>78</td>
</tr>
<tr>
<td>5.5.1 Descriptive Statistics</td>
<td>78</td>
</tr>
<tr>
<td>Base-case Model Descriptive Statistics</td>
<td>78</td>
</tr>
<tr>
<td>Sensitivity Model Descriptive Statistics</td>
<td>79</td>
</tr>
<tr>
<td>5.5.2 Primary Outcome Results: Base-case and Sensitivity Analyses Results for Targeted (TGD) Agent Use</td>
<td>83</td>
</tr>
<tr>
<td>5.5.3 Balancing Outcome Results: Base-case and Sensitivity Analyses Results for Non-Targeted (NTGD) and Total (TTL) antibiotic use</td>
<td>85</td>
</tr>
<tr>
<td>5.4 Discussion</td>
<td>89</td>
</tr>
<tr>
<td>5.5 Conclusion</td>
<td>93</td>
</tr>
<tr>
<td>Chapter 6 Trends in the Affiliated Long-term Care Facility in Relation to Acute Care Antimicrobial Stewardship Program Implementation</td>
<td>94</td>
</tr>
</tbody>
</table>
Resistance Trends in the Affiliated Long-term Care Facility in Relation to Acute Care Antimicrobial Stewardship Program Implementation ................................................. 95

6.1 Preface ................................................................................................................. 95

6.2 Background ......................................................................................................... 95

6.2.1 Objective and Hypothesis ................................................................................. 96

6.3 Methods ................................................................................................................ 96

6.3.1 Study Design .................................................................................................... 96

6.3.2 Study Setting and Population .......................................................................... 97

6.3.3 Outcomes .......................................................................................................... 98

6.3.4 Data Collection and Preparation ..................................................................... 99

6.3.5 Statistical Analyses .......................................................................................... 100

6.4 Results .................................................................................................................. 103

6.4.1 Descriptive Statistics ....................................................................................... 103

6.4.2 Primary Outcome Results – Long-term care facility-associated antibiotic resistant organisms (LTCF-ARO) ................................................................. 103

6.4.3 Secondary Outcome Results – Long-term care facility-associated multidrug-resistant organisms (LTCF-MDRO) ............................................................ 104

6.5 Discussion ............................................................................................................ 109

6.6 Conclusion .......................................................................................................... 113

Chapter 7 Discussion of Thesis Research Findings .................................................. 114

7 Discussion of Thesis Research Findings .................................................................. 115

7.1 Preface .................................................................................................................. 115

7.2 Summary of Thesis Findings .............................................................................. 115

7.2.1 Acute Care Facility Antimicrobial Resistance (AMR) ................................. 118

7.2.2 Acute Care Facility Antimicrobial Use (AMU) .............................................. 119

7.2.3 Long-term Care Facility (LTCF) Antimicrobial Resistance (AMR) ............ 120

7.3 Strengths and Significance of Thesis Findings .................................................... 121
7.4 Limitations of Thesis Research ......................................................... 128

Chapter 8 Conclusion ................................................................................. 132

8 Conclusion .............................................................................................. 133

References .................................................................................................. 135

Appendices ................................................................................................. 154
List of Tables

Table 2-1 Select list of passive and/or complimentary antimicrobial stewardship interventions. 18

Table 2-2 Select timeline of activities to enhance antibiotic prescribing at Sunnybrook Health Sciences Centre acute care facility. .......................................................... 23

Table 4-1. Assumptions and conditions for the acute care antibiotic resistance models. Items in bolded font represent changes to the base-case assumptions and conditions. .......................... 48

Table 4-2. Base-case descriptive data for clinical isolates, patient days, and mean length of stay (LOS) at the acute care facility. .................................................................................. 51

Table 4-3. Base-case descriptive data for hospital-acquired and community-acquired clinical isolates, antibiotic-resistant organisms, and multidrug-resistant organisms at the acute care facility. ........................................................................................................... 52

Table 4-4. Inferential statistics for hospital-acquired antibiotic-resistant organisms in the acute care facility .................................................................................................................. 56

Table 4-5. Inferential statistics for hospital-acquired multidrug-resistant organisms in the acute care facility ........................................................................................................................ 58

Table 4-6. Inferential statistics for community-acquired antibiotic-resistant organisms in the acute care facility .................................................................................................................. 60

Table 4-7. Inferential statistics for community-acquired multidrug-resistant organisms in the acute care facility .................................................................................................................. 62

Table 5-1. Descriptive data for the acute care antibiotic use base-case models. ................. 80

Table 5-2. Descriptive data for the acute care antibiotic use sensitivity models. ................... 81

Table 5-3. Inferential statistics for rates of “targeted” antimicrobial use for both the base-case and sensitivity model conditions........................................................................................................... 84

Table 5-4. Inferential statistics for rates of “non-targeted” antimicrobial use for both the base-case and sensitivity model conditions................................................................. 86
Table 5. Inferential statistics for rates of “total” antimicrobial use for both the base-case and sensitivity model conditions. ................................................................. 88

Table 6-1. Descriptive data for clinical isolates and patient days in the long-term care facility. 105

Table 6-2. Descriptive data for clinical isolates, antibiotic-resistant organisms, and multidrug-resistant organisms from the long-term care facility. ................................................................. 106

Table 6-3. Inferential statistics for clinical isolates, antibiotic-resistant organisms, and multidrug-resistant organisms from the long-term care facility. ................................................................. 108

Table 7-1. Inferential statistics for major study outcomes. .................................................. 116

Table 7-2. Application of the interrupted time series risk of methodological bias tool to the hospital-acquired antibiotic resistant organism and hospital-acquired multidrug-resistant organism outcomes ................................................................. 124

Table 7-3. Application of the risk of microbial bias criteria to the hospital-acquired antibiotic resistant organism and hospital-acquired multidrug-resistant organism outcomes ............... 126
List of Figures

Figure 2-1. How antimicrobial resistance occurs. ................................................................. 8

Figure 2-2. How antimicrobial resistance spreads. ................................................................. 11

Figure 2-3 Number of new antibiotic agents approved by the Food and Drug Administration between 1940 to 2018. ............................................................................................................. 12

Figure 4-1. Trends in hospital-acquired antibiotic-resistant organisms and community-acquired antibiotic-resistant organisms. ....................................................................................................................... 53

Figure 4-2. Trends in hospital-acquired multidrug resistant organisms and community-acquired multidrug resistant organisms. ........................................................................................................... 54

Figure 5-1. Trends in “Targeted”, “Non-targeted”, and “Total” antibiotic use at Sunnybrook Health Sciences Centre acute care facility. ........................................................................................................... 82

Figure 6-1. Trends in long-term care facility-acquired antibiotic-resistant organisms and multidrug resistant organisms. ................................................................................................................... 107

Figure 7-1. Trends in acute care antibiotic resistance, acute care antibiotic use, and long-term care antibiotic resistance at Sunnybrook Health Sciences Centre. ........................................ 117
List of Appendices

Appendix 1. Studies to be considered for inclusion in EPOC reviews....................................... 155

Appendix 2. Risk of bias tool for studies with a separate control group...................................... 157

Appendix 3. Risk of bias tool for interrupted time series.............................................................. 159

Appendix 4. Tool to assess microbial risk of bias ........................................................................ 160
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>AMU</td>
<td>Antimicrobial use (interchangeable with antibiotic use)</td>
</tr>
<tr>
<td>ARO</td>
<td>Antibiotic-resistant organism</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute rate reduction</td>
</tr>
<tr>
<td>AS</td>
<td>Antibiotic stewardship (interchangeable with antimicrobial stewardship)</td>
</tr>
<tr>
<td>ASP</td>
<td>Antimicrobial stewardship program</td>
</tr>
<tr>
<td>Base</td>
<td>Base-case model</td>
</tr>
<tr>
<td>CA-</td>
<td>Community-acquired</td>
</tr>
<tr>
<td>CA-ARO</td>
<td>Community-acquired antibiotic-resistant organism</td>
</tr>
<tr>
<td>CAD</td>
<td>Canadian dollar</td>
</tr>
<tr>
<td>CA-MDRO</td>
<td>Community-acquired multidrug-resistant organism</td>
</tr>
<tr>
<td>CARSS</td>
<td>Canadian Antimicrobial Resistance Surveillance System</td>
</tr>
<tr>
<td>CBA</td>
<td>Controlled Before-After</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>DoVA</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>EPOC</td>
<td>Effective Practice, Organisation of Care</td>
</tr>
<tr>
<td>ESBL</td>
<td>Extended spectrum beta-lactamase</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GDP</td>
<td>Gross domestic product</td>
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<tr>
<td>GNB</td>
<td>Gram negative bacilli</td>
</tr>
<tr>
<td>GPC</td>
<td>Gram positive cocci</td>
</tr>
<tr>
<td>HA-</td>
<td>Hospital-acquired</td>
</tr>
<tr>
<td>HA-ARO</td>
<td>Hospital-acquired antibiotic-resistant organism</td>
</tr>
<tr>
<td>HA-MDRO</td>
<td>Hospital-acquired multidrug-resistant organism</td>
</tr>
<tr>
<td>HH</td>
<td>Hand Hygiene</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Disease Society of America</td>
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<tr>
<td>IPC</td>
<td>Infection Prevention and Control</td>
</tr>
</tbody>
</table>
ITS  Interrupted time series
IV-to-PO  Intravenous-to-Oral
LOS  Length of stay
LTCF  Long-term care facility
MDRO  Multidrug-resistant organism
MRSA  Methicillin-resistant S.aureus
NCCID  National Collaboration Center for Infectious Diseases
NPV  Net present value
NRT  Non-randomized trial
NTGD  Non-targeted
NTGD AMU  Non-targeted antimicrobial use
PAF  Prospective audit-and-feedback
PAF-ASP  Prospective audit-and-feedback antimicrobial stewardship program
PD  Patient days
PO  Oral
Post  Post-intervention period
Post-Period RRR  Post-Intervention Period Relative Rate Reduction
PRA  Preauthorization
Pre  Pre-intervention period
ROP  Required Organizational Practice
RRR  Relative rate reduction
RT  Randomized trial
SB-AST  Sunnybrook Antimicrobial Stewardship Team
Sens  Sensitivity model
Sens1  Sensitivity model #1
Sens2  Sensitivity model #2
Sens3  Sensitivity model #3
Sens4  Sensitivity model #4
Sens5  Sensitivity model #5
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEA</td>
<td>Society for Healthcare Epidemiology of America</td>
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<tr>
<td>SHSC</td>
<td>Sunnybrook Health Sciences Centre</td>
</tr>
<tr>
<td>spp.</td>
<td>Species</td>
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<td>SSR</td>
<td>State of the Science Review</td>
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<tr>
<td>TGD</td>
<td>Targeted</td>
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<td>TGD AMU</td>
<td>Targeted antimicrobial use</td>
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<td>TTL</td>
<td>Total</td>
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<tr>
<td>TTL AMU</td>
<td>Total antimicrobial use</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>USD</td>
<td>American dollar</td>
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<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Chapter 1
Introduction
1 Introduction

Antimicrobial resistance (AMR) is increasing worldwide and represents a serious threat to modern medicine\(^1\). Excessive and inappropriate antimicrobial use (AMU) has been a key driver of the AMR problem\(^1\). Therefore, promoting responsible AMU via the practice of antimicrobial stewardship (AS) was one of five fundamental strategies identified in the World Health Organization’s global action plan to combat AMR\(^1\). AMR is particularly problematic in institutional settings; accordingly, implementation of institutional antimicrobial stewardship programs (ASPs) has been identified as a method to reduce inappropriate AMU and contain the global AMR problem\(^2\)–\(^4\).

Although existing evidence demonstrates positive impact of ASPs on prescribing behaviors, AMU, and drug-acquisition costs\(^4\)–\(^7\), the effect on nosocomial AMR remains unclear\(^4\),\(^8\). Definitive evidence demonstrating significant and sustained improvements in institutional resistance rates is required to prove the effectiveness of these programs, clarify the ASP-AMU-AMR relationship, and shape policies to support ASP activities. This research project was designed to fill this gap in AS literature and used robust methodology to evaluate the temporal change in the institutional burden of AMR and inpatient AMU at Sunnybrook Health Sciences Centre (SHSC) associated with implementation of the site’s comprehensive prospective audit-and-feedback (PAF) ASP.

SHSC implemented a multidisciplinary PAF-ASP in the Bayview Campus acute care facility of the on October 1st, 2009\(^9\). SHSC is a tertiary referral teaching hospital located in Toronto with approximately 627 acute care beds and 530 long-term care beds\(^10\). This research utilized patient-level data, robust interrupted time series (ITS) models, and innovative aggregate AMR and AMU metrics to evaluate ASP-associated changes in the rates of acute care AMR and AMU. Changes in community AMR and a possible indirect effect of the acute care program on AMR in the adjoining long-term care facility (LTCF) were also explored. The following chapters provide an in-depth description of the global AMR problem, the methods and results of three studies conducted to evaluate the impact of the SHSC PAF-ASP on AMR and AMU outcomes, and the collective significance of the findings.
Chapter 2
Literature Review
2 Literature Review

2.1 Preface

This chapter discusses the antimicrobial resistance (AMR) phenomenon, the causes and consequences of the global AMR problem, and select strategies to combat AMR including the practice of Antimicrobial Stewardship (AS). The terms “antimicrobial” and “antibiotic” are often used interchangeably although strict dictionary definitions are distinct\textsuperscript{11,12}. These terms are used interchangeably in this report to describe drugs used to treat and prevent bacterial diseases.

2.2 Antimicrobial Resistance

AMR refers to the ability of a bacterium to grow in the presence of a drug that would normally kill it or suppress its growth\textsuperscript{13}. AMR is a naturally occurring phenomenon. Some species of bacteria have an intrinsic, or “innate,” ability to resist the activity of an antimicrobial agent. However, resistance can also “emerge” in species that are typically susceptible if an isolate acquires a resistance gene via random chromosomal mutations or horizontal DNA transfer\textsuperscript{14}. These resistance genes enable the bacterium to evade antibiotic activity in one of three ways: (1) by altering the structure of the antibiotic target site, (2) by promoting cellular changes that reduce antibiotic access to the target site, and/or (3) by encoding the production of enzymes that inactivate the antibiotic. The methicillin-resistance exhibited by many \textit{Staphylococcus aureus} isolates can be attributed to a chromosomal mutation in the penicillin-binding protein gene, and this is an example of a mutation leading to resistance via alteration of antibiotic target-site\textsuperscript{15}. Mutations in the gene regulating expression of a multidrug efflux pump in \textit{Pseudomonas aeruginosa} have been linked to the aminoglycoside resistance seen in cystic fibrosis patients, and this is an example of a mutation leading to resistance via impeded target site access\textsuperscript{16}. The high-level carbapenem resistance seen among New Delhi metallo-\textbeta-lactamase-producing \textit{Enterobacteriaceae} is due to acquisition and expression of a plasmid-borne \textit{bla}_{NDM} gene, and this is an example of resistance due to enzyme-mediated antibiotic deactivation\textsuperscript{17}.

Although the prevalence of “emergently” resistant strains was once negligible, these types of antibiotic-resistant organisms (ARO) are now encountered at alarmingly high frequencies and represent a serious threat to global public health. The prevalence and diversity of AROs have
increased dramatically over the past half-century and has now reached an unprecedented global high\textsuperscript{18}. Multidrug-resistant organisms (MDRO) are routinely encountered in the inpatient setting, and these antibiotic-resistant superbugs are responsible for at least 1 in 7 hospital-acquired infections in American acute care facilities\textsuperscript{19}. In fact, 15 ARO families have now been classified by the Centre for Disease Control and Prevention (CDC) as representing “urgent” or “serious” domestic threats\textsuperscript{20}, and the World Health Organization (WHO) has released a “priority list of antibiotic-resistant bacteria” that currently pose the greatest threat to human health\textsuperscript{21}.

Infections with pan-drug resistant bacterial strains have been documented in Europe and Asia\textsuperscript{22–24}, and the immediate precursors to pan-drug resistance have been identified in Canada\textsuperscript{25,26}. Although Canadian rates of MDRO remain relatively low, recent data suggests that the prevalence of extended-spectrum beta-lactamase (ESBL) producing organisms and MRSA may be on the rise. From 2007 to 2011, the relative incidence of ESBL-producing \textit{E. coli} isolated in the inpatient setting increased from 3.4\% to 7.1\%, and the proportion of ESBL-producing \textit{K. pneumoniae} increased from 1.5\% to 4.0\%\textsuperscript{27}. Furthermore, from 2011 to 2016, reports from sentinel hospitals showed that MRSA infection rates increased from 2.84 cases per 10 000 patient days (PD) to 3.13 cases per 10 000 PD, with pediatric sites showing a five-fold increase in hospital-acquired (HA) MRSA bloodstream infections (i.e., rising from 0.08 cases/10 000 PD in 2011 to 0.43 cases/10 000 PD in 2016)\textsuperscript{28}. In addition, a possible signal towards an increased prevalence of carbapenemase-producing \textit{Enterobacteriaceae} in community-settings has been detected; the number of cases reported to public health laboratories jumped from 4 cases in 2009 to 779 cases in 2016\textsuperscript{28}.

AMR is already directly impacting patient outcomes. AMR infections are associated with longer illness duration, increased frequency and length of hospital stay, treatment failures, and increased risk of mortality\textsuperscript{29,30}. AMR eliminates conventional treatment options and necessitates use of more toxic and less effective second and third line antibiotic options. This increases the risk of antibiotic-associated adverse effects and reduce the chances of cure. AMR can also delay time to appropriate therapy due to a mismatch between the pathogen susceptibility profile and empiric therapy administered, which is a predictor of mortality in sepsis\textsuperscript{31}. 


Infectious diseases have been a leading cause of morbidity and mortality for most of human history, and the discovery and subsequent use of antibiotics to combat infections is considered one of the pillars of modern medicine. The advent of antibiotic therapy reduced the absolute risk of infection-related death as much as 75% and significantly contributed to increases in average human life expectancy. Access to effective antibiotic therapy also facilitated many major medical and surgical advancements in the 20th century and reduced the risk of infectious complications from major surgeries procedures, organ transplantation, and cancer chemotherapy.

By eliminating effective chemotherapeutic options, AMR threatens a return to the pre-antibiotic era where simple infections can kill and life-saving procedures are too risky to perform. Indeed, infection-related morbidity and mortality are once again on the rise. The CDC estimates that over 23 000 American citizens die from antibiotic-resistant infections each year, and the annual global death toll is currently estimated at 700,000 lives. If current trends continue, AMR-attributable mortality is projected to reach 10 million by the year 2050 with a cumulative economic cost over $100 trillion USD. The economic toll of AMR is well described: Drug-resistant infections require more expensive antibiotics (i.e., antibiotics of last resort), require more prolonged and complex care, and cause greater productivity losses. This inflates direct healthcare costs and indirect costs to society. In Canada, total annual medical care costs associated with AROs are estimated to exceed $1 billion. In the United States, direct medical costs are estimated at $20 billion, and indirect societal costs are estimated at $35 billion per year. Several reports have highlighted the enormous global economic impact that AMR will incur. If current trends continue, the annual AMR-attributable global GDP shortfall is projected to be between $1 to $3.4 trillion USD by the year 2030. By the year 2050, the global annual GDP is projected to drop between 1.1% to 3.8%—which is comparable to the losses provoked by the 2008-2009 global financial crisis. Given the catastrophic clinical and economic cost associated with AMR, world health leaders have recognized that urgent action is needed to correct the causes of AMR and curb this growing threat.
2.3 Causes of the Antimicrobial Resistance Problem

Although many factors have contributed to the global AMR crisis, inappropriate and excessive antimicrobial use (AMU) is at the core of the problem\textsuperscript{38}. Several lines of convergent independent research strongly suggest a causal relationship between AMU and AMR\textsuperscript{2}. For example, population-level trends in AMU have been shown to parallel population-level trends in AMR prevalence, and local densities of AMU predict the local densities of AROs (i.e., ARO prevalence in hospitals exceeds that seen in the community, and hospital wards with higher rates of AMU have higher rates of AROs). Patients with antibiotic-resistant infections are also more likely to have previously received antibiotic therapy compared to controls, and patients with longer durations of antibiotic exposure are more likely to be colonized with resistant organisms\textsuperscript{2}.

Generally speaking, antibiotic exposure does not \textit{cause} resistance; instead, it creates conditions favouring the survival and reproduction of existing microbes with resistant phenotypes. Figure 1 provides a visual representation of the selective process by which AMR emerges\textsuperscript{39}. Each time a person takes an antibiotic, sensitive bacteria of both the pathogenic species and the non-pathogenic commensal population are killed and resistant bacteria are left to grow and multiply. Repeated exposure promotes the selection of increasingly resistant strains. The current AMR problem is the end-product of decades of excessive and indiscriminate AMU and continued selection and spread of increasingly drug-resistant strains. Global antibiotic consumption increased 65\% over the past 16 years alone\textsuperscript{40}, and reports suggest that between 20-50\% of human AMU is unnecessary or inappropriate\textsuperscript{20,41,42}.

Health care practitioners and the general public have conceptualized antibiotics as a cheap and inexhaustible “commons” for quite some time – a natural resource capable of providing immediate comfort/relief to which everyone in society is entitled at little to no immediate cost\textsuperscript{43}. This attitude, and our “pill for every ill” mentality, promoted the over-consumption of antibiotics, net increases in AMR, and reductions in the therapeutic efficacy of these life-saving resources\textsuperscript{43}. Antibiotics are routinely prescribed to “treat” viral and non-infectious illnesses that do not need or respond to antibiotics, and they are frequently used for prophylaxis in situations
Figure 2-1. How antimicrobial resistance occurs.
Antibiotic exposure creates a selective pressure favouring the survival and reproduction of existing microbes with resistant phenotypes. In some cases, bacteria are able to transfer these resistance genes to other isolates. Reproduced with permission from MeMed and available at http://www.med.com/html5/?_id=11489&did=2466&G=11051&SM=11489.
where no benefit has been established\textsuperscript{44}. Unsubstantiated fears regarding the “undertreatment” of infections have promoted the use of unnecessarily long durations of therapy (i.e., extended for longer than required to cure the infections)\textsuperscript{45}, and broad-spectrum agents are commonly used in cases where targeted (i.e., narrow spectrum) therapy would provide comparable efficacy and minimize “collateral damage” to the host microbiome\textsuperscript{44}. These problems are exacerbated by the fact that antimicrobial drugs are sold as over-the-counter products in much of the world, and the general public can self-medicate without any oversight by health care professionals\textsuperscript{46}. Of note, non-prescription use accounts for 19–100\% of human antimicrobial consumption in countries outside North America and Northern Europe\textsuperscript{46}.

Unfortunately, inappropriate AMU is not confined to human medicine. High volumes of antibiotics are also used in the agricultural sector—particularly in settings of industrial livestock production. The volume of antibiotics used in food animals grossly exceeds that used in human medicine. For example, approximately 82\% of the 1.4 million kilograms of antimicrobials distributed and sold throughout Canada in 2014 were used in livestock, with only 18\% attributed to human use\textsuperscript{47}. Misuse in this sector is demonstrated by the high proportion used to “promote growth” and “prevent” disease (90\% in Canada) and low proportion used for the active treatment of disease (10\% in Canada)\textsuperscript{47}. This high volume of agricultural use and misuse is seen in many countries all over the world\textsuperscript{48}, and these practices promote the selection and emergence of AMR in the same manner as in humans.

Although high volumes of AMU and high rates of misuse drive the emergence of resistance, suboptimal sanitation and infection control practices have facilitated the spread of ARO and AMR resistant genes and amplified the problem\textsuperscript{49}. Animal-to-human transmission can occur via direct contact and consumption of food animals harboring AROs and indirectly through contact and consumption of produce grown with ARO-contaminated water or soil\textsuperscript{48}. Humans can also act as vectors and pass AROs to other people in their community via direct contact or contact via shared items/surfaces. Hospitalized patients are a significant reservoir of resistant organisms, and patients who are carriers of resistant microorganisms act as a source of infection for others. Suboptimal hand-hygiene, sanitation, environmental cleaning, and infection control practices facilitate human-to-human, human-to-environment, and environment-to-human transfer\textsuperscript{49}. Figure
2 provides a visual representation and summary of the transmission pathways that have promoted the spread of ARO and the current AMR problem\(^{39}\).

Diminishing interest from the pharmaceutical sector is another factor that has contributed to the current AMR problem. Figure 3 shows the number of new antibiotic agents approved by the United States Food and Drug Administration (FDA) for each decade from 1940 to present. The majority of antibiotics available for use today were discovered in the mid-to-late 20\(^{th}\) century\(^{50}\)—over 20 new classes of antibiotics and many more analogs reached the market between 1940 to 1980\(^{50}\). AROs emerged during this time, and the medical community was aware; however, antibiotic drug development kept pace with the emergence of antibiotic drug-resistant bacteria, and, for this reason, treatment was not compromised. Unfortunately, pharmaceutical sector research and development in the field of antibiotics slowed significantly after the 1980s, and 15 out of 18 of the largest companies ultimately abandoned the space entirely\(^{33}\). Access and consumption of antibiotics continued to increase, and with the absence of new drugs in the pipeline to counter AMR, MDRO have emerged to which no effective treatment is available.

Economic and regulatory barriers made antibiotic development an unattractive endeavor. The antibiotic market is a particularly challenging space. Antibiotic profit margins are much smaller than in other therapeutic areas, and for this reason, antibiotic development is not seen as an “economically wise” investment\(^{33}\). Antibiotics suffer from poor “Net Present Values” (NPVs), which is a complex profitability metric pharmaceutical companies use to evaluate potential development projects\(^{51}\). NPVs reflect the likelihood of achieving returns, as well as the overall revenue and the cost and capital required to fund the project. A high NPV suggests a high likelihood of returning significant profits, and high NPV projects are more likely to be pursued. A low or negative NPV suggests restrictive costs and/or a low chance of achieving a significant return\(^{51}\).
Figure 2-2. How antimicrobial resistance spreads.
Antibiotic use in humans and animals promotes the emergence and selection of antimicrobial resistant organism. These organisms can then be transferred to and between other humans, animals, and the environment via direct and indirect contact. Reproduced with permission from MeMed and available at http://www.memed.com/html5/?_id=11489&did=2466&G=11051&SM=11489
Figure 2-3 Number of new antibiotic agents approved by the Food and Drug Administration (FDA) between 1940 to 2018.
The number of new antibiotics developed and approved each decade increased from the 1940s to the 1980s, decreased from 1990s to 2000s, but has increased from 2010 to present (2018). Adapted from\textsuperscript{33,52-57}
Sales volume is a key determinant of rewards in the conventional pharmaceutical business model, and antibiotics do not perform favorably in this domain. Antibiotics are curative and are generally used for very short periods of time. Consequently, they are less attractive than drugs for chronic illnesses are non-curative and used across the lifespan. Efforts to preserve the effectiveness of new antibiotic agents curtail use even further and exacerbate this issue. For example, infectious disease experts recommend restraint on the use of new antibiotics to prevent the emergence of resistance, but this type of restraint is not recommended for new agents in other therapeutic areas (i.e., diabetes, chronic obstructive pulmonary disorder, psychiatric conditions, etc.).

The availability, ease of use, and low cost of existing antibiotic agents also contributes to their low NPV. Most antibiotics are off patent and supplied as generics at very low costs. Payers expect new agents to be similarly priced, and this expectation limits return on investment and reduces economic appeal. For example, the average price for a 10 day course of treatment with a new antibiotic was $600 USD at the turn of the 21st century, while the average price for a 10 day course of treatment with a new anti-cancer drug was $1455 USD. Regulatory changes in the 1990s and 2000s increased the costs of drug development, these drawbacks in sales volume and market price made it difficult for drug companies to recuperate these growing costs, and this ultimately led to the drying of the antibiotic pipeline.

2.4 World Health Assembly Response to the Global Resistance Crisis

In 2015, the World Health Assembly officially recognized the potentially catastrophic consequences of the growing AMR problem and adopted a global action plan to combat this growing threat. By supporting the global action plan, the 194 WHO member states committed to implement federal action plans on AMR addressing the following key objectives by the year 2017:

1. to improve awareness and understanding of AMR through effective communication, education and training;

2. to strengthen the knowledge and evidence base [on AMR] through surveillance and research;
(3) to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;

(4) to optimize the use of antimicrobial medicines in human and animal health;

(5) to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Many projects to meet these objectives are underway. Major international and federal initiatives aimed at financially incentivizing antibiotic research and development have been implemented. In Canada, innovative research projects related to vaccine development (i.e., conjugate Neisseria vaccine, cattle and chicken vaccines, genomics-based vaccine), the microbiome, probiotics, and therapeutic monoclonal antibodies are being pursued. The Public Health Agency of Canada also published a pan-Canadian framework to guide policy and coordinate action across all sectors. Pan-Canadian standards for livestock care, evidence-based IPC guidelines, and immunization programs have been developed to reduce the risk of ARO transmission between food animals, humans, and the environment. The Canadian Antimicrobial Resistance Surveillance System (CARSS) was created to enhance surveillance and the ability to identify threats and changes in AMR and AMU patterns.

Promoting the responsible use of antibiotics in human and animal health has also been identified as a priority. This practice is known as antimicrobial stewardship (AS). The Canadian government has created regulations to promote AS in agricultural sector. Manufacturers, importers, and compounders of antimicrobials for veterinary use must now report sales to the government to assist with monitoring efforts. Products containing antibiotic agents (i.e., medicated livestock feed) are now prohibited from listing growth promotion claims on labels and packaging, and all antibiotic products intended for veterinary use that were previously available over-the-counter have been moved to the prescription (Pr) drug list.

Although the Canadian government has not taken legislative action to improve the use of antibiotics in human medicine, a National Action Plan on Antimicrobial Stewardship has been drafted by HealthCareCAN and the National Collaboration Centre for Infectious Diseases (NCCID). Healthcare institutions have long been recognized as significant sources of AMR.
given their high density of sick patients and high rates of inpatient AMU, and Accreditation Canada has taken a leading role in promoting AS in these settings. Accreditation Canada introduced an acute care facility AS Required Organizational Practice (ROP) in 2013 and expanded this ROP to inpatient rehabilitation, cancer care, complex continuing care centres in 2014. The major test for compliance is that a structured Antimicrobial Stewardship Program (ASP) is in place. Accreditation Canada does not require long-term care facilities (LTCF) to have ASP in place at this time, but this would be a natural expansion of the ROP with the next iteration.

2.5 Antimicrobial Stewardship Programs (ASPs)

Evidence-based guidelines published by the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have informed the development and implementation of ASPs in acute care centres. These guidelines define AS as “coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen including dosing, duration of therapy, and route of administration.” The primary goal of AS is to optimize clinical outcomes, such as the odds of cure, and minimize the risk of antibiotic-related adverse effects. Examples of antibiotic-related adverse effects include antimicrobial-associated toxicities (i.e., vancomycin-induced renal toxicity), the selection of pathogenic organisms (i.e., C. difficile associated diarrhea and fungal superinfections), and the emergence of antimicrobial resistance. Reducing healthcare costs without adversely impacting quality of care is a secondary ASP objective.

It is advised that a multidisciplinary team coordinate the ASP. Ideally, the team should include an infectious diseases physician, clinical pharmacist, clinical microbiologist, infection control professional, hospital epidemiologist, and information system specialist. This six-membered team has the range of expertise to design and implement a comprehensive ASP, foster appropriate inpatient antibiotic prescribing practices, actively monitor AMU and AMR, and minimize the secondary spread of resistance. If assembling this optimal six-membered team is not possible, the minimum recommendation is for a two-membered team comprised of an infectious diseases physician and a clinical pharmacist with infectious diseases training (i.e., clinicians able to assess and advise on the appropriateness of inpatient antibiotic prescriptions).
The guidelines recognize that local practice patterns and the availability of resources to support AS efforts will influence the design and ultimate capacity of the ASP, but the IDSA-SHEA strongly recommend using pre-authorization (PRA) and/or prospective audit-and-feedback (PAF) as the “core” ASP activity\(^2,3\). PRA and PAF are described as “active” behavior change interventions and have been shown to consistently reduce antibiotic exposure and decrease drug-acquisition costs\(^2-6,72,73\). The guidelines recommend that passive AS interventions, such as didactic-style education, be used to complement core PRA and PAF strategies. Passive interventions have been shown to increase prescriber knowledge but are generally less effective than active strategies for altering antibiotic prescribing behaviors\(^74\). PRA and PAF are described in the following paragraphs. A select list of passive or complimentary AS initiatives is provided in Table 2-1.

PRA typically involves the “restriction” of a small number of antibiotic agents. The prescriber must request approval to order these agents prior to their use, and an ASP member grants or declines approval after reviewing the patient case\(^2\). Prescriber compliance is mandatory, and therefore this strategy provides direct control over the use of all “restricted” agents\(^3\). The PRA strategy targets empiric AMU (i.e., given that PRA intervenes before antibiotics are started), and it is particularly effective when a rapid reduction in the use of a specific agent is desired (i.e., antibiotic shortage or outbreak scenarios)\(^2,3\). Disadvantages of the PRA strategy include the following: (a) it generally targets a small number of antibiotic agents, (b) it impedes prescriber autonomy and can potentially delay the administration of a life-saving therapy, (c) it is more likely to “squeeze the balloon” and significantly inflate use of non-restricted agents, and (d) it has limited impact on downstream prescribing such as antibiotic streamlining and duration of therapy\(^2-4\). Streamlining has been shown to substantially decrease inappropriate use, and the reduced ability of the PRA strategy to offer this service is a notable limitation\(^2,3\).

In contrast to PRA, PAF typically targets a larger number of antibiotic agents, and the dedicated ASP clinician engages the prescriber after the antibiotic has been administered (i.e., typically after 2 to 3 days of therapy have elapsed)\(^2,3\). Relevant microbiology and other types of investigations are usually available and are used to inform ASP suggestions. Prescriber compliance with the unsolicited recommendations is voluntary; therefore, PAF is considered to be a “persuasive” intervention, and the AS clinician often provides case-specific education with
the suggestion to optimize the likelihood of acceptance\textsuperscript{2-4}. Benefits of PAF include increased impact on de-escalation and duration of therapy, increased visibility of the ASP, increased engagement and educational benefits to the prescribing clinician, and maintained prescriber autonomy. Limitations include that it is more time consuming and costly than other strategies, and that specialized infrastructure or software is often required to identify patients eligible for stewardship review.
Table 2-1 Select list of passive and/or complimentary antimicrobial stewardship interventions.

<table>
<thead>
<tr>
<th>The 2007 and 2016 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for developing and implementing institutional antimicrobial stewardship programs²,³ recommend the use of pre-authorization (PRA) and/or prospective audit-and-feedback (PAF) as the core component of the program. PRA and PAF are considered to be “active” interventions. Active interventions are more effective than “passive” interventions for changing behavior. The IDSA-SHEA suggest incorporating passive interventions into the ASP as supportive or complementary strategies. A select list of passive strategies endorsed by the IDSA-SHEA are as follows²,³:</th>
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<tr>
<td>• Delivery of AS education via meetings, seminars, and didactic lectures</td>
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<tr>
<td>• Development and distribution of educational pamphlets and materials</td>
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<tr>
<td>• Development of institutional antibiograms, stratified antibiograms, treatment guidelines, and clinical pathways</td>
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<tr>
<td>• Interventions to encourage routine “self-stewardship” in prescribers such as computerized clinical decision support at the time of prescribing, antibiotic order forms, antibiotic time-outs, and automatic stop orders and substitution policies</td>
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<tr>
<td>• Interventions to increase appropriate use of oral (PO) antibiotics</td>
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<tr>
<td>• Interventions to reduce antibiotic therapy to the shortest effective duration</td>
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<tr>
<td>• Pharmacokinetic monitoring and adjustment programs for aminoglycosides and vancomycin</td>
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<tr>
<td>• Alternative dosing strategies for broad-spectrum β-lactams</td>
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<tr>
<td>• Allergy assessments and penicillin skin testing</td>
</tr>
<tr>
<td>• Cascade microbiology sensitivity reporting</td>
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<tr>
<td>• Use of rapid diagnostic tests</td>
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</table>
2.6 **Antimicrobial Stewardship at Sunnybrook Health Science Centre**

Sunnybrook Health Sciences Centre (SHSC) is a multi-site academic health centre affiliated with the University of Toronto and located in Toronto, Ontario, Canada. The sites include the Bayview Campus, Holland Centre, and St. John’s Rehab facility. The Bayview Campus is home to a 627-bed acute care tertiary referral teaching hospital, a 530-bed long-term care facility (LTCF), and the Sunnybrook Research Institute\(^\text{10}\). The acute care facility provides the full range of acute medical and surgical services with specialized care programs in critical care, musculoskeletal care, trauma, cardiology, oncology, brain science, and maternal and perinatal care. The Holland Centre has annual volumes of approximately 5,000 elective orthopedic surgical cases and more than 30,000 ambulatory care visits and is a leader in traumatic injury management, joint reconstruction and replacement, complex upper and lower limb surgery, sports and activity-related injury management, rehabilitation, and rheumatology\(^\text{75}\). St. John’s rehab offers inpatient rehabilitation services, outpatient rehabilitation services, and community rehabilitation programs and wellness clinics to enhance the recovery from amputations, traumatic injuries, and various complex medical conditions and surgical interventions\(^\text{76}\).

On October 1\(^\text{st}\), 2009, SHSC launched a multidisciplinary PAF-ASP Pilot program in the Bayview Campus Level III critical care units (i.e., “ICU Pilot”). This was a planned intervention to determine the effectiveness and feasibility of using a PAF strategy to improve inpatient AMU at SHSC, as the IDSA-SHEA guidelines recommended using PAF as a core ASP component. Of note, various passive interventions to guide inpatient antimicrobial prescribing had been introduced in the years preceding PAF-ASP implementation, including educational in-services, antibiotic restriction policies (i.e., for carbapenems, IV ciprofloxacin, IV/PO levofloxacin), automatic substitution policies, cascade microbiology sensitivity reporting, and publication of the SHSC Antimicrobial Handbook. The SHSC Antimicrobial Handbook included antibiograms, antibiotic monographs, indication-specific guidelines, automatic substitution policies, and antibiotic dosing protocols. This Handbook was annually distributed as a hardcopy to medical and pharmacy staff, was available for pick up in the SHSC Drug Information Clinic for interested clinicians, and was available online as a pdf. All of these initiatives pre-dated the PAF-ASP ICU Pilot by over 3 years, and many had been implemented prior to the year 2001.
The ICU Pilot program consisted of pharmacotherapeutic assessment of “targeted” (TGD) antibiotic orders for Level III critical care patients on day-3 and day-10 of therapy. A dedicated stewardship pharmacist reviewed these prescriptions and identified opportunities to optimize antimicrobial therapy (i.e., alter duration of therapy, narrow/broaden spectrum of antibiotic activity, increase/decrease dose or frequency of administration, IV-to-PO or PO-to-IV conversion). Opportunities to optimize therapy reviewed with the senior infectious disease pharmacist and infectious diseases staff physician, and, once approved, the stewardship pharmacist communicated the AS team’s suggestion back to the most responsible physician verbally and in writing. The most responsible physician maintained the authority to accept or decline these suggestions. This PAF service ran Monday through Friday, and prescriptions with day-3 or day-10 of therapy falling on Saturdays or Sundays were reviewed on Friday and Monday, respectively. TGD agents included ceftriaxone, ceftazidime, piperacillin-tazobactam, meropenem, ertapenem, levofloxacin, ciprofloxacin, and vancomycin. These agents were selected as TGD antibiotics since resistance to these broad-spectrum agents can significantly compromise therapy.

In the 12-month period following implementation of the ICU Pilot program, the AS Team reviewed 717 antibiotic prescriptions and made 217 recommendations to optimize therapy. The most responsible physician actioned 178 (82%) of these suggestions. An analysis comparing ICU rates TGD AMU in the 12-month period preceding the intervention to the 12-month period following detected a 22% reduction in TGD AMU (p<0.0001). This was associated with a $95,000 savings in direct antibiotic expenditures. No statistically significant changes in control or tracer outcomes were detected, including use of stress ulcer prophylaxis in ICU patients, use of non-targeted antibiotic agents in ICU patients, and use of TGD agents in ward patients.

Based on the success in the ICU Pilot, the PAF-ASP was rolled out to 6 medical and surgical wards using a randomized stepped wedge design beginning November 1st, 2010 (i.e., “Ward Roll-Out”). Differences between the ICU Pilot and the Ward Roll-Out programs were as follows: (a) two stewardship pharmacists reviewed orders for targeted agents to identify opportunities for optimization, (b) the stewardship pharmacists reviewed orders for both ICU and ward patients, and (c) moxifloxacin was added to the list of TGD agents. In the 12-month period following the Ward Roll-Out program, the AS Team reviewed 2733 antibiotic prescriptions and
made 1285 recommendations to optimize therapy, and the primary care team actioned 1028 (80%) of these suggestions\(^7\). An analysis comparing rates TGD AMU in the 12-month period preceding the intervention to the 12-month period following it detected a 21% reduction in TGD AMU (\(p=0.004\)) among patients qualifying for the stewardship intervention. No statistically significant reduction in TGD AMU were detected in an analysis of all admitted patients (-1.2%, \(p=0.9\)), and this observation was attributed to the short median length of stay in ward patients (i.e., only 4 days)\(^7\).

The SHSC acute care ASP became increasingly comprehensive in the years following the Ward Roll-Out program. By the end of this thesis data collection period, September 30th, 2016, the SHSC acute care PAF-ASP provided daily consultations to three intensive-care (critical care-medicine, critical care-cardiac surgery, critical care-burns) and 11 non-intensive-care medical and surgical services (general medicine, general medicine-stroke, cardiology, nephrology, neurosurgery, vascular surgery, orthopedic surgery, general surgery-colorectal, general surgery-hepatopancreatobiliary, general surgery-trauma, general surgery-thoracic). TGD agents were audited on days 3, 7, and 14 of therapy, resulting in between 5-30 new consults each day. Pharmacotherapeutic assessments were conducted by two full-time stewardship pharmacists (2.0 full-time equivalent) and one part-time clinical pharmacy fellow (0.5 full-time equivalent), and the list of TGD agents had expanded to include aminoglycosides (i.e., IV gentamicin, tobramycin, and amikacin) in addition to the previously identified agents (i.e., IV meropenem, ertapenem, piperacillin/tazobactam, ceftriaxone, ceftazidime, and vancomycin; plus IV/oral (PO) ciprofloxacin, levofloxacin, and moxifloxacin).

Table 2-2 provides a list of policies, practices, and technologies that were introduced post-PAF-ASP implementation that complement the practice of AS at SHSC (i.e., “passive” strategies that support the core PAF activity). Most of the passive interventions implemented pre-PAF-ASP were maintained or enhanced. The notable exceptions are the restriction policies for IV ciprofloxacin, IV/PO levofloxacin, and ertapenem. These policies were lifted in the years following PAF-ASP implementation.

In January 2018, Accreditation Canada identified the Sunnybrook Antimicrobial Stewardship Team (SB-AST) as a Leading Practice in the acute care sector, recognizing the program to be
particularly innovative and effective in improving quality. On January 2, 2018, the SHSC ASP expended its team and its program to offer PAF at the Bayview Campus LTCF, the Holland Centre, and St. John’s Rehab facilities. Of note, the SHSC acute care facility and LTCF share the same geographical site (i.e. the Bayview Campus). The acute care facility also shares personnel, policies, and educational resources with the LTCF. Consequently, it is possible that LTCF prescribers were exposed to elements of the acute care ASP prior to the 2018 LTCF-PAF expansion, and that this exposure positively influenced antimicrobial prescribing and rates of AMR in the LTCF between 2009 and 2016.
Table 2-2 Select timeline of activities to enhance antibiotic prescribing at Sunnybrook Health Sciences Centre acute care facility

Sunnybrook Health Sciences Centre (SHSC) implemented a prospected audit-and-feedback (PAF) antimicrobial stewardship program (ASP) initiative in October 2009. Various passive interventions to guide inpatient antimicrobial prescribing had been introduced in the years preceding PAF-ASP implementation, including educational in-services, cascade microbiology sensitivity reporting, publication of the SHSC Antimicrobial Stewardship Handbook, automatic substitution policies, and antibiotic restriction policies for carbapenems, IV ciprofloxacin, and IV/PO levofloxacin. A select list of changes to the active and passive interventions and strategies that occurred post-PAF-ASP implementation, as well as the approximate date of these changes, is provided in the table below.

<table>
<thead>
<tr>
<th>Item</th>
<th>Approximate Date</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation of the “ICU Pilot”</td>
<td>October 2009</td>
<td>PAF of orders for TGD agents on day 3 and day 10 of therapy for Level III critical care patients</td>
</tr>
<tr>
<td>“Ward Roll-Out” of PAF to six general medicine and general surgery wards</td>
<td>April 2011</td>
<td>PAF of orders for TGD agents on day 3 and day 10 of therapy for Level III critical care patients and patients on 6 general surgery and general medicine wards</td>
</tr>
<tr>
<td>Use of rapid diagnostic tests to assist with diagnosis of viral respiratory infections</td>
<td>November 2011</td>
<td>Reporting of nasopharyngeal swab viral polymerase chain reaction test results in patient electronic health records</td>
</tr>
<tr>
<td>Use of continuous infusion of vancomycin in select patients</td>
<td>2012</td>
<td>To minimize toxicity and optimize benefits of vancomycin therapy</td>
</tr>
<tr>
<td>Ciprofloxacin IV, levofloxacin IV/PO, and ertapenem removed from list of restricted agents</td>
<td>~2013</td>
<td>Patients on wards eligible to receive ciprofloxacin IV, levofloxacin IV/PO, and ertapenem without pre-authorization</td>
</tr>
<tr>
<td>Use of rapid bacterial pathogen identification technology</td>
<td>August 2014</td>
<td>Use of MALDI-TOF (Matrix Assisted Laser Desorption/Ionization-Time of Flight) for bacterial identification</td>
</tr>
<tr>
<td>Regularly scheduled clinical education sessions to incoming medical residents</td>
<td>2015</td>
<td>Noon rounds 2-4 times per year to enhance knowledge on key stewardship topics</td>
</tr>
<tr>
<td>Allergy assessments and beta-lactam allergy skin testing</td>
<td>October 5, 2015</td>
<td>To reduce unnecessary use of second and third line antibiotics</td>
</tr>
<tr>
<td>SHSC Antimicrobial Handbook transitioned to an online platform</td>
<td>November 2015</td>
<td>Many new guidelines and antibiotic monographs have been developed since transitioning to the online App, and visibility and use of the Handbook have increased\textsuperscript{79}. The AST App was awarded Canadian Society of Hospital Pharmacy Ontario Branch Innovative Information Technology Award in 2017\textsuperscript{80}.</td>
</tr>
<tr>
<td>“Just-in-time” antibiotic pharmacotherapeutic assessments for all patients on antibiotics (regardless of agent) on hospital wards with <em>C. difficile</em> infection outbreaks</td>
<td>May 17, 2017</td>
<td>Partnered initiative the SHSC Infection and Prevention Control Team</td>
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\textsuperscript{79} doi:10.12968/hq.2017.38.8.104591

\textsuperscript{80} doi:10.12968/hq.2017.38.8.104591
2.7 Evidence for the Impact of Antimicrobial Stewardship Interventions on Relevant Outcomes

The positive impact of AS interventions on prescribing behaviors, antimicrobial use, and drug-acquisition costs is well established⁴⁻⁷. Evidence also suggests that ASP are mortality neutral and otherwise safe⁴,⁶.

A systematic review and meta-analyses of 89 studies⁵, published by the Cochrane Effective Practice, Organisation of Care (EPOC) Group in 2013, found that persuasive ASP interventions were associated with 18%-33% improvements in antibiotic prescribing measures and restrictive ASP interventions were associated with 17%-40% improvements in antibiotic prescribing measures⁵. Persuasive interventions were defined as strategies that advised physicians on how to prescribe or provided feedback about their prescribing practices, and included audit-and-feedback, educational outreach initiatives, dissemination of educational resources, and reminders⁵. Restrictive interventions were defined as those that imposed limits on the freedom of prescribers to order certain agents, typically through changes to the hospital antibiotic formulary or organizational policy (i.e. expert approval or PRA)⁵. Restrictive interventions were found to outperform persuasive strategies at the 1-month post-implementation mark, but no statistically significant differences between PRA and PAF were found at 6-, 12-, or 24-months post-implementation. Clinical outcome data was limited at the time this review was published, but the meta-analyses detected a signal favouring ASPs for reducing mortality (i.e. ASP exposure was associated with an 8% reduction in the relative risk of patient mortality; 95% CI from -6% to 19%)⁵.

A systematic review conducted by the Department of Veterans Affairs (DoVA)⁶ identified 35 additional studies that met the EPOC Group’s quality criteria, but that had been missed or published after the EPOC review described above⁵. The DoVA review⁶ found PRA and PAF were consistently associated with improvements in prescribing and AMU outcomes (i.e. 5/5 PRA studies reporting prescribing outcomes had results favouring PRA, and 13/14 PAF studies reporting prescribing outcomes had results favouring PAF). In contrast, the results from studies on other intervention types was found to be more mixed (i.e. guidelines with feedback, guidelines without feedback, protocols, computerized decision support). The review⁶ found PRA
and PAF interventions were clinically neutral (i.e., 14/16 studies were found to report no significant effect on mortality or length of stay, and 2/16 studies were found to report ASP-associated improvements), and that all PAF and PRA studies reporting financial outcomes detected decreases in drug and/or payer costs (i.e., 9/9 PAF studies and 1/1 PRA study). A separate systematic review and meta-analyses on economic outcomes confirmed these findings and determined that hospital ASPs were associated with a 34% reduction in overall antibiotic costs (95% CI: 26% to 42%), a 19% reduction in total antibiotic consumption (95% CI: 8% to 30%), a 27% reduction in targeted antibiotic consumption (95% CI: -1% to 52%), and a 9% reduction in the relative length of stay (95% CI: 5% to 13%).

An updated version of the EPOC Group review was published in 2017. This review included over 220 studies meeting the EPOC quality criteria, and found that ASPs (collectively) improved the appropriateness of antibiotic prescribing by 15% (95% CI: 14% to 16% improvement), reduced the duration of antibiotic courses of therapy by 1.95 days (95% CI: -2.22 days to -1.67 days), and reduced TGD antibiotic consumption by 25% (95% CI: 13% to 37% reduction). Mean length of hospital stay was found to be reduced by 1.1 days (95% CI: -0.7 days to -2.5 days), and no statistically significant differences in mortality was detected (0 more deaths per 100 participants, 95% CI: 1 to 0). Accordingly, the authors concluded that ASPs improve the appropriateness of prescribing and reduce the duration of treatment with a high degree of certainty.

The 2017 EPOC Group review also used meta-regression evaluate the impact of different ASP strategies, such as restriction, enablement, and prescriber feedback on antibiotic prescribing outcomes. Enablement was defined as “increasing means/reducing barriers to increase capability or opportunity.” Restriction was defined as “using rules to reduce the opportunity to engage in the target behavior.” Enablement was found to enhance prescribing compliance for all intervention types (β_{RCT studies} + 15, p<0.05; β_{ITS studies} +11, p<0.05), and also when added to restriction (β_{ITS enablement studies} +20, p<0.05). The addition of prescriber feedback to enablement interventions further enhanced the effectiveness of these strategies (β_{ITS restriction studies} +40, p<0.05). Restriction was found to enhance prescribing compliance (β_{RCT studies} +35, p<0.05; β_{ITS studies} = +28, p<0.05), but restrictive interventions were less likely to have sustained effects at 12-months post-implementation if they lacked an enabling component (+30% likelihood of
sustained effects favouring addition of enablement, 95% CI: -7% to +66%). These findings reinforce the notion that increasingly “active” ASP interventions have more significant and sustained effects on antibiotic prescribing behaviors.

In stark contrast to the high-certainty evidence on prescribing and AMU, there remains a paucity of high-quality data describing the impact of these programs on microbial outcomes\(^4,8,72,73\). The authors of the 2017 EPOC Group Review\(^4\) indicated that “…small number of studies, the heterogeneity of intervention targets and prescribing outcomes, and the wide confidence intervals for estimated relative effects” prohibited accurate qualitative and/or quantitative synthesis of microbial outcome data. As a result, they concluded that there was “very low certainty evidence [regarding] the effect of [these] interventions on reducing \(C.\text{difficile}\) infections….resistant gram-negative bacteria…and resistant gram-positive bacteria”\(^4\). A State of the Science Review (“SSR”)\(^8\) published in July 2018 reiterated these findings, and concluded that “there is no solid evidence that ASPs are effective in reducing antibiotic resistance in hospital settings.”

Less than 30 of the 220 studies included in 2017 EPOC Group review\(^4\) reported AMR outcomes. Of these studies, only 7 were assessed to have low risk of methodological bias\(^82-89\). Only 2 of these studies were assessed to have low risk of both methodological and microbiological bias as the EPOC Group’s quality assessment criteria—a study by Aldeyab et al.\(^82\) and a study by Willemsen et al.\(^83\). These studies\(^82,83\) are discussed below. This writer applied the EPOC Group’s risk of bias criteria\(^4,81,89\) to the 26 studies included in the SSR review\(^8\), and none of these studies were found to be at low risk of both methodological and microbiological bias. Therefore, none of the studies included in the SSR review\(^8\) are discussed in any further detail.

Aldeyab et al.\(^82\) used a 4-year ITS design (2-year pre-intervention period; 2-year post-intervention period) to evaluate the impact of a policy to restrict high-risk antibiotics (i.e., second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones, clindamycin) on the incidence of MRSA. MRSA incidence was assessed as the primary outcome, but there was no distinction made between colonization and infection. Implementation of this ASP was associated with a statistically significant improvement in MRSA trend (-0.00561/100 bed-days per month, \(p=0.0057\)), but no change MRSA level (incidence) was detected\(^82\).
Willemsen et al.\textsuperscript{83} used a 2-year ITS design and Bayesian model averaging to examine the impact of 4 staggered interventions to optimize ciprofloxacin use (i.e., an IV-to-PO policy, pocket prescribing guidelines, enhanced laboratory reports, and then audit-and-feedback). Ciprofloxacin use was assessed as the primary outcome. The susceptibility of hospital-acquired \textit{E.coli} isolates to ciprofloxacin, cefuroxime, ceftazidime, trimethoprim-sulfamethoxazole, and tobramycin were assessed as secondary outcomes. \textit{E.coli} resistance to ciprofloxacin was found to be increasing by 5%/year in the pre-intervention period. The analyses found that implementation of the pocket guidelines or PAF was associated with a significant reduction in the level of ciprofloxacin resistance (this was not able to be clarified any further), but no changes in the trend of ciprofloxacin resistance. Rates cefuroxime and ceftazidime resistance increased across the study period (i.e., no changes in level or trend were found), and rates of trimethoprim-sulfamethoxazole and tobramycin resistance remained static\textsuperscript{83}.

To the best of this writer’s knowledge, these two studies\textsuperscript{82,83} represent the existing body of high-quality ASP literature reporting AMR outcomes. Neither study provides definitive evidence regarding the effect of these programs on the collective burden of AMR. The next chapter of this thesis discusses the limitations of the AMR literature in more detail and introduces the research project that was designed to minimize these problems and clarify the AS-AMU-AMR relationship.
Chapter 3
Thesis Research Rationale
3 Thesis Research Rationale

3.1 Preface

As described in Chapter 2, antimicrobial resistance (AMR) is increasing worldwide and represents a serious threat to modern medicine\(^1\). Excessive and inappropriate antimicrobial use (AMU) has been a key driver of the AMR problem\(^1\). Therefore, promoting responsible AMU via the practice of antimicrobial stewardship (AS) was one of five fundamental strategies identified in the World Health Organization’s global action plan to combat AMR\(^1\). AMR is particularly problematic in institutional settings; accordingly, implementation of institutional antimicrobial stewardship programs (ASPs) has been identified as a method to reduce inappropriate AMU and contain the global AMR problem\(^2\)–\(^4\).

Although existing evidence demonstrates positive impacts on prescribing behaviors, AMU, and drug-acquisition costs\(^4\)–\(^7\), the effect on nosocomial AMR remains unclear\(^4\)–\(^8\). Definitive evidence demonstrating significant and sustained improvements in institutional resistance rates is required to prove the effectiveness of these programs, clarify the ASP-AMU-AMR relationship, and shape policies to support ASP activities. This research project was designed to fill this gap in AS literature and evaluated the impact of the Sunnybrook Health Sciences Centre (SHSC) acute care prospective audit-and-feedback (PAF) ASP using robust methodology. Project rationale, overarching research question, and specific objectives are discussed in the following sections of this chapter.

3.2 Description of Research Problem

Despite an increasing body of evidence evaluating ASP initiatives, there remains a paucity of high-quality data describing the impact of these programs on resistance in hospital-acquired (HA) pathogens\(^4\)–\(^8\),\(^72\),\(^73\). Only 27 of the 780 (3.5\%) full-text articles assessed for inclusion in a Cochrane review on interventions to improve hospital antibiotic prescribing\(^4\) reported on AMR outcomes using methods that met the Cochrane Collaboration’s Effective Practice and Organization of Care (EPOC) Group minimum quality criteria\(^81\). However, meeting minimum EPOC criteria does not guarantee rigorous or relevant results, and threats to internal validity limit causal conclusions in 93\% (25/27) of the studies identified\(^77\),\(^84\),\(^86\)–\(^88\),\(^90\)–\(^107\). Few studies
identified AMR as their primary outcome\textsuperscript{82,99,101} or assessed AMR outcomes in concurrent control groups\textsuperscript{103,119}. Other studies were underpowered or applied suboptimal statistical tests to reach their conclusions\textsuperscript{99,110,111}. However, failure to address potential confounding from non-ASP interventions (i.e., concurrent IPC interventions) was the most prevalent limitation\textsuperscript{77,84,86,88,90–97,100,102–107,112}. Overall, only 2 of these 27 studies (7\%)\textsuperscript{82,83} were found to report AMR outcomes with low risk of both methodological and microbial bias. The EPOC minimum quality criteria (i.e., study design criteria)\textsuperscript{81}, methodological risk bias criteria\textsuperscript{89}, and microbial risk of bias criteria\textsuperscript{4,5} are provided in Appendices 1-4.

Collective interpretation of the ASP-AMR literature is further complicated by the diversity of interventions and outcomes assessed. For example, interventions range from the use of rapid diagnostic tests\textsuperscript{93}, to the circulation of educational guidelines\textsuperscript{103}, to formulary restriction of a single agent\textsuperscript{113}, to comprehensive prospective audit-and-feedback (PAF) of over 10 broad-spectrum agents\textsuperscript{9,77}. These interventions are known to have differential effects on prescribing and AMU\textsuperscript{2–4,74}, but it is not possible to determine their differential effects on resistance due to the small number of studies reporting AMR outcomes (i.e., only 3/11 studies with low risk of methodological bias examine the impact of PAF\textsuperscript{82,83,111} on AMR).

Attempting to pool AMR results presents a unique set of problems. The spectrum of microbial outcomes assessed in each study is generally narrow and often unique (i.e., focused on one or two organisms and/or sensitivity profiles with little between-study overlap AMR outcomes)\textsuperscript{8}. As such, the unintended impact on non-target resistance profiles is an important outcome that remains unknown. Interpreting AMR findings is made further difficult by between- and within-study differences in the directions of the reported AMR results. Studies reporting on the same microorganism-antibiotic pairs have found conflicting results\textsuperscript{8}. For example, Lawes et al\textsuperscript{114} reported a statistically significant 46\% reduction in hospital MRSA prevalence after implementation of a mixed restrictive/persuasive intervention, while Carling et al\textsuperscript{115} reported no effect. Studies reporting multiple resistance profiles rarely find consistency in the direction of each individual AMR effect. For example, only 7 of the 26 studies (29\%) included in a recent review\textsuperscript{8} reported statistically significant positive findings for all antiibiogram pathogen-susceptibility pairs assessed\textsuperscript{85,112,114,116–119}. In contrast, 10 of the 26 studies (38\%) reported mixed effects (i.e. positive effects on some AMR outcomes and neutral/negative effects on
others, 4 studies (35%) reported strictly negative effects (i.e., no improvement in any pathogen-susceptibility pairs assessed), and the remaining final 5 studies (19%) had “non- interpretable” results.

To date, no study has adequately captured the long-term impact of a hospital-wide ASP on the collective burden of AMR using robust methodology. The two studies that have assessed AMR outcomes with low risk of methodological and microbial bias focused on a very narrow spectrum of resistance profiles: Aldeyab et al. focused exclusively Methicillin-resistant S. aureus (MRSA) colonization/infection rates (i.e., with no distinction between clinical and screening swabs), and Willemsen et al. focused exclusively on E. coli antibiogram changes to ciprofloxacin, cefuroxime, ceftazidine, trimethoprim-sulfamethoxazole, and tobramycin. Neither study addressed the impact on non-target pathogen-susceptibility pairs or provided a comprehensive assessment of ASP impact on all clinically relevant resistance profiles.

Definitive evidence showing collective, sustained improvements in institutional AMR is needed to validate AS theory, guide AS best practice, and further AS science. The absence of solid data is a major barrier to advancement of the AS field and has been cited as a barrier to ASP support. An urgent need for high-quality, coordinated studies on this topic has been repeatedly identified. The objective of this research was to answer those calls.

### 3.3 Overarching Research Objective

This research sought to evaluate the impact of the SHSC acute care ASP on the institutional burden of AMR and inpatient AMU. SHSC implemented a multidisciplinary PAF-ASP at the Bayview Campus acute care facility on October 1st, 2009. The core ASP activity is an “active” PAF intervention wherein the AS team reviews orders for targeted (TGD) antibiotics and provides suggestions to optimize therapy to the primary care team. The program also has several “passive” elements incorporated into its structure to complement the active PAF core, including antibiotic use policies, educational initiatives, and an online SHSC Antimicrobial Handbook App with therapeutic guidelines, antibiotic monographs, and antibiograms.

This research used patient-level data, robust interrupted time series (ITS) models, and innovative aggregate AMR metrics to generate high-quality evidence regarding the impact of this ASP on
institutional AMR and evaluate changes in the susceptibility of over 15 bacterial pathogens to over 15 antimicrobial agents. The ITS is a robust quasi-experimental design regarded as the strongest method for evaluating the longitudinal effects of an intervention. This design meets the EPOC Group minimum quality criteria, and this research was designed to be at low risk of bias as per the standard Cochrane risk of bias criteria and EPOC risk of microbial bias criteria.

The absence of standardized metrics to reflect the collective impact of ASPs on the full spectrum of clinically relevant pathogens and resistance profiles is a major barrier to AS research. To address this problem and capture the impact of ASPs on the institutional burden of AMR, two novel aggregate AMR metrics were developed: The monthly incidence of hospital-acquired antibiotic-resistant organisms (ARO) standardized by 10 000 PD (i.e. # HA-ARO/10 000 PD/month) and the monthly incidence of HA-multidrug-resistant organisms (MDRO) (i.e. # HA-MDRO/10 000 PD/month). To strengthen the causal inferences of HA-ARO and HA-MDRO findings, concurrent rates of community-acquired ARO and MDRO (i.e., # CA-ARO/10 000 PD/month; # CA-MDRO/10 000 PD/month) were assessed as controls. Rates AMU in the community and the incidence of antibiotic-resistant bacteria isolated in community settings should be unaffected by an acute care PAF-ASP. Therefore, these metrics serve to increase the methodological rigor of this study by enabling identification of secular trends that may influence study conclusions.

To support the acute care AMR outcomes and deepen understanding of the ASP-AMU-AMR relationship, robust ITS models were also used to characterize and quantify changes in institutional AMU. Reporting concurrent AMU outcomes is necessary to validate AMR findings, and demonstrating paralleled impact on institutional AMR and institutional AMU is necessary to corroborate the biological plausibility of the AS hypothesis (i.e. ASP-associated reductions in AMU remove the selective pressure favouring the persistence of ARO and incur reductions in ARO prevalence). Aggregate metrics were developed to reflect the collective impact of the ASP on AMU, and these included the institution-wide use of TGD agents (i.e. agents audited by the SHSC PAF-ASP), institution-wide use of non-targeted (NTGD) agents, and institution-wide total (TTL) AMU in days of therapy (DOT). These metrics were quantified
at monthly time intervals and standardized by 10 000 PD (i.e. # DOT targeted agents/10 000 PD/month) in the same way as the AMR outcomes.

The final component of this research project was an exploratory study to characterize trends in AMR at the SHSC long-term care facility (LTCF). The SHSC LTCF is geographically adjacent to the acute care centre and shares personnel, policies, and educational resources with the acute care centre. AMR is not routinely surveyed in LTCF, and there is little observational or interventional research describing the trends in LTCF AMR over time\textsuperscript{138–140}. For these reasons, an exploratory study describing the trends in LTCF AMR was warranted. Given the possibility that LTCF prescribers were exposed to the passive elements of the acute care ASP (i.e. via the LTCF sharing personnel, policies, and educational resources with the acute care facility), trends in LTCF AMR were assessed in relation to acute care PAF-ASP implementation. LTCF AMR was assessed using metrics akin to those used to characterize acute care AMR: Monthly incidence of LTCF-acquired ARO and MDRO (i.e., # LTCF-ARO/10 000 PD/month; # LTCF-MDRO/10 000 PD/month).

### 3.4 Overarching Research Question

What is the impact of the SHSC PAF-ASP on the aggregate burden of AMR and inpatient AMU in the acute care facility and the aggregate burden of AMR in the adjoining LTCF?

### 3.5 Specific Research Objectives and Hypotheses

#### 3.5.1 Evaluate the Impact of the Sunnybrook Health Sciences Centre Acute Care Antimicrobial Stewardship Program on the Burden of Resistance in the Acute Care Facility

The primary objective of this research was to evaluate the impact of the SHSC PAF-ASP on the institutional burden of AMR, as measured by the change in HA-ARO and HA-MDRO incidence in the 84 months (7 years) following program implementation. It was hypothesized that reductions in HA-ARO and HA-MDRO rates would be detected. Concurrent trends in CA-ARO and CA-MDRO were assessed as controls. It was hypothesized that improvements in CA-ARO and CA-MDRO would not be detected. The methods and results of the study conducted to evaluate this objective are discussed in Chapter 4.
3.5.2 Evaluate the Impact of the Sunnybrook Health Sciences Centre Acute Care Antimicrobial Stewardship Program on Rates of Antibiotic Consumption in the Acute Care Facility

The secondary objective of this research was to evaluate the impact of the SHSC PAF-ASP on institutional AMU, as measured by the change TGD antibiotic consumption in the 84 months (7 years) following program implementation. It was hypothesized that improvements in TGD AMU would be detected as these agents are audited by the PAF intervention. Changes in the rates of NTGD AMU and TTL AMU were evaluated as balancing metrics, and improvements in these outcomes were not anticipated. The methods and results of the study conducted to evaluate this objective are discussed in Chapter 5.

3.5.3 Explore and Characterize Trends in Resistance in the Affiliated Long-term Care Facility in Relation to Implementation of an Acute Care Antimicrobial Stewardship Program

The tertiary objective of this research was to explore and characterize trends in SHSC LTCF AMR in relation to acute care PAF-ASP implementation, as measured by changes in incidence of LTCF-ARO and LTCF-MDRO. No hypothesis regarding the presence or direction of an effect was proposed given the exploratory nature of this study. The methods and results of the study conducted to evaluate this objective are discussed in Chapter 6.
Chapter 4
Impact of the Sunnybrook Health Sciences Centre Acute Care Prospective Audit-and-Feedback Antimicrobial Stewardship Program on the Burden of Resistance in the Acute Care Facility
Impact of the Sunnybrook Health Sciences Centre 
Acute Care Prospective Audit-and-Feedback 
Antimicrobial Stewardship Program on the Burden of 
Resistance in the Acute Care Facility

4.1 Preface

This chapter describes the methods and findings of the study conducted to evaluate the primary 
objective of this thesis research: Evaluating the impact of the Sunnybrook Health Sciences 
Centre (SHSC) prospective audit-and-feedback (PAF) antimicrobial stewardship program (ASP) 
on the burden of antimicrobial resistance (AMR) in the acute care facility. Differences in the 
incidence and trend of hospital-acquired antibiotic-resistant organisms (HA-ARO) and hospital-
acquired multidrug-resistant organisms (HA-MDRO) in the years preceding the intervention and 
the years following the intervention were used to infer program impact. Since the burden of 
AMR in the community should be unaffected by an acute care ASP, differences in the incidence 
and trend of community-acquired antibiotic-resistant organisms (CA-ARO) and community-
acquired multidrug-resistant organisms (CA-MDRO) were assessed as controls.

4.2 Background

AMR is increasing worldwide and represents a serious threat to modern medicine\textsuperscript{18}. AMR is particularly problematic in institutional settings and is correlated with increased antimicrobial 
use (AMU)\textsuperscript{69,70}. In an attempt to try and curtail antibiotic misuse resulting in increased AMR, infectious diseases societies from North America and Europe recommended institution of 
multidisciplinary hospital ASPs\textsuperscript{2,3,141}. Existing evidence demonstrates the positive effect of ASPs 
on prescribing behaviors, AMU, and drug-acquisition costs\textsuperscript{4–7}, but the effect on nosocomial 
AMR is less clear.

Despite an increasing body of evidence evaluating AS initiatives, there remains a paucity of 
high-quality data evaluating the impact ASPs on resistance in hospital-acquired (HA-) 
pathogens\textsuperscript{4,5,8}. Fewer than 30 publications reporting ASP-AMR outcomes meet the minimum 
quality criteria outlined by the Cochrane Collaboration’s Effective Practice and Organization of
Care (EPOC) Group, and studies meeting the minimum quality criteria suffer from significant internal validity threats. For example, over 90% (25/27) of studies reporting ASP-medicated AMR outcomes included in a recently published systematic review were assessed as having moderate or high risk of methodological or microbial bias.

No study meeting the minimum EPOC criteria has evaluated the collective impact of an ASP across all clinically important bacterial pathogens, and between-study differences in AMR outcomes make comparative or collective assessments inappropriate or impossible. Few studies report outcomes for the same bacterial susceptibility profiles, and the results from studies with comparable outcomes are inconsistent due to the different interventions and metrics employed. For example, Lawes et al reported a statistically significant 46% reduction in hospital MRSA prevalence after implementation of a mixed restrictive/persuasive intervention, while Carling et al reported no effect.

Definitive evidence showing collective, sustained improvements, in institutional AMR is needed to validate AS theory, further AS science, and guide ASP best practice. SHSC implemented a multidisciplinary PAF-ASP on October 1st, 2009. Currently, the SHSC PAF-ASP provides automatic consultations for three intensive-care and 11 non-intensive-care medical and surgical services by reviewing orders for targeted antibiotic agents on days 3, 7, and 14 of therapy and making suggestions to optimize therapy. Research conducted in the early phases of the SHSC PAF-ASP demonstrated positive effects on institutional AMU and antibiogram changes in keeping with AMR improvements. This study built on those early phase findings and used innovative AMR outcome metrics and a rigorous methodology to characterize the impact of this program on the institutional burden of AMR.

4.3 Objective and Hypothesis

This study sought to evaluate the impact of the SHSC PAF-ASP on the institutional burden of AMR, as measured by the change in HA-ARO and HA-MDRO incidence in the 7-year (84-month) period following program implementation. It was hypothesized that reductions in HA-ARO and HA-MDRO rates would be detected. CA-ARO and CA-MDRO rates were assessed as controls. It was hypothesized that improvements in CA-ARO and CA-MDRO would not be detected.
4.4 Methods

4.4.1 Study Design

Changes in the institutional burden AMR in relation to SHSC PAF-ASP implementation were assessed using retrospective interrupted time series (ITS) analyses. The ITS is a robust quasi-experimental design, and it is the most appropriate design for evaluating longitudinal effects of population-level interventions over time\textsuperscript{137,142,143}. Implementation of the SHSC PAF-ASP on October 1\textsuperscript{st}, 2009 was the intervention for this study. The monthly incidence rates of HA-resistant bacteria in the post-intervention period (i.e. in the presence of the PAF-ASP) were compared to monthly incidences of HA-resistant bacteria in the pre-intervention period (i.e. in the absence of the PAF-ASP), such that the pre-intervention period served as a historic control. The relative reduction in the collective incidence of HA-resistant bacteria from the pre- to post-intervention period (i.e. Post-Period Relative Rate Reduction, “Post-Period RRR”), and the difference in the pre- and post-intervention period monthly trends over time, were used to infer program impact. Since the incidence of community-acquired (CA-) resistant isolates should be unaffected by an acute care PAF-ASP targeting inpatient antibiotic use. Therefore, changes in the relative incidence and trends of CA-resistant isolates were assessed in the same manner as concurrent external controls.

The “base-case” model utilized pre- and post-intervention periods 84 months in duration (pre-intervention period: October 2002 – September 2009; post-intervention period: October 2009 – September 2016). The decision to use an 84-month pre-intervention period for the base-case model was somewhat arbitrary; an 84-month post-intervention period was available for the PAF-ASP at the time of study design, and an 84-months pre-intervention period was selected to achieve pre- and post-intervention periods of symmetrical durations. Base-case model conditions and assumptions were altered to create various sensitivity models and validate base-case findings. Sensitivity models are discussed in Section 4.4.5.2 of this report and summarized in Table 4-1.

4.4.2 Study Setting and Population

SHSC is a multi-site academic health centre affiliated with the University of Toronto and located in Toronto, Ontario, Canada. The Bayview Site is home to a 627-bed acute care tertiary referral
teaching hospital and a 530-bed long-term care facility (LTCF). The acute care facility provides the full range of acute medical and surgical services with specialized care programs in critical care, musculoskeletal care, trauma, cardiology, oncology, brain science, and maternal and perinatal care.

All non-duplicate clinical isolates for target bacterial species isolated from adult patients admitted to the SHSC acute care facility during the defined study period were included in this analysis (excluding mothers admitted to the Women and Babies program, as the PAF-ASP does not consult for these patients). Clinical isolate was defined as a positive bacterial culture grown from a clinical specimen. Clinical specimen was defined as a specimen collected for the purpose of assisting with the diagnosis of an infection (i.e., blood, urine, sputum, etc.). Isolates grown from screening swabs, surveillance swabs, or other cultures sent for infection prevention and control (IPC) purposes were excluded from this analysis (i.e., nasal and rectal swabs).

Clinical isolates of the following common nosocomial pathogens were included in this analysis: *Escherichia coli, Klebsiella* spp., *Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia* spp., *Serratia* spp., *Citrobacter* spp., *Enterobacter* spp., *Pseudomonas aeruginosa, Acinetobacter* spp., *Enterococcus* spp., and *Staphylococcus aureus*. Duplicate isolates were removed from the data set to minimize bias. For the base-case data set, duplicate isolates were defined as same-species isolates with identical susceptibility profiles collected from the same inpatient within 14 days.

### 4.4.3 Outcomes

#### 4.4.3.1 Primary Outcomes

PAF-ASP associated changes in the monthly incidence of HA-ARO were assessed as the primary outcome (i.e. monthly HA-ARO incidence rate = number of HA-ARO identified in study month X standardized by the number of patient days (PD) in study month X for the entire acute care facility). For the base-case model, HA-isolate was defined as an isolate grown from a clinical specimen collected greater than 48 hours after admission (i.e. > 48 hours); this was in keeping with the standard definition of hospital-acquired infection. ARO was defined as a clinical isolate of any target bacterial species exhibiting resistance to at least one therapeutically active antibiotic agent. Isolates were classified as susceptible or resistant in accordance with
the Clinical and Laboratory Standards Institute (CLSI) guidelines active at the time of collection (i.e., as determined by the SHSC Microbiology Laboratory at the time of sensitivity testing).\textsuperscript{147} Isolates with intermediate susceptibility were considered resistant.

A PAF-ASP associated change in the burden of HA-ARO was assessed by comparing the mean monthly HA-ARO incidence rate in the pre-intervention period to the mean monthly HA-ARO incidence rate in the post-intervention period. Differences were reported as the relative rate reduction in the post-intervention period (i.e., Post-Period Relative Rate Reduction, “Post-Period RRR\textsubscript{HA-ARO}”; reported as % incidence reduction/post-period). The presence of a PAF-ASP associated change in HA-ARO incidence rate trend was also assessed, and pre- and post-intervention trend estimates were determined to further characterize PAF-ASP impact (“Trend\textsubscript{HA-ARO,pre}” and “Trend\textsubscript{HA-ARO,post}”; reported as Δ% incidence/month).

### 4.4.3.2 Secondary Outcomes

PAF-ASP associated changes in the monthly incidence of HA-MDRO were assessed as the secondary outcome (i.e., monthly HA-MDRO incidence rate = number of HA-MDRO identified in study month X standardized by the number of patient days (PD) in study month X for the entire acute care facility). MDRO was defined as a clinical isolate of any target bacterial species exhibiting resistance to three or more antibiotic classes.\textsuperscript{146} The definition for HA-isolate and the criteria used to classify isolates as susceptible or resistant described in Section 4.4.3.1 were applied.

A PAF-ASP associated change in the burden of HA-MDRO was assessed by comparing the mean monthly HA-MDRO incidence rate in the pre-intervention period to the mean monthly HA-MDRO incidence rate in the post-intervention period. Differences were reported as the relative rate reduction in the post-intervention period (i.e., Post-Period Relative Rate Reduction, “Post-Period RRR\textsubscript{HA-MDRO}”; reported as % incidence reduction/post-period). The presence of a PAF-ASP associated change in HA-MDRO incidence rate trend was also assessed, and pre- and post-intervention trend estimates were determined to further characterize PAF-ASP impact (“Trend\textsubscript{HA-MDRO,pre}” and “Trend\textsubscript{HA-MDRO,post}”; reported as Δ% incidence/month).
4.4.3.3 Control Outcomes

Changes in the monthly incidence of CA-ARO and CA-MDRO were assessed as control outcomes (i.e. monthly CA-ARO incidence rate = number of CA-ARO identified in study month X standardized by the number of patient days (PD) in study month X for the entire acute care facility; monthly CA-MDRO incidence rate = number of CA-MDRO identified in study month X standardized by the number of patient days (PD) in study month X for the entire acute care facility). For base-case models, CA-isolate was defined as an isolate grown from a clinical culture collected within 48 hours of admission (i.e. <48 hours). The definitions for ARO and MDRO and the criteria used to classify isolates as susceptible or resistant described in Section 4.4.3.1 and Section 4.4.3.2 were applied.

Changes in burden of CA-AMR were assessed by comparing mean monthly incidence rates in the pre-intervention period to mean monthly incidence rate in the post-intervention period. Differences were reported as relative rate reductions in post-intervention period incidence (i.e. “Post-Period RRR\textsubscript{CA-ARO} and “Post-Period RRR\textsubscript{CA-MDRO}”; reported as % incidence reduction/post-period). The presence of PAF-ASP associated changes in CA-ARO and CA-MDRO incidence rate trends were also assessed, and pre- and post-intervention trend estimates were determined (“\text{Trend}_{\text{CA-ARO,pre}}”, “\text{Trend}_{\text{CA-ARO,post}}”, “\text{Trend}_{\text{CA-MDRO,pre}}”, and “\text{Trend}_{\text{CA-MDRO,post}}”; reported as Δ% incidence/month).

4.4.4 Data Collection and Preparation

4.4.4.1 Microbiology Data

Patient-level data for clinical isolates of target bacterial species collected from adult inpatients between October 1\textsuperscript{st}, 2002 to September 30\textsuperscript{th}, 2016 were retrospectively extracted from the SHSC Microbiology Department Database into a Microsoft Excel spreadsheet. The following parameters were extracted for each clinical isolate: Patient identifier, patient age and sex, patient date of admission, date and location of culture collection (i.e. ward location), specimen type (blood, sputum, urine, wound, CSF, etc.), bacterial species (\textit{Escherichia coli, Klebsiella} spp., \textit{Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia} spp., \textit{Serratia} spp., \textit{Citrobacter} spp., \textit{Enterobacter} spp., \textit{Pseudomonas aeruginosa, Acinetobacter} spp.,
Staphylococcus aureus, Enterococcus spp.), and isolate susceptibility profile as tested and reported by the Microbiology Laboratory at the time of collection.

4.4.4.2 Administrative Data

PD data and length of stay (LOS) data were retrospectively extracted from the SHSC Health Data Resources Database into a Microsoft Excel database. PD data was extracted as institution-wide aggregate count for each study month. Mean LOS for all acute care inpatients was also extracted for each study month.

4.4.5 Statistical Analyses

4.4.5.1 Base-Case Model

4.4.5.1.1 Descriptive Statistics

The following descriptive statistics were reported for the base-case study period: (a) patient count, (b) percentage of male patients, (c) mean patient age, and (d) counts and proportions of isolates from urine, blood, respiratory, and other sample types. Total PD count, mean monthly PD count, and mean length of stay (LOS) were reported for the complete study period, the pre-intervention period, and the post-intervention period.

Standardized total counts (N* = total count/10 000 PD/period) and standardized mean monthly counts (μ* = monthly count/10 000 PD/period) were determined for various groups of clinical isolates and for HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO. These were reported for the complete study period, the pre-intervention period, and the post-intervention period. Pre- to post-intervention unadjusted relative rate reductions (unadjusted RRR = 100% − [μ*post/μ*pre]) and unadjusted absolute rate reductions (unadjusted ARR = μ*pre − μ*post) were reported for descriptive purposes.

4.4.5.1.2 Inferential Statistics

The presence of PAF-ASP associated changes in HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO were tested using Poisson regression generalized linear mixed models. The presence of PAF-ASP associated reductions in the burden of HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO (i.e. Post-period RRR) were assessed using the “Relative Rate Reduction (RRR)
Regression Model” described below. The presence of PAF-ASP associated changes in the trends of HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO, and estimates of the pre- and post-intervention period monthly trends (i.e. Trend\textsubscript{pre} and Trend\textsubscript{post}), were assessed using the “Trend Regression Models” described below.

Relative Rate Reduction (RRR) Regression Model

Differences in the relative incidence of HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO in the pre- and post-intervention periods were tested using Poisson regression models of the following form:

\[ \text{Ln (Monthly Count/Bed Occupancy)} = \beta_1(\text{Study Period}) + \beta_2(\text{Season}) \]

The outcome variable was monthly ARO and MDRO count (“Monthly Count”) standardized by institutional patient load (“Bed Occupancy” in PD). “Study Period” was included as fixed component and assessed as the main predictor (0 = pre-intervention period; 1 = post-intervention period). “Season” was included as a fixed component to adjust for the effect of season on AMU and therefore ARO and MDRO incidence (1 = March, April, May; 2 = June, July, August; 3 = September, October, November; 4 = December, January, February). Study month was treated as a random component and modelled from a distribution with an autoregressive correlation structure. The autoregressive correlation structure assumed that time points closer together were more similar than time points further apart.

\( \beta_1 \) and \( \beta_2 \) represent the model-adjusted estimates for the effects of Study Period and Season on ARO and MDRO incidence. A statistically significant difference in pre- and post-intervention period incidence was inferred when the p-value for the \( \beta_1 \) parameter was equal or less than 0.05. The incidence rate ratio (IRR) for pre- to post-intervention period incidences of ARO and MDRO were obtained by exponentiating the \( \beta_1 \) parameter (i.e. \( e^{\beta_1} = \text{IRR} = \frac{\text{Rate}_{\text{post-period}}}{\text{Rate}_{\text{pre-period}}} \)). The Post-Period RRR was obtained by taking the difference between the IRR and 100% (i.e. Post-Period RRR\textsubscript{base} = 100% – IRR) and reported as the percent reduction in post-period incidence (Post-Period RRR = % incidence reduction/post-period). Post-Period RRR greater than ± 10% were considered clinically significant. \( \beta_2 \) parameters and the impact of
season on AMR are not discussed further as these items are not directly relevant to this study’s objective.

**Trend Regression Models**

PAF-ASP associated changes in the trajectories, or “trends”, of HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO incidence were tested using interaction models of the following form:

\[
\text{Ln (Monthly Count/Bed Occupancy)} = \beta_3(\text{Study Period}) + \beta_4(\text{Season}) + \beta_5(\text{Study Month}) + \beta_6(\text{Study Month*Study Period})
\]

This model had four fixed components: “Study Period”, “Season”, “Study Month”, and “Study Month*Study Period”. Study Month was included as a fixed component because the month-to-month change in ARO and MDRO counts (i.e. “trends”) were being assessed. The interaction between Study Phase*Study Month was included as a fixed factor to specifically test for a difference between pre- and post-intervention period trends. A statistically significant difference in pre- and post-intervention period trend was inferred when the p-value for the \(\beta_6\) parameter was equal or less than 0.05.

When the \(\beta_6\) parameter was statistically significant, pre- and post-intervention period trend estimates were characterized by running the follow-up model below:

Study Phase 0: \[\text{Ln (Monthly Count/Bed Occupancy)} = \beta_7(\text{Study Month})\]

Study Phase 1: \[\text{Ln (Monthly Count/Bed Occupancy)} = \beta_8(\text{Study Month})\]

A statistically significant pre-intervention period trend was inferred when the p-value for the \(\beta_7\) parameter was equal or less than 0.05. Pre-intervention period trend estimates (i.e. “Trend\text{pre}”) were obtained by exponentiating \(\beta_7\) parameter (i.e. \(\text{Trend}_{\text{pre}} = e^{\beta_7}\)) and were reported as the percent change in incidence each month (\(\text{Trend}_{\text{pre}} = \% \Delta \text{ incidence/month}\)). \(\text{Trend}_{\text{pre}}\) with p-values <0.05 were deemed statistically significant.

A statistically significant post-intervention period trend was inferred when the p-value for the \(\beta_8\) parameter was equal or less than 0.05. Post-intervention period trend estimates (i.e. “Trend\text{post}”) were obtained by exponentiating \(\beta_8\) parameter (i.e. \(\text{Trend}_{\text{post}} = e^{\beta_8}\)) and were reported as the
percent change in incidence use each month (Trend\textsubscript{post} = % Δ incidence /month). Trend\textsubscript{post} with p-values <0.05 were deemed statistically significant.

### 4.4.5.2 Sensitivity Models

A variety of sensitivity analyses were run for the primary (HA-ARO), secondary (HA-MDRO) and control outcomes (CA-ARO, CA-MDRO). These sensitivity analyses are described in the following subsections and summarized in Table 4-1. The subscript “base” was used to denote base-case model parameters (i.e. “Post-Period RRR\textsubscript{base}”, “Trend\textsubscript{pre,base}”, and “Trend\textsubscript{post,base}”). The subscripts “Sens1”, “Sens2”, “Sens3”, “Sens4”, and “Sens5” were used to denote sensitivity model parameters (i.e. “Post-Period RRR\textsubscript{sens1}”, “Trend\textsubscript{pre,sens1}”, and “Trend\textsubscript{post,sens1}”).

#### Sensitivity Model #1 (“Sens1”)

The first sensitivity model modified the base-case definition of “duplicate isolate”. The base-case definition for duplicate isolates were same-species isolates with identical susceptibility profiles collected from a single inpatient within 14 days. Since no standard definition of duplicate isolate exists\textsuperscript{149}, the de-duplication period (i.e. time period used to define a duplicate isolate) was extended from 14 days (base-case definition) to 30 days to create the “Sens1” model. If \( \geq 5\% \) of the base-case isolates were excluded from the Sens1 data set, the Sens1 data set would be reanalyzed using the RRR and Trend Poisson regression models to yield “Post-Period RRR\textsubscript{sens1}”, “Trend\textsubscript{pre,sens1}”, and “Trend\textsubscript{post,sens1}”.

#### 4.4.5.2.1 Sensitivity Model #2 (“Sens2”)

The second sensitivity model modified the base-case definitions of “HA” and “CA” isolates. A 48 hour cut-off was applied in the base-case model, which is consistent with the standard definition of hospital-acquired infection\textsuperscript{144,145}. However, the 48-hour cut-off is somewhat arbitrary and potentially over-estimate rates of HA-isolates\textsuperscript{150,151}. Therefore, the HA- and CA-isolate cut-off was extended to 72 hours to create the “Sens2” model. The Sens2 data set was reanalyzed using the RRR and Trend Poisson Regression models to yield “Post-Period RRR\textsubscript{sens2}”, “Trend\textsubscript{pre,sens2}”, and “Trend\textsubscript{post,sens2}”.
4.4.5.2.2 Sensitivity Model #3 ("Sens3")

The third sensitivity model modified the base-case definitions of “HA” and “CA” isolates by extending the 48-hour cut-off to a 96-hour cut-off. This produced the “Sens3” model and data set, and the Sens3 data set was reanalyzed using the RRR and Trend Poisson Regression models to yield “Post-Period RRR\textsubscript{Sens3}”, “\text{Trend}\text{pre}\text{,sens3}”, and “\text{Trend}\text{post}\text{,sens3}”.

4.4.5.2.3 Sensitivity Model #4 ("Sens4")

Two additional predictor variables were added to the base-case model to create the “Sens4” sensitivity model: (a) mean monthly LOS, and (b) monthly positive culture rate. Both these variables represented important potential confounders. SHSC internal reports suggested inpatient mean LOS had decreased over the 14-year study period. It was possible that launch of the “Choosing Wisely” campaigns in the post-intervention period decreased culture requisition rates. Both factors could have decreased ARO incidences and biased base-case findings. To control for these potential confounders, RRR and Trend Poisson Regression models were re-run with mean monthly LOS and monthly positive culture rate included as additional fixed components to yield “Post-Period RRR\textsubscript{Sens4}”, “\text{Trend}\text{pre}\text{,sens4}”, and “\text{Trend}\text{post}\text{,sens4}”.

4.4.5.2.4 Sensitivity Model #5 ("Sens5")

The fifth sensitivity model modified the length of base-case pre-intervention period to control for the potential effect of an IPC intervention launched 23-months prior to the PAF-ASP. SHSC launched a Hand Hygiene (HH) Campaign in November 2007. SHSC internal reports (unpublished data) indicated that institutional HH rates remained constant from November 2007 to September 2016; however, it remained possible that implementation of the HH campaign could have altered ARO prevalence in the pre-intervention period and biased base-case findings. Therefore, to eliminate any variability in ARO and MDRO rates attributable to the HH campaign, an abbreviated pre-intervention period of 23 months (November 2007- September 2009) was utilized for the Sen5 model. With constant HH rates from the start to the end of the Sens5 study period, conclusion regarding the impact of the PAF-ASP on pre- to post-intervention changes in AMR can be made with a higher degree of certainty. Abbreviating the pre-intervention period in this way was appropriate because the decision to use 84-months in the base-case model was somewhat arbitrary (i.e. 84-months was used in the base-case model to
achieve pre- and post-intervention periods of symmetrical length). The Sens5 data set was reanalyzed using the RRR and Trend Poisson Regression models to yield “Post-Period RRR\_sens5”, “Trend\_pre,sens5”, and “Trend\_post,sens5”.

### 4.4.5.3 Model Fitting

It is suggested that time series data sets include at least 9 pre-intervention period time points and 9 post-intervention period time points to provide enough variability to fit the model\(^\text{152}\). However, it is generally agreed that more time points are better. Another rule of thumb is that there should be at least 10 time points per fixed component (i.e. predictor variable) in a multi-variable model to avoid over-parameterization\(^\text{148}\). In addition, it is encouraged that each time point have at least 100 observations to minimize the number of outliers and provide more stable estimates\(^\text{152}\).

For this study, base-case RRR models had 2 predictor variables (Study Period, Season) and base-case Trend models had a maximum of 4 predictor variables (Study Period, Season, Study Month, Study Month*Study Period). The sensitivity models had a maximum of 4 predictors in the RRR model (Sens4 model: Study Period, Season, Mean LOS, Monthly Positive Culture Count) and a maximum of 6 variables in the Trend models (Sens4 model: Study Period, Season, Mean LOS, Monthly Positive Culture Count, Study Month, Study Month*Study Period). The base-case data set had 168 time points. The sensitivity models had between 107 and 168 time points (Sens 5: 107 time points). Therefore, even the model with the smallest number of time points (i.e. 107) and the largest number of predictors (i.e. 6) had a time point-to-predictor ratio exceeding the 10:1 general rule of thumb. Institution-wide aggregate HA-ARO incidences were anticipated to exceed counts of 100 per month. For these reasons, adequate fitting of the models was anticipated.
Table 4-1. Assumptions and conditions for the acute care antibiotic resistance models. Items in bolded font represent changes to the base-case assumptions and conditions.

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Assumptions</th>
<th>Model Conditions</th>
<th>Description and Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base-case</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“HA” isolate definition</td>
<td>Pre-intervention period duration</td>
<td>• Symmetrical 84-month pre- and post-intervention periods (arbitrary pre-intervention period duration)</td>
</tr>
<tr>
<td></td>
<td>“CA” isolate definition</td>
<td>Post-intervention period duration</td>
<td>• Definition for “HA” and “CA” isolates in keeping with the traditional definitions for “HA infection” and “CA infection”</td>
</tr>
<tr>
<td></td>
<td>“Duplicate” isolate definition</td>
<td>Covariates</td>
<td>• Deduplication window set at 14 days (double the mean length of stay for SHSC inpatients)</td>
</tr>
<tr>
<td></td>
<td>HA: Collected &gt;48 hours after admission</td>
<td>Pre-period: 84 months (Oct 2002- Sept 2009)</td>
<td>• Season included as covariate</td>
</tr>
<tr>
<td></td>
<td>CA: Collected ≤48 hours of admission</td>
<td>Post-period: 84 months (Oct 2009- Sept 2016)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duplicate: Identical isolate collected from the same patient ≤ 14 days</td>
<td>Covariates: Season</td>
<td></td>
</tr>
<tr>
<td><strong>Sens1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HA: Collected &gt;48 hours after admission</td>
<td>Pre-period: 84 months (Oct 2002- Sept 2009)</td>
<td>• Lengthened the base-case deduplication window from 14 days to 30 days</td>
</tr>
<tr>
<td></td>
<td>CA: Collected ≤48 hours of admission</td>
<td>Post-period: 84 months (Oct 2009- Sept 2016)</td>
<td>• No standard definition for “duplicate isolate” exists</td>
</tr>
<tr>
<td></td>
<td>Duplicate: Identical isolate collected from the same patient ≤ 30 days</td>
<td>Covariates: Season</td>
<td>• 14 day base-case deduplication window was arbitrarily defined</td>
</tr>
<tr>
<td><strong>Sens2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HA: Collected &gt;72 hours after admission</td>
<td>Pre-period: 84 months (Oct 2002- Sept 2009)</td>
<td>• Altered base-case definition for “HA” and “CA” isolates.</td>
</tr>
<tr>
<td></td>
<td>CA: Collected ≤72 hours of admission</td>
<td>Post-period: 84 months (Oct 2009- Sept 2016)</td>
<td>• The 48-hour cut-off period is somewhat arbitrary and potentially over-estimate “HA” rates</td>
</tr>
<tr>
<td></td>
<td>Duplicate: Identical isolate collected from the same patient ≤ 14 days</td>
<td>Covariates: Season</td>
<td>• “HA” and “CA” cut-off period extended from 48 hours to 72 hours</td>
</tr>
</tbody>
</table>

HA, hospital-acquired; CA, community-acquired; Sens1, sensitivity model #1; Sens2, sensitivity model #2
Table 4-1 (continued). Assumptions and conditions for the acute care antibiotic resistance models. Items in bolded font represent changes to the base-case assumptions and conditions.

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Assumptions</th>
<th>Model Conditions</th>
<th>Description and Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens3</td>
<td><strong>HA</strong>: Collected &gt;96 hours after admission &lt;br&gt;<strong>CA</strong>: Collected ≤96 hours of admission &lt;br&gt;Duplicate: Identical isolate collected from the same patient ≤ 14 days</td>
<td>Pre-period: 84 months (Oct 2002- Sept 2009) &lt;br&gt;Post-period: 84 months (Oct 2009- Sept 2016) &lt;br&gt;Covariates: Season</td>
<td>• Altered base-case definition for “HA” and “CA” isolates. &lt;br&gt;• The 48-hour cut-off period is somewhat arbitrary and potentially over-estimate “HA” rates (^{130,151}) &lt;br&gt;• “HA” and “CA” cut-off period extended from 48 hours to 96 hours</td>
</tr>
<tr>
<td>Sens4</td>
<td><strong>HA</strong>: Collected &gt;48 hours after admission &lt;br&gt;<strong>CA</strong>: Collected ≤48 hours of admission &lt;br&gt;Duplicate: Identical isolate collected from the same patient ≤ 14 days</td>
<td>Pre-period: 84 months (Oct 2002- Sept 2009) &lt;br&gt;Post-period: 84 months (Oct 2009- Sept 2016) &lt;br&gt;Covariates: Season, mean LOS, positive culture rate</td>
<td>• Two additional predictor variables added to the base-case model: (a) mean monthly length of stay (mean LOS), and (b) monthly positive culture rate &lt;br&gt;• Both variables represented important potential confounders as changes in the post-intervention period may have biased the base-case findings</td>
</tr>
<tr>
<td>Sens5</td>
<td><strong>HA</strong>: Collected &gt;48 hours after admission &lt;br&gt;<strong>CA</strong>: Collected ≤48 hours of admission &lt;br&gt;Duplicate: Identical isolate collected from the same patient ≤ 14 days</td>
<td>Pre-period: 23 months (Nov 2007- Sept 2009) &lt;br&gt;Post-period: 84 months (Oct 2009- Sept 2016) &lt;br&gt;Covariates: Season</td>
<td>• Base-case model used symmetrical 84-month pre- and post-intervention periods; however, use an 84-month base-case pre-intervention period was somewhat arbitrary, &lt;br&gt;• Pre-intervention period abbreviated to 23-months to minimize potential bias related to implementation of the SHSC Hand Hygiene campaign in November 2007</td>
</tr>
</tbody>
</table>

HA, hospital-acquired; CA, community-acquired; Sens3, sensitivity model #3; Sens4, sensitivity model #4; Sens5, sensitivity model #5
4.5 Results

4.5.1 Descriptive Statistics – Base Case

Over the 168-month (14-year) base-case study period, 54,602 unique bacterial isolates were identified ($n_{HA-isolates} = 28,444$, $n_{CA-isolates} = 26,158$). These isolates were collected from 34,124 inpatients (mean age = 67 years, 45% male). The majority of isolates were gram negative bacilli (GNB; $n_{GNB} = 41,678$, 76%). The majority of GNB isolates were Enterobacteriaceae ($n_{Enterobacteriaceae} = 34,686$, 83%), and over 50% of the Enterobacteriaceae were E. coli ($n_{E.coli} = 19,200$). The majority of isolates were grown from urinary cultures ($n_{urine} = 27,779$, 51%), the remaining were isolated from blood ($n_{blood} = 7,492$, 14%), respiratory cultures ($n_{respiratory} = 7,661$, 14%), and other sites ($n_{other} = 11,673$, 21%). Base-case standardized isolate counts and other descriptive statistics are provided in Table 4-2. Post-intervention period isolate counts and PD counts were higher than pre-intervention period counts. Post-intervention period mean LOS was lower than pre-intervention period mean LOS, but inferential tests were not applied to the descriptive data set to establish the presence or absence of statistically significant differences.

Approximately 75% of isolates exhibited resistance to at least one therapeutically active antibiotic agent ($n_{ARO} = 41,002$) with 31% classified as multidrug resistant ($n_{MDRO} = 17,072$). Standardized counts ($N^*$), mean monthly counts ($\mu^*$), unadjusted RRR, and unadjusted ARR for HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO are summarized in Table 4-3. Unadjusted RRR for HA-ARO, HA-MDRO, CA-ARO, and CA-MDRO were 9% reduction/post-period, 14% reduction/post-period, -46% reduction/post-period, and -71% reduction/post-period, Unadjusted ARR were 10 HA-ARO isolates/10,000 PD, 7 HA-MDRO isolates/10 000 PD, -31 CA-ARO isolates/10 000 PD, and -17 CA-MDRO isolates/10 000 PD.

A visual representation of HA-ARO and CA-ARO tends over time (n/10,000 PD/month) is provided in Figure 4-1. Figure 4-2 provides a visual representation of HA-MDRO and CA-MDRO trends over time (n/10,000 PD/month).
Table 4-2. Base-case descriptive data for clinical isolates, patient days, and mean length of stay (LOS) at the acute care facility.

Standardized isolate counts (N*), standardized mean monthly isolate rates (μ*), patient days (PD), and mean length of stay (LOS) for the complete study period, the pre-intervention period, and the post-intervention period. Counts and mean monthly counts are standardized by 10 000 PD. Pre- to post-intervention unadjusted relative rate reductions (RRR) are reported as percentages (%). Pre- to post-intervention unadjusted absolute rate reductions (ARR) are reported as standardized mean rates (Δμ* = rate/10 000 PD).

<table>
<thead>
<tr>
<th></th>
<th>Complete Study Period</th>
<th>Pre-Intervention Period</th>
<th>Post-Intervention Period</th>
<th>Unadjusted RRR</th>
<th>Unadjusted ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*</td>
<td>42440</td>
<td>19928</td>
<td>22512</td>
<td></td>
<td></td>
</tr>
<tr>
<td>μ*</td>
<td>253</td>
<td>237</td>
<td>268</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>32354</td>
<td>15001</td>
<td>17352</td>
<td>-16%</td>
<td>-28</td>
</tr>
<tr>
<td>E. coli</td>
<td>26864</td>
<td>12110</td>
<td>14754</td>
<td>-22%</td>
<td>-31</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>14862</td>
<td>6624</td>
<td>8237</td>
<td>-24%</td>
<td>-19</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>5285</td>
<td>2332</td>
<td>2953</td>
<td>-27%</td>
<td>-7</td>
</tr>
<tr>
<td>Other spp. (^1)</td>
<td>1627</td>
<td>739</td>
<td>888</td>
<td>-20%</td>
<td>-2</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>5090</td>
<td>2414</td>
<td>2675</td>
<td>-11%</td>
<td>-3</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>5036</td>
<td>2622</td>
<td>2414</td>
<td>8%</td>
<td>2</td>
</tr>
<tr>
<td>Gram Positive</td>
<td>453</td>
<td>269</td>
<td>184</td>
<td>32%</td>
<td>1</td>
</tr>
<tr>
<td>S. aureus</td>
<td>10086</td>
<td>4927</td>
<td>5159</td>
<td>-5%</td>
<td>-3</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>8005</td>
<td>4106</td>
<td>3900</td>
<td>5%</td>
<td>2</td>
</tr>
<tr>
<td>Patient Days</td>
<td>2081</td>
<td>821</td>
<td>1260</td>
<td>-53%</td>
<td>-5</td>
</tr>
<tr>
<td>Mean LOS (days)</td>
<td></td>
<td>7.5 days</td>
<td>8.5 days</td>
<td>6.4 days</td>
<td>75%</td>
</tr>
</tbody>
</table>

* Standardized by 10 000 PD

\(^1\)Citrobacter spp., Enterobacter spp., M. morganii, Providencia spp., Serratia spp.

Values in red font suggest increases; values in green font suggest decreases.
Table 4-3. Base-case descriptive data for hospital-acquired (HA-) and community-acquired (CA-) clinical isolates, antibiotic-resistant organisms (ARO), and multidrug-resistant organisms (MDRO) at the acute care facility.

Standardized counts (N*) and standardized mean monthly incidence rates (μ*) for the complete study period, the pre-intervention period, and the post-intervention period. Counts and mean monthly incidence rates are standardized by 10,000 PD. Pre- to post-intervention unadjusted relative rate reductions (RRR) are reported as percentages (%). Pre- to post-intervention unadjusted absolute rate reductions (ARR) are reported as standardized mean rates (Δμ* = rate/10,000PD).

<table>
<thead>
<tr>
<th></th>
<th>Complete Study Period</th>
<th>Pre-Intervention Period</th>
<th>Post-Intervention Period</th>
<th>Unadjusted RRR</th>
<th>Unadjusted ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*</td>
<td>42440</td>
<td>19928</td>
<td>22512</td>
<td>-13%</td>
<td>-31</td>
</tr>
<tr>
<td>HA-ARO</td>
<td>17352</td>
<td>9078</td>
<td>8274</td>
<td>9%</td>
<td>10</td>
</tr>
<tr>
<td>HA-MDRO</td>
<td>7800</td>
<td>4208</td>
<td>3591</td>
<td>14%</td>
<td>7</td>
</tr>
<tr>
<td>CA-ARO</td>
<td>13998</td>
<td>5709</td>
<td>8289</td>
<td>-46%</td>
<td>-31</td>
</tr>
<tr>
<td>CA-MDRO</td>
<td>5465</td>
<td>2039</td>
<td>3246</td>
<td>-71%</td>
<td>-17</td>
</tr>
</tbody>
</table>

* Standardized by 10,000 PD

Values in red font suggest increases; values in green font suggest decreases
Figure 4-1. Trends in hospital-acquired antibiotic-resistant organism (HA-ARO) and community-acquired antibiotic-resistant organism (CA-ARO).

Trends in HA-ARO (BLUE LINE) and CA-ARO (RED LINE) monthly incidence at Sunnybrook Health Sciences Centre (SHSC) across the 14-year base-case study period (84-month pre-intervention period; 84-month post-intervention period). Monthly incidence is shown as an aggregate count standardized by 10,000 patient days (# ARO/10,000 PD). The pivots in HA-ARO trend coinciding with implementation of the SHSC prospective audit-and-feedback antimicrobial stewardship program (PAF-ASP) (BLACK ARROW) suggest that PAF-ASP implementation was associated with an improvement in HA-ARO rate. CA-ARO continued on an upward trajectory post-PAF-ASP implementation, suggesting no PAF-ASP-associated improvement in CA-ARO rate.
**Figure 4-2. Trends in hospital-acquired multidrug resistant organism (HA-MDRO) and community-acquired multidrug resistant organism (CA-MRO).**

Trends in HA-MDRO (GREEN LINE) and CA-MDRO (ORANGE LINE) monthly incidence at Sunnybrook Health Sciences Centre (SHSC) across the 14-year base-case study period (84-month pre-intervention period; 84-month post-intervention period). Monthly incidence is shown as an aggregate count standardized by 10,000 patient days (# MDRO/10,000 PD). The pivots in HA-MDRO trend coinciding with implementation of the SHSC prospective audit-and-feedback antimicrobial stewardship program (PAF-ASP) (BLACK ARROW) suggest that PAF-ASP implementation was associated with an improvement in HA-MDRO rate. The CA-MDRO continued on an upward trajectory post-PAF-ASP implementation, suggesting no PAF-ASP-associated improvement in CA-MDRO rate.
4.5.2 Primary Outcome: Hospital-Acquired Antibiotic Resistant Organisms – Base-Case and Sensitivity Analyses Results

Table 4-4 summarizes the base-case and sensitivity model findings for HA-ARO. Statistically significant reductions in post-intervention period HA-ARO incidence were detected for the base-case and all eligible sensitivity models. The base-case model found HA-ARO incidence decreased 9.3% in the post-intervention period (Post-Period RRR\textsubscript{HA-ARO,base} = 9.3% reduction/post-period, p=0.0278). Sensitivity models found post-period reductions ranging from 9.5% reduction/post-period (Sens4, p<0.0001) to 16.2% reduction/post-period (Sens5, p=0.0097). All Post-Period RRR\textsubscript{HA-ARO} were deemed clinically significant as they approximated or exceeded 10% in magnitude.

Trend model β6 parameters were statistically significant for the base-case and all sensitivity models run. Accordingly, pre- and post-intervention period trends (Trend\textsubscript{pre} and Trend\textsubscript{post}) were characterized. For all scenarios, HA-ARO trends were found to be increasing prior to PAF-ASP implementation (Trend\textsubscript{HA-ARO,pre} range = +0.1% incidence/month to +1.2% incidence/month; p-value range = <0.0001 to 0.0507) and decreasing post-PAF-ASP implementation (Trend\textsubscript{HA-ARO,post} range = -0.02% incidence/month to -0.2% incidence/month; p-value <0.0001 for all scenarios).

Since only 1.5% of isolates were removed from the base-case data set when the de-duplication window was extended from 14 days to 30 days (i.e. 828 isolates eliminated), RRR Poisson Regression or Trend Poisson Regression models for HA-ARO were not re-run for the Sens1 dataset.
Table 4-4. Inferential statistics for hospital-acquired antibiotic-resistant organisms (HA-ARO) in the acute care facility.

Data presented includes relative reduction in post-intervention period incidence (Post-Period RRR\(_{HA-ARO}\)), pre-intervention period trend (Trend\(_{HA-ARO,pre}\)) and post-intervention period trend (Trend\(_{HA-ARO,post}\)).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period RRR(_{HA-ARO})</th>
<th>Trend(_{HA-ARO,pre})</th>
<th>Trend(_{HA-ARO,post})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>Base-Case</td>
<td>9.3%</td>
<td>0.0278</td>
<td>+0.5%</td>
</tr>
<tr>
<td>Sens1</td>
<td>N/A</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Sens2</td>
<td>10.1%</td>
<td>0.0282</td>
<td>+0.5%</td>
</tr>
<tr>
<td>Sens3</td>
<td>10.6%</td>
<td>0.0377</td>
<td>+0.5%</td>
</tr>
<tr>
<td>Sens4</td>
<td>9.5%</td>
<td>&lt;0.0001</td>
<td>+0.1%</td>
</tr>
<tr>
<td>Sens5</td>
<td>16.2%</td>
<td>0.0097</td>
<td>+1.2%</td>
</tr>
</tbody>
</table>

Values in black font indicate no change; values in red font indicate increases; values in green font indicate decreases.
4.5.3 Secondary Outcome: Hospital-Acquired Multidrug-Resistant Organisms – Base-Case and Sensitivity Analyses Results

Table 4-5 summarizes the RRR and the Trend findings for HA-MDRO base-case and sensitivity models. Non-statistically significant reductions in post-intervention period HA-MDRO incidence were detected for the base-case, Sens 2, and Sens3 models (Post-Period RRR_{HA-MDRO} range = 12.6% to 14.0% reduction/post-period; p-value range = 0.1292 to 0.1319). No change was detected for the Sens4 model (Post-Period RRR_{HA-MDRO,sens4} = -1.4% reduction/post-period, p= 0.8877); however, a statistically significant 25.3% reduction in post-period HA-MDRO incidence was found for the Sens5 model (Post-Period RRR_{HA-MDRO,sens5} = 25.3% reduction/post-period, p= 0.0089). With the exception of the Sens4 model results, all Post-Period RRR_{HA-MDRO} exceeded 10% in magnitude and were therefore deemed clinically significant.

Trend model β6 parameters were statistically significant for the base-case and all sensitivity models run. Accordingly, pre- and post-intervention period trends (Trend_{pre} and Trend_{post}) were characterized. For all scenarios, HA-MDRO trends were found to be increasing prior to PAF-ASP implementation (Trend_{HA-MDRO,pre} range = +1.0% incidence/month to +1.4% incidence/month; p-values <0.0001 for all scenarios) and decreasing post-PAF-ASP implementation (Trend_{HA-MDRO,post} range = -0.3% incidence/month to -0.4% incidence/month; p-values <0.0001 for all scenarios).

Since only 1.5% of isolates were removed from the base-case data set when the de-duplication window was extended from 14 days to 30 days (i.e. 828 isolates eliminated), RRR Poisson Regression or Trend Poisson Regression models for HA-MDRO were not re-run for the Sens1 dataset.
Table 4-5. Inferential statistics for hospital-acquired multidrug-resistant organisms (HA-MDRO) in the acute care facility.
Data presented includes relative reduction in post-intervention period incidence (Post-Period RRR\textsubscript{HA-MDRO}), pre-intervention period trend (Trend\textsubscript{HA-MDRO,pre}) and post-intervention period trend (Trend\textsubscript{HA-MDRO,post}).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period RRR\textsubscript{HA-MDRO}</th>
<th>Trend\textsubscript{HA-MDRO,pre}</th>
<th>Trend\textsubscript{HA-MDRO,post}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>Base-Case</td>
<td>12.6%</td>
<td>0.1319</td>
<td>+1.0%</td>
</tr>
<tr>
<td>Sens1</td>
<td>N/A</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Sens2</td>
<td>13.4%</td>
<td>0.1293</td>
<td>+1.0%</td>
</tr>
<tr>
<td>Sens3</td>
<td>14.0%</td>
<td>0.1292</td>
<td>+1.0%</td>
</tr>
<tr>
<td>Sens4</td>
<td>-1.4%</td>
<td>0.8877</td>
<td>+1.0%</td>
</tr>
<tr>
<td>Sens5</td>
<td>25.3%</td>
<td>0.0089</td>
<td>+1.4%</td>
</tr>
</tbody>
</table>

Values in black font indicate no clinically or statistically significant change; values in red font indicates statistically significant increases; values in green font indicate statistically significant decreases; values in blue font represent clinically significant decreases with $p > 0.05$. 

58
4.5.4 Control Outcomes – Base-Case and Sensitivity Analyses Results

4.5.4.1 Community-Acquired Antibiotic-Resistant Organisms

Table 4-6 summarizes the RRR and the Trend findings for CA-ARO base-case and sensitivity models. Clinically and statistically significant increases in post-intervention period CA-ARO incidence were detected for the base-case, Sens 2, Sens3, and Sens4 models (Post-Period RRR_{CA-ARO} range = -25.6% reduction/post-period to -40.4% reduction/post-period; p<0.0001 for all scenarios). No clinically or statistically significant change was found with the Sens5 model (Post-Period RRR_{CA-ARO,sens5} = 3.3% reduction/post-period, p=0.7573).

Trend model β6 parameters were statistically significant for the base-case, Sens2, Sens3 and Sens5 models. Accordingly, pre- and post-intervention period trends (Trend_{pre} and Trend_{post}) were characterized. For all scenarios, CA-ARO trends were found to be increasing both before and after PAF-ASP implementation (Trend_{CA-ARO,pre} range = +0.4% incidence/month to +1.3% incidence/month, p-values <0.001 for all conditions; Trend_{CA-ARO,post} = +0.5% incidence/month and p<0.0001 for all conditions). The Trend model β6 parameters was not statistically significant for the Sens4 model, and a consistent trend of +0.4% incidence/month was found (Trend_{CA-ARO,pre} = Trend_{CA-ARO,post} = 0.4% incidence/month, p<0.0001).

Since only 1.5% of isolates were removed from the base-case data set when the de-duplication window was extended from 14 days to 30 days (i.e. 828 isolates eliminated), RRR Poisson Regression or Trend Poisson Regression models for CA-ARO were not re-run for the Sens1 dataset.
Table 4-6. Inferential statistics for community-acquired antibiotic-resistant organisms (CA-ARO) in the acute care facility.
Data presented includes relative reduction in post-intervention period incidence (Post-Period RRR\textsubscript{CA-ARO}), pre-intervention period trend (Trend\textsubscript{CA-ARO,pre}) and post-intervention period trend (Trend\textsubscript{CA-ARO,post}).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period RRR\textsubscript{CA-ARO}</th>
<th>Trend\textsubscript{CA-ARO,pre}</th>
<th>Trend\textsubscript{CA-ARO,post}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>Base-Case</td>
<td>-40.4%</td>
<td>&lt;0.0001</td>
<td>+0.4%</td>
</tr>
<tr>
<td>Sens1</td>
<td>N/A</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Sens2</td>
<td>-37.7%</td>
<td>&lt;0.0001</td>
<td>+0.4%</td>
</tr>
<tr>
<td>Sens3</td>
<td>-34.9%</td>
<td>&lt;0.0001</td>
<td>+0.4%</td>
</tr>
<tr>
<td>Sens4</td>
<td>-25.6%</td>
<td>&lt;0.0001</td>
<td>+0.4%</td>
</tr>
<tr>
<td>Sens5</td>
<td>3.3%</td>
<td>0.7573</td>
<td>+1.3%</td>
</tr>
</tbody>
</table>

Values in black font indicate no change; values in red font indicate increases; values in green font indicate decreases
### 4.5.4.2 Community-Acquired Multidrug-Resistant Organisms

Table 4-7 summarizes the RRR and the Trend findings for CA-MDRO base-case and sensitivity models. Clinically and statistically significant increases in post-intervention period CA-MDRO incidence were detected for the base-case and Sens5 models (Post-Period RRR\textsubscript{CA-MDRO} range = -41.4\% reduction/post-period to -68.7\% reduction/post-period; p<0.0001 for all scenarios).

Trend model β6 parameters were statistically significant for the base-case and all eligible sensitivity models. Accordingly, pre- and post-intervention period trends (Trend\textsubscript{pre} and Trend\textsubscript{post}) were characterized. For all scenarios, CA-MDRO trends were found to be increasing both before and after PAF-ASP implementation (Trend\textsubscript{CA-MDRO, pre} range = +0.8\% incidence/month to +2.3\% incidence/month, p-values <0.001 for all conditions; Trend\textsubscript{CA-MDRO, post} = +0.4\% incidence/month to +0.5\% incidence/month, and p<0.0001 for all conditions).

Only 1.5\% of base-case isolates were eliminated when the de-duplication window was extended from 14 days to 30 days (i.e. 828 isolates eliminated). Therefore, the RRR Poisson Regression or Trend Poisson Regression models for CA-ARO were not re-run for the Sens1 dataset. RRR Poisson Regression Models for the Sens2, Sens3, and Sens4 scenarios did not converge. Lack of convergence is an indication that the data did not fit the model well. Consequently, Post-Period RRR\textsubscript{CA-MDRO, sens2}, Post-Period RRR\textsubscript{CA-MDRO, sens3}, and Post-Period RRR\textsubscript{CA-MDRO, sens3} could not be determined.
Table 4-7. Inferential statistics for community-acquired multidrug-resistant organisms (CA-MDRO) in the acute care facility.

Data presented includes relative reduction in post-intervention period incidence (Post-Period $\text{RRR}_{\text{CA-MDRO}}$), pre-intervention period trend ($\text{Trend}_{\text{CA-MDRO,pre}}$) and post-intervention period trend ($\text{Trend}_{\text{CA-MDRO,post}}$).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period $\text{RRR}_{\text{CA-MDRO}}$</th>
<th>$\text{Trend}_{\text{CA-MDRO,pre}}$</th>
<th>$\text{Trend}_{\text{CA-MDRO,post}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>Base-Case</td>
<td>-68.7%</td>
<td>&lt;0.0001</td>
<td>+0.9%</td>
</tr>
<tr>
<td>Sens1</td>
<td>N/A</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Sens2</td>
<td>Model did not converge</td>
<td>+0.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sens3</td>
<td>Model did not converge</td>
<td>+0.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sens4</td>
<td>Model did not converge</td>
<td>+0.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sens5</td>
<td>-41.4%</td>
<td>&lt;0.0001</td>
<td>+2.3%</td>
</tr>
</tbody>
</table>

Values in black font indicate no change; values in red font indicate increases; values in green font indicate decreases.
4.6 Discussion

This study used ITS Poisson regression models to evaluate the impact of the SHSC PAF-ASP on institutional rates of AMR in the 7-year (84-month) period following program implementation. Clinically and statistically significant reductions in the primary outcome (post-intervention period incidence of HA-ARO) were detected for all base-case and sensitivity analyses (Post-Period RRR_{HA-ARO} range = 9.3% to 16.2% reduction/post-period; p-value range = <0.0001 to 0.0377). Results from the Trend models supported these findings, and statistically significant “pivots” in HA-ARO trend associated with PAF-ASP implementation were found for all base-case and sensitivity scenarios. Monthly HA-ARO trends were positive in all pre-intervention period models (Trend_{HA-ARO,pre} range = +0.1% to +1.2% incidence/month; p-value range = <0.0001 to 0.0507), suggesting the monthly HA-ARO burden was increasing in the absence of a dedicated PAF-ASP. Monthly HA-ARO trends were negative in all post-intervention period models (Trend_{HA-ARO,post} range = -0.02% to -0.2% incidence/month; p-value <0.0001 for all scenarios), suggesting the monthly HA-ARO burden started to decrease with the PAF-ASP in place.

In contrast, clinically and statistically significant increases in CA-ARO incidence in the range of 25.6% to 40.4% were detected in the majority models (i.e. base-case, Sens2, Sens3, Sens4) (Post-Period RRR_{CA-ARO} range = -25.6% reduction/post-period to -40.4% reduction/post-period; p<0.0001 for all scenarios). CA-ARO is the control outcome for HA-ARO. Trend analyses demonstrated increasing rates of CA-ARO in both the pre- and post-intervention periods, suggesting the monthly CA-ARO burden continued to increase in the absence of a dedicated ASP (Trend_{CA-ARO,post} = +0.4% to 0.5% incidence/month, p<0.0001 for each condition).

Although the Sens5 analysis did not detect a statistically significant increase in CA-ARO post-period incidence (Post-Period RRR_{CA-ARO,sens5} = 3.3% reduction/post-period, p=0.7573), the largest reduction in HA-ARO was found in the corresponding primary outcome analysis (Post-Period RRR_{HA-ARO,sens5} = 16.2% reduction/post-period, p=0.0097). Therefore, these findings still suggest that PAF-ASP presence produced greater improvement in relative AMR.

The presence of PAF-ASP associated improvements in HA-ARO incidence and trend, paralleled by the lack of improvement (or worsening) in CA-ARO incidence and trend, suggest that implementation of the SHSC PAF-ASP was associated with clinically and statistically significant
reductions in the institutional burden of AMR. An estimate of the absolute impact of this program on the clinical burden of AMR in the 2017-2018 fiscal year can be obtained by multiplying the unadjusted ARR_{HA-ARO} rate (10 HA-ARO/10 000 PD) by the 2017-2018 bed occupancy rate (219 817 PD/fiscal year). This estimate suggests that the PAF-ASP prevented the emergence of 220 HA-ARO last year.

Findings for the secondary outcome and corresponding control, HA-MDRO and CA-MDRO, were similar to HA-ARO and CA-ARO findings. A clinically significant reduction in HA-MDRO burden was detected in the base-case model (Post-Period \( \text{RRR}_{HA-MDRO,\text{base}} = 12.6\% \) reduction/post-period, \( p=0.1319 \)), whereas a clinically and statistically significant increase was detected in the base-case model for CA-MDRO (Post-Period \( \text{RRR}_{CA-MDRO,\text{base}} = -68.7\% \) reduction/post-period, \( p<0.0001 \)). Clinically significant HA-MDRO reductions were found for most HA-MDRO sensitivity models, while increases in resistance were found for all convergent CA-MDRO sensitivity analyses. Statistically significant PAF-ASP-associated pivots in HA-MDRO trends were found for all scenarios (Trend\( _{HA-MDRO,\text{pre}} \) range = +0.1% to +1.4% incidence/month, \( p\)-values <0.0001 for all scenarios; Trend\( _{HA-MDRO,\text{post}} \) range = -0.3% to -0.4% incidence/month, \( p\)-values <0.0001 for all scenarios), whereas CA-MDRO trend continued on an upward trajectory throughout the post-intervention period in all models (Trend\( _{CA-MDRO,\text{post}} \) = +0.4% to +0.5% incidence/month, \( p<0.0001 \) for all conditions).

The HA-MDRO and CA-MDRO findings suggest that exposure to a dedicated PAF-ASP results in greater improvement in relative AMR, but the results for these outcomes were not as robust as the ARO findings. For example, the magnitude of most Post-Period \( \text{RRR}_{HA-ARO} \) met the clinical significance cut-off, but only one model detected a statistically significant effect (Post-Period \( \text{RRR}_{HA-MDRO,\text{sens5}} = 25.3\% \) reduction/post-period, \( p=0.0089 \)). Given that HA-MDRO was the only group with an unadjusted ARR < |10| (i.e. unadjusted ARR\( _{HA-ARO} = 7 \) HA-ARO/10 000 PD, as shown in Table 3), the lack of significance is likely due to inadequate power. Other issues include the lack of an HA-MDRO effect in the Sens4 RRR model (Post-Period \( \text{RRR}_{HA-MDRO,\text{sens4}} = -1.4\% \) reduction/post-period), and the lack of convergence for the CA-MDRO Sens2, Sens 3 and Sens4 RRR analyses. Lack of convergence indicates that the data did not fit the model well. This is usually because there is not enough data (i.e. too few observations) for the computer to solve the equation. The lack of convergence in the CA-MDRO Sens4 model makes
interpretation of the Post-Period RRR_{HA-MDRO,Sens4} findings difficult. Although these sensitivity model issues reduce the strength of the MDRO findings, the results from the base-case RRR, Sens5 RRR, and all the Trend analyses remain positive, and support the research hypothesis that PAF-ASP presence was associated with clinically significant improvements in MDRO burden. An estimate of the absolute impact of this program on the clinical burden of AMR in the 2017-2018 fiscal year can be obtained by multiplying the unadjusted ARRHA-MDRO rate (7 HA-MDRO/10,000 PD) by the 2017-2018 bed occupancy rate (219,817 PD/fiscal year)^{10}, and this estimate suggests that the PAF-ASP prevented the emergence of 154 HA-MDRO last year.

Reducing AMR is a major incentive for ASPs. To the best of this writer’s knowledge, this is the first study to evaluate the effectiveness of an acute care ASP for reducing the aggregate burden of institutional AMR using robust methodology. There have been numerous calls for this data\(^4,^{8,72,73}\). However, very few studies have sought to analyze this matter, and limitations in scope, scale, and methodological rigor limit the degree to which the small body of existing evidence can be applied to practice\(^4,^8\). This study utilized a robust controlled ITS design, a practical composite endpoint, and an extended study period in an effort to overcome many of these limitations.

The ITS is a robust quasi-experimental design endorsed by the Cochrane Effective Practice and Organisation of Care (EPOC) Group\(^81\). It is particularly well-suited for assessing the effects of population-level interventions over time, and, therefore, well-suited for the objective of this study. The ITS design minimizes threats to internal validity by incorporating a historic control group into the analysis (i.e. pre-intervention period) and requiring multiple observations be reported for both the pre- and post-intervention period groups\(^{142}\). To further enhance validity, this study also compared changes in the primary and secondary outcomes (HA-ARO, HA-MDRO) to concurrent external controls (CA-ARO, CA-MDRO), and is the first study to compare nosocomial and community AMR rates in this way.

The novel metrics developed to characterize AMR are another strength of this study. No standard metric to quantify the collective burden of AMR burden exists\(^{72,73}\); therefore, composite outcome metrics were designed to capture a wide-variety of clinically important pathogens and resistance profiles (i.e. institutional ARO and MDRO incidence-densities; # ARO/10,000 PD and
We posit that these metrics reflect the overall institutional burden of AMR and are practical and easy to understand. The limitations of these metrics include the following: (a) the AMR burden captured in this study likely underestimates the true incidence of emergently resistant bacteria and overestimate the rates of ARO and MDRO infections, (b) the HA- and CA-criteria have not been validated for determining the time of organism acquisition, and (c) the HA- and CA-criteria do not account for recent healthcare exposure or prolonged ARO or MDRO carriage.

However, the use of composite AMR endpoints spanning many species and resistance profiles helped guard against statistical power and model fitting issues for the primary outcome (i.e. allowed us to build time series with over 100 monthly time points and obtain incidence rates of approximately 100 HA-ARO/10,000 PD per time point\textsuperscript{152}). In turn, this allowed changes in both the relative incidence and trends of resistant isolates to be characterized using comprehensive multivariable Poisson regression models that adjusted for several potential confounders (i.e. hospital-occupancy, autocorrelation, seasonal variability in ARO and MDRO incidence, LOS, culture requisition rate, HH campaign). The flexibility of these models was another strength of this study, and altering base-case model assumptions (i.e. definitions for “HA”, “CA”, and “duplicate” isolates) and conditions (i.e. pre-intervention period length, covariates) in sensitivity analyses allowed us to minimize the risk of bias and validate primary outcome findings.

An obvious limitation of this study is its quasi-experimental design. Although the ITS is a robust longitudinal design, randomized controlled trials remain the gold standard for establishing causality. Like all the retrospective designs, there remains some risk of unrecognized or uncharacterizable confounders biasing the results. For this reason, the results of this study do not definitively establish a cause-and-effect relationship between SHSC PAF-ASP implementation and the observed reductions HA-ARO and HA-MDRO burden. However, the relatively consistent improvements in HA-AMR, coupled with the consistent worsening in CA-AMR, strengthens the likelihood of a causal relationship, and prospective randomized controlled trials of this scale are unlikely to be conducted given the complex nature of ASP interventions.

Furthermore, a significant amount of effort was put forth to control for potential confounders that were identified, such as hospital bed-occupancy, seasonal variations, patient length of stay, culture requisition rate, and outcome definition assumptions. To this writer’s knowledge, this is
the first study to consider many of these factors and incorporate them into the analyses. It is possible that changes in ARO screening policies, compliance with contact precautions, or environmental cleaning practices occurred in the post-intervention period and positively biased study results. However, reliable data or implementation dates to characterize any such changes were not available to include in the base-case or sensitivity models.

Additional limitations include the proportional nature of the Poisson regression output, the specificity of the effects, and the generalizability of the results. Although Poisson regression is the most appropriate technique for assessing changes in count-based data, effect estimates are calculated in proportional terms (i.e. effects are calculated as relative percentages as opposed to absolute changes). Consequently, unadjusted ARRs must be utilized if an “absolute” estimate of the effect is desired. Use of the unadjusted ARR likely provides a reasonable approximation of the effect, but it certainly compromises the precision. The inability to differentiate between the specific effect of the PAF-intervention and the effect of the supportive or “passive” elements of the ASP (i.e. medical education, launch of the online SHSC Handbook App, etc.) is also a limitation. However, proactive strategies (such as PAF) are known to be more effective than passive strategies for producing behavior changes, and no major change in the passive elements coincided with PAF-ASP implementation. For these reasons, it is reasonable to assume that PAF is driving the effects detected in this study. The generalizability of the results is another limitation this research. Few sites have a PAF intervention as comprehensive as SHSC, and the transferability of the findings to other ASP programming is therefore unclear. However, other hospitals could use the findings of this study to justify implementation of PAF-ASPs similar to the SHSC model or employ the robust methodology to characterize the impact of their existing ASP on institutional AMR.

The use of a composite endpoint was a strength in that it provided the necessary sensitivity to detect statistically significant differences in the primary endpoint; however, a limitation of this approach was that it did not provide any information regarding the impact of the PAF-ASP on specific ARO subgroups (i.e. genus and/or species-level changes) or specific bug-drug sensitivity profiles. Characterizing the macro-level effect (i.e. PAF-ASP impact on the collective, aggregate burden of AMR at SHSC) was the objective of this study, and given the positive findings of this study, investigating the impact on bacterial subgroups and specific sensitivity profiles within this
data set is a natural direction for future work. Cross-correlating trends in specific AMR profiles to trends in antibiotic use is another possibility, as SHSC inpatient antibiotic use data was also collected as part of this thesis project. Although some research of this nature has been conducted, additional studies could be used to validate existing findings and evaluate relationships that have gone unexamined to date.

4.7 Conclusion

Implementation of the SHSC PAF-ASP was associated with significant and sustained reductions in the burden of nosocomial AMR, as demonstrated by the 9.3% reduction in HA-ARO incidence and the 12.6% reduction in HA-MDRO incidence detected in the post-intervention period of the base-case analyses. The observed 40.4% rise in CA-ARO incidence and 68.7% rise in CA-MDRO incidence during the same period further strengthens the causal inference of PAF-ASP curbing development of AMR.
Chapter 5
Impact of the Sunnybrook Health Sciences Centre Acute Care Prospective Audit-and-Feedback Antimicrobial Stewardship Program on Antibiotic Consumption in the Acute Care Facility
5 Impact of the Sunnybrook Health Sciences Centre Acute Care Prospective Audit-and-Feedback Antimicrobial Stewardship Program on Rates of Antibiotic Consumption in the Acute Care Facility

5.1 Preface

The previous chapter described the impact of the Sunnybrook Health Sciences Centre (SHSC) prospective audit-and-feedback (PAF) antimicrobial stewardship program (ASP) on the burden of antimicrobial resistance (AMR) in the acute care facility by evaluating differences in the incidence and trend of hospital-acquired antibiotic-resistant organisms (HA-ARO) and hospital-acquired multidrug-resistant organisms (HA-MDRO) between the pre- and post-intervention periods.

This chapter describes the methods and findings of the study that was conducted to address the secondary objective of this thesis research: Evaluating the impact of the SHSC PAF-ASP on the institutional consumption of antibiotic drugs. The SHSC PAF-ASP audits the use of several broad-spectrum and second-line antibiotic agents for systemic use, which are referred to as “targeted” (TGD) agents. Differences in the incidence and trend of TGD antimicrobial use (AMU) in the years preceding the intervention and the years following the intervention were used to infer program impact. Changes in the incidence and trends of “non-targeted” (NTGD), and “total” (TTL) AMU were assessed as balancing outcomes.

5.2 Background

SHSC piloted a multidisciplinary PAF-ASP in Level III intensive care units (ICU) on October 1st, 2009 (i.e. “ICU Pilot”). Based on the success of this pilot, the PAF-ASP was rolled out to ward patients using a stepped-wedge design on October 1st, 2010 (i.e. “Ward Roll-Out”). Currently, the SHSC PAF-ASP provides automatic consultations for three intensive-care and 11 non-intensive-care medical and surgical services by reviewing orders for TGD agents on days 3, 7, and 14 of therapy and making suggestions to optimize therapy.
As described in Thesis Chapter 4, the SHSC PAF-ASP was associated with sustained institutional reductions in nosocomial AMR across the 7 years following implementation (Post-Period $\text{RRR}_{\text{HA-ARO,base}} = 9.3\%$ reduction/post-period, $p=0.023$; Post-Period $\text{RRR}_{\text{HA-MDRO,base}} = 12.3\%$ reduction/post-period, $p=0.132$). ASP-mediated reductions in inpatient AMU are thought to be driving this effect based on the well-known association between increased rates of AMR and increased rates of AMU\textsuperscript{69,70}. In this case, the proposed mechanism is that ASP-mediated reductions in AMU remove the selective pressure favouring the persistence of resistant pathogens, the removal of the selective pressure allows non-resistant isolates to grow and compete with AROs, and this gradually reduces the relative prevalence of AROs.

Research conducted in the early phases of the SHSC PAF-ASP\textsuperscript{9,77} found the program was associated with statistically significant improvements in inpatient AMU. A one-year follow-up assessment of the ICU Pilot found that PAF-ASP implementation was associated with a statistically significant 22\% reduction in TGD AMU (-22\% TGD agent days of therapy (DOT), $p<0.0001$)\textsuperscript{9}, and a one-year follow-up assessment of the Ward Roll-Out found PAF-ASP presence was associated with a 21\% decrease in TGD antibiotic consumption among qualifying patients (-21\% TGD agent DOT, $p=0.004$)\textsuperscript{77}. Annual evaluation has demonstrated a sustained reduction in TGD antibiotic consumption from baseline at SHSC. However, a cumulative follow-up spanning the time since implementation has not been completed to determine if the reductions in inpatient AMU detected in the early phases of the PAF-ASP have been maintained. Demonstrating persistent reduction in TGD agent consumption 7 years post-implementation would not only testify to the sustainability of the program on AMU outcomes, it would also validate the primary AMR findings of this thesis research (as described in Thesis Chapter 4) showing that institutional reductions in nosocomial AMR are paralleled by institutional reductions in AMU.

5.3 Objective and Hypothesis

This study sought to evaluate the impact of the PAF-ASP on the institutional consumption of AMU as measured by the change in incidence of TGD AMU use in the 7-year (84-month) period following program implementation. It was hypothesized that improvements in inpatient use of TGD agents would be detected as these antibiotics are audited as part of the PAF-ASP. NTGD
and TTL AMU were evaluated as balancing metrics. Improvements in NTGD AMU and TTL AMU incidence were not anticipated.

5.4 Methods

5.4.1 Study Design

Changes in inpatient antibiotic consumption in relation to SHSC PAF-ASP implementation were evaluated using retrospective interrupted time series (ITS) analyses. The ITS is a robust quasi-experimental design, and is the most appropriate design for evaluating the longitudinal effects of population-level interventions over time. Implementation of the SHSC PAF-ASP on October 1st, 2009 was the intervention for this study. Monthly incidence rates of TGD AMU in the post-intervention period (i.e. in the presence of the PAF-ASP) were compared to monthly incidence rates of TGD AMU in the pre-intervention period (i.e. in the absence of the PAF-ASP), such that the pre-intervention period served as a historic control. Relative reductions in the monthly incidence rates of TGD AMU from the pre- to post-intervention period (i.e. Post-Period Relative Rate Reduction, “Post-Period RRR”), and differences in the pre- and post-intervention period trends of monthly TGD AMU, were used to infer program impact. NTGD AMU and TTL AMU were assessed as balancing metrics.

The “base-case” model utilized pre- and post-intervention periods 84 months in duration (pre-intervention period: October 1, 2002 – September 30, 2009; post-intervention period: October 1, 2009 – September 30, 2016). The decision to use an 84-month pre-intervention period for the base-case model was somewhat arbitrary; an 84-month post-intervention period was available for the PAF-ASP at the time of study design, and an 84-months pre-intervention period was selected to achieve pre- and post-intervention periods of symmetrical durations. The base-case model pre-intervention period was altered to create a single sensitivity model. Details of this sensitivity model are provided in the Statistical Analyses Section 5.4.5.3.

5.4.2 Study Setting and Population

SHSC is a multi-site academic health centre affiliated with the University of Toronto and located in Toronto, Ontario, Canada. The Bayview Site is home to a 627-bed acute care tertiary referral teaching hospital and a 530-bed long term care facility (LTCF). The acute care facility provides
the full range of acute medical and surgical services with specialized care programs in critical care, musculoskeletal care, trauma, cardiology, oncology, brain science, and maternal and perinatal care. Antibiotic consumption for all adult patients admitted to the Bayview campus during the defined study period were included in these analyses (excluding mothers admitted to the Women and Babies program, as the PAF-ASP does not consult for these patients).

5.4.3 Outcomes

5.4.3.1 Primary Outcome

PAF-ASP associated changes in the monthly incidence rate of TGD AMU were assessed as the primary outcome (i.e. monthly TGD AMU incidence rate = number of TGD agent days of therapy (DOT) dispensed in study month X standardized by the number of patient days (PD) in study month X for the entire acute care facility). TGD antibiotics were defined as Anatomical Therapeutic Chemical (ATC) class J01 agents (Antibacterials for Systemic Use) audited by the antimicrobial stewardship team (meropenem, ertapenem, ceftriaxone, ceftazidime, piperacillin/tazobactam, intravenous vancomycin, moxifloxacin, levofloxacin, ciprofloxacin, amikacin, gentamicin, and tobramycin).

A PAF-ASP associated change in overall TGD agent consumption was assessed by comparing the mean monthly TGD AMU incidence rate in the pre-intervention period to the mean monthly TGD AMU incidence rate in the post-intervention period. Differences were reported as the relative reduction in TGD AMU incidence in the post-intervention period (i.e. Post-Period Relative Rate Reduction, “Post-Period RRR<sub>TGD</sub>”; reported as % incidence reduction/post-period). The presence of a PAF-ASP associated change in TGD AMU incidence rate trend was also assessed, and pre- and post-intervention trend estimates were determined to further characterize PAF-ASP impact (“Trend<sub>TGD,pre</sub>” and “Trend<sub>TGD,post</sub>”; reported as Δ% incidence/month).

5.4.3.2 Balancing Outcomes

PAF-ASP associated changes in the monthly incidence rate of NTGD AMU and TTL AMU were assessed as the balancing outcomes (i.e. monthly NTGD AMU incidence rate = number of NTGD DOT dispensed in study month X standardized by the number of patient days (PD) in study month X for the entire acute care facility; monthly TTL AMU incidence rate = TTL
number of TGD and NTGD DOT dispensed in study month X standardized by the number of patient days (PD) in study month X for the entire acute care facility). TTL antibiotics was defined as all J01 agents. NTGD antibiotics were defined as J01 agents not audited by the SHSC PAF-ASP\textsuperscript{154}.

PAF-ASP associated changes in overall NTGD agent consumption and TTL antibiotic consumption were assessed by comparing the mean monthly AMU incidence rates in the pre-intervention period to the mean monthly AMU incidence rates in the post-intervention period. Differences were reported as the relative reduction in AMU incidence in the post-intervention period (i.e. Post-Period Relative Rate Reduction, “Post-Period $\text{RRR}_{\text{NTGD}}$” and Post-Period $\text{RRR}_{\text{TTL}}$”; reported as % incidence reduction/post-period). The presence of a PAF-ASP associated changes in NTGD AMU and TTL AMU incidence rate trends were also assessed, and pre- and post-intervention trend estimates were determined to further characterize PAF-ASP impact (“Trend$_{\text{NTGD,pre}}$”, “Trend$_{\text{NTGD,post}}$”, “Trend$_{\text{TTL,pre}}$”, and “Trend$_{\text{TTL,post}}$”; reported as $\Delta$% incidence/month).

5.4.4 Data Collection and Preparation

5.4.4.1 Antimicrobial Use Data

DOT-level data for all J01 agents dispensed from the SHSC inpatient pharmacy to inpatients at the Bayview campus from October 1\textsuperscript{st}, 2002 to September 30\textsuperscript{th}, 2016 were retrospectively extracted from the SHSC Pharmacy Department Database into a Microsoft Excel (MS Excel) spreadsheet. The following parameters were extracted for each DOT: Patient identifier (Hospital File Number), patient location (inpatient ward unit), generic antibiotic name, route of administration, and dispense date (DD/MM/YYYY). DOTs dispensed to outpatient locations and the Women & Babies unit were removed from the data set. A pivot table was used to organize individual DOTs into aggregate monthly DOT counts for each antibiotic agent. Aggregate monthly DOT counts for each antibiotic agent were organized into monthly TGD, NTGD, and TTL DOT counts.
5.4.4.2 Administrative Data

PD data was retrospectively extracted from the SHSC Health Data Resources Database into a MS Excel database. Data was extracted in the form of aggregate PD counts for the entire acute care facility for each month in the study period.

5.4.5 Statistical Analyses

5.4.5.1 Descriptive Statistics

Standardized DOT counts \(N^* = \text{DOT}/10,000\ PD\) and standardized mean monthly rates \(\mu^* = \text{mean monthly DOT count}/10,000\ PD\) for TGD, NTGD, and TTL AMU were calculated for the complete study period, the pre-intervention period, and the post-intervention period for the base-case and sensitivity model. Total PD count and mean monthly PD count were also reported. Pre-to post-intervention unadjusted relative rate reductions for TGD, NTGD, and TTL AMU (i.e. unadjusted \(\text{RRR} = 100\% - \left[\frac{\mu^*_{\text{post}}}{\mu^*_{\text{pre}}}\right]\)) and unadjusted absolute rate reductions (i.e. unadjusted \(\text{ARR} = \mu^*_{\text{pre}} - \mu^*_{\text{post}}\)) were reported for descriptive purposes.

5.4.5.2 Inferential Statistics

The presence of PAF-ASP associated changes in TGD, NTGD, and TTL AMU were tested using Poisson regression generalized linear mixed models. The presence of PAF-ASP associated reductions in the overall consumption of TGD, NTGD, and TTL AMU (i.e. Post-period RRR) were assessed using the “Relative Rate Reduction (RRR) Regression Model” described below\(^{148}\). The presence of PAF-ASP associated changes in the trends of TGD, NTGD, and TTL AMU, and estimates of the pre- and post-intervention period monthly trends (i.e. Trend\(_{\text{pre}}\) and Trend\(_{\text{post}}\)), were assessed using the “Trend Regression Models” described below\(^{148}\).

Relative Rate Reduction (RRR) Regression Model

Differences in the relative rates of TGD, NTGD, and TTL AMU in the pre- and post-intervention periods were tested using Poisson regression models of the following form:

\[
\ln \left(\frac{\text{AMU/Bed Occupancy}}{\text{Bed Occupancy}}\right) = \beta_1(\text{Study Period}) + \beta_2(\text{Season})
\]
Monthly rate of AMU (“AMU” in DOT) standardized by institutional patient load (“Bed Occupancy” in PD) was the outcome variable. “Study Period” was included as fixed component and assessed as the main predictor (0 = pre-intervention period; 1 = post-intervention period). “Season” was included as a fixed component to adjust for the effect of season on AMU (1 = March, April, May; 2 = June, July, August; 3 = September, October, November; 4 = December, January, February). Study month was treated as a random component and modelled from a distribution with an autoregressive correlation structure. The autoregressive correlation structure assumed that time points closer together were more similar than time points further apart.

β1 and β2 represent the model-adjusted estimates for the effects of Study Period and Season on AMU. A statistically significant difference in pre- and post-intervention period rates of AMU were inferred when the p-value for the β1 parameter was equal or less than 0.05. The incidence rate ratio (IRR) for pre- to post-intervention period rates of AMU were obtained by exponentiating the β1 parameter (i.e. \( e^{β1} = \text{IRR} = \frac{\text{Rate}_{\text{post-period}}}{\text{Rate}_{\text{pre-period}}} \)). The Post-Period RRR was obtained by taking the difference between the IRR and 100% (i.e. Post-Period RRR = 100% – IRR) and reported as the percent reduction in post-period use (Post-Period RRR = % incidence reduction/period). Post-Period RRR greater than ± 10% were considered clinically significant. β2 parameters and the impact of season on antibiotic were not evaluated or further discussed as they are not directly relevant to this study’s objective.

**Trend Regression Models**

PAF-ASP associated changes in the trajectories, or “trends”, of TGD, NTGD, and TTL AMU were tested using interaction models of the following form:

\[
\ln \left( \frac{\text{AMU}}{\text{Bed Occupancy}} \right) = β3(\text{Study Period}) + β4(\text{Season}) + β5(\text{Study Month}) + β6(\text{Study Month} \ast \text{Study Period})
\]

This model had four fixed components: “Study Period”, “Season”, “Study Month”, and “Study Month \ast \text{Study Period}”. Study Month was included as a fixed component because the month-to-month change in AMU (i.e. “trend”) was being assessed. The interaction between Study Phase \ast \text{Study Month} was included as a fixed factor to specifically test for a difference between pre- and post-intervention period trends. A statistically significant difference in pre- and post-
intervention period trend was inferred when the p-value for the β6 parameter was equal or less than 0.05.

When the β6 parameter was statistically significant, pre- and post-intervention period trend estimates were characterized by running the follow-up model below:

Study Phase 0: \[ \text{Ln (AMU/Bed Occupancy)} = \beta_7(\text{Study Month}) \]

Study Phase 1: \[ \text{Ln (AMU/Bed Occupancy)} = \beta_8(\text{Study Month}) \]

A statistically significant pre-intervention period trend was inferred when the p-value for the β7 parameter was equal or less than 0.05. Pre-intervention period trend estimates (i.e. “Trend\textsubscript{pre}”) were obtained by exponentiating β7 parameter (i.e. \( \text{Trend}_{\text{pre}} = e^{\beta_7} \)) and were reported as the percent change in AMU each month (\( \text{Trend}_{\text{pre}} = \% \Delta \text{incidence/month} \)). Trend\textsubscript{pre} with p-values <0.05 were deemed statistically significant.

A statistically significant post-intervention period trend was inferred when the p-value for the β8 parameter was equal or less than 0.05. Post-intervention period trend estimates (i.e. “Trend\textsubscript{post}”) were obtained by exponentiating β8 parameter (i.e. \( \text{Trend}_{\text{post}} = e^{\beta_8} \)) and were reported as the percent change in AMU each month (\( \text{Trend}_{\text{post}} = \% \Delta \text{incidence/month} \)). Trend\textsubscript{post} with p-values <0.05 were deemed statistically significant.

5.4.5.3 Sensitivity Model

Given that the duration of the base-case pre-intervention period was somewhat arbitrary, and the majority of published studies evaluating the impact of ASPs on AMU employ pre-interventions periods between 12-24 months length, a sensitivity model with an abbreviated pre-intervention period was built. This sensitivity model had asymmetrical pre- and post-intervention periods of 23 months and 84 months in duration (pre-intervention period November 2007 – September 2009; post-intervention period October 2009 – September 2016). Use of this abbreviated pre-intervention period facilitated comparison between the finding of this study and the existing body of existing literature. A 23-month pre-intervention period with a starting month of November 2007 was selected to be consistent with the Sens5 sensitivity analyses performed on the AMR outcome dataset described in Thesis Chapter 4.4.5.2.5.
5.4.5.4 Model Fitting

It is suggested that time series data sets include at least 9 pre-intervention period time points and 9 post-intervention period time points to provide enough variability to fit the model\textsuperscript{152}. However, it is generally agreed that more time points are better. Another rule of thumb is that there should be at least 10 time points per fixed component (i.e. predictor variable) in a multi-variable model to avoid over-parameterization\textsuperscript{148}. In addition, it is encouraged that each time point have at least 100 observations to minimize the number of outliers and provide more stable estimates\textsuperscript{152}.

For this study, RRR models had 2 predictor variables and Trend models had a maximum of 4 predictor variables. The base-case and sensitivity data sets consisted of 168 time points and 107 time points, respectively. Therefore, even the model with the smallest number of time points (i.e. 107) and the largest number of predictors (i.e. 4) exceeded the 10:1 general rule of thumb (i.e. 10 time points: 1 predictor). Monthly rates of institutional TGD, NTGD, and TTL AMU were anticipated to exceed 100 DOT per month. For these reasons, adequate fitting of the models was anticipated.

5.5 Results

5.5.1 Descriptive Statistics

Base-case Model Descriptive Statistics

Data was extracted for 1 222 442 individual antibiotic DOTs across the 168-month base-case study period ($n_{\text{TGD,base}} = 607 \, 344 \, \text{DOT}; n_{\text{NTGD,base}} = 615 \, 098 \, \text{DOT}, n_{\text{TTL,base}} = 1 \, 222 \, 442 \, \text{DOT}$). A total of 2 150 353 PD were identified for the base-case data set, with a mean monthly PD rate of 12 799 PD/month. Base-case standardized DOT counts ($N^*$), standardized mean monthly counts ($\mu^*$), unadjusted RRRs, and unadjusted ARRs are provided in Table 5-1. Base-case unadjusted RRR and ARR suggested deceased rates of TGD, NTGD, and TTL use. Unadjusted RRR for TGD AMU, NTGD AMU, and TTL AMU were 10% reduction/post-period, 23% reductions/post-period, and 17% reduction/post-period. Unadjusted ARR were 293 TGD DOT/10,000 PD, 769 NTGD DOT/10,000 PD, and 1063 TTL DOT/10,000 PD. A visual representation of TGD, NTGD, and TTL AMU trends (DOT/10,000 PD/month) across the base-case study period is provided in Figure 5-1.
Sensitivity Model Descriptive Statistics

Data was extracted for 790,9651 individual antibiotic DOTs across the 107-month sensitivity model study period ($n_{TGD, sens} = 409,133$ DOT; $n_{NTGD, sens} = 381,803$ DOT; $n_{TTL, sens} = 790,9651$ DOT). A total of 1,448,254 PD were identified for the sensitivity data set, with a mean monthly PD rate of 13,535 PD/month. Sensitivity model standardized DOT counts ($N^*$), standardized mean monthly counts ($\mu^*$), unadjusted RRRs, and unadjusted ARRs are provided in Table 5-2. Sensitivity model unadjusted RRR and ARR suggested deceased rates of TGD, NTGD, and TTL use. Sensitivity model unadjusted RRRs were the same for all outcomes—a 21% reduction/post-period for TGD, NTGD, and TTL AMU. Unadjusted ARR were 732 TGD DOT/10,000 PD, 670 NTGD DOT/10,000 PD, and 1404 TTL DOT/10,000 PD.
Table 5-1. Descriptive data for the acute care antibiotic use base-case models.
Standardized days of therapy (DOT) counts (N*) and standardized mean monthly DOT counts (μ*) for “targeted” (TGD), “non-targeted” (NTGD), and “total” (TTL) antimicrobial use (AMU) for the complete study period, the pre-intervention period, and the post-intervention period. DOT counts are standardized by 10 000 PD. Pre- to post-intervention unadjusted relative rate reductions (RRR) are reported as percentages (%). Pre- to post-intervention unadjusted absolute rate reductions (ARR) are reported as standardized mean rates (Δμ* = rate/10 000PD).

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<th>Post-Intervention Period</th>
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<th>Unadjusted ARR</th>
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* Standardized by 10 000

Values in red font suggest increases; values in green font suggest decreases
Table 5-2. Descriptive data for the acute care antibiotic use sensitivity models.

Standardized days of therapy (DOT) counts (N*) and standardized mean monthly DOT counts (μ*) for “targeted” (TGD), “non-targeted” (NTGD), and “total” (TTL) antimicrobial use (AMU) for the complete study period, the pre-intervention period, and the post-intervention period. DOT counts are standardized by 10,000 PD. Pre- to post-intervention unadjusted relative rate reductions (RRR) are reported as percentages (%). Pre- to post-intervention unadjusted absolute rate reductions (ARR) are reported as standardized mean rates (Δμ* = rate/10,000PD).

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<td>226088</td>
<td>2692</td>
<td>21%</td>
</tr>
<tr>
<td>μ*&lt;sub&gt;pre&lt;/sub&gt;</td>
<td>3424</td>
<td>78747</td>
<td>226088</td>
<td>2692</td>
<td>21%</td>
</tr>
<tr>
<td>N*&lt;sub&gt;post&lt;/sub&gt;</td>
<td>152046</td>
<td>6611</td>
<td>437416</td>
<td>5207</td>
<td>21%</td>
</tr>
<tr>
<td>μ*&lt;sub&gt;post&lt;/sub&gt;</td>
<td>6611</td>
<td>152046</td>
<td>437416</td>
<td>5207</td>
<td>1404</td>
</tr>
</tbody>
</table>

* Standardized by 10,000 PD

Values in red font suggest increases; values in green font suggest decreases
Figure 5-1. Trends in “Targeted” (Panel A), “Non-targeted” (Panel B), and “Total” (Panel C) antibiotic use at Sunnybrook Health Sciences Centre (SHSC) acute care facility.

Trends shown for the 14-year base case study period (84-month pre-intervention period; 84-month post-intervention period). Antimicrobial use (AMU) is shown in days of therapy standardized by 10,000 patient days (# DOT/10,000 PD). The pivots in targeted, non-targeted, and total AMU trends coinciding with implementation of the SHSC prospective audit-and-feedback antimicrobial stewardship program (PAF-ASP) (BLACK ARROW) suggest that PAF-ASP implementation was associated with improvements in the trend of inpatient antibiotic use.
5.5.2 Primary Outcome Results: Base-case and Sensitivity Analyses Results for Targeted (TGD) Agent Use

Table 5.3 summarizes the base-case and sensitivity model findings for TGD AMU. No statistically significant change in relative TGD AMU incidence was detected for the base-case scenario (Post-Period $\text{RRR}_{\text{TGD, base}} = 2.1\%$ reduction/post-period, $p=0.7288$). However, the Trend analysis $\beta_6$ parameter used to infer a PAF-ASP associated change in TGD AMU trend was statistically significant, and pre- and post-intervention period trends were characterized. A “pivot” in pre- to post-intervention trend of TGD AMU was detected, such that use was increasing prior to PAF-ASP implementation ($\text{Trend}_{\text{TGD, pre, base}} = +0.7\%$ incidence/month, $p<0.0001$) and decreasing afterwards ($\text{Trend}_{\text{TGD, post, base}} = -0.2\%$ incidence/month, $p<0.0001$).

A statistically significant 12.3% reduction in TGD AMU was detected in the post-intervention period when an abbreviated pre-intervention period was utilized (i.e. the sensitivity model conditions; Post-Period $\text{RRR}_{\text{TGD, sens}} = 12.3\%$ reduction/post-period, $p=0.023$). The $\beta_6$ Trend parameter was also significant for this model, and a PAF-ASP associated pivot in TGD use was once again detected ($\text{Trend}_{\text{TGD, pre, sens}} = +0.2\%$ incidence/month, $p=0.0007$; $\text{Trend}_{\text{TGD, post, sens}} = -0.2\%$ incidence/month, $p<0.0001$).
Table 5-3. Inferential statistics for rates of “targeted” (TGD) antimicrobial use (AMU) for both the base-case and sensitivity model conditions.
Data presented includes relative reduction in post-intervention period use (Post-Period RRR\textsubscript{TGD}), pre-intervention period trend (Trend\textsubscript{TGD,pre}), and post-intervention period trend (Trend\textsubscript{TGD,post}).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period RRR\textsubscript{TGD}</th>
<th>Trend\textsubscript{TGD,pre}</th>
<th>Trend\textsubscript{TGD,post}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>Base-case TGD AMU</td>
<td>2.1%</td>
<td>0.7288</td>
<td>+0.7%</td>
</tr>
<tr>
<td>Sensitivity TGD AMU</td>
<td>12.3%</td>
<td>0.0296</td>
<td>+0.2%</td>
</tr>
</tbody>
</table>

Values in black font represent no change; values in red font represent increases; values in green font represent decreases.
5.5.3 Balancing Outcome Results: Base-case and Sensitivity Analyses
Results for Non-Targeted (NTGD) and Total (TTL) antibiotic use

5.5.3.1 Non-Targeted (NTGD) Agent Use

Table 5.4 summarizes the base-case and sensitivity model findings for NTGD AMU. No statistically significant difference in the relative rate of NTGD AMU was detected in the base-case or sensitivity model scenario (Post-Period RRR\textsubscript{NTGD,base} = 7.1% reduction/post-period, \(p=0.2163\); Post-Period RRR\textsubscript{NTGD,sens} = 0.6% reduction/post-period, \(p=0.9220\)).

Trend model \(\beta_6\) parameters were statistically significant in both the base-case and sensitivity models, and pre- and post-intervention period trends were characterized. For the base-case model, a “pivot” in pre- to post-intervention trend of NTGD use was detected. NTGD use was found to be increasing prior to PAF-ASP implementation (Trend\textsubscript{NTGD,pre,base} = +0.2% incidence/month, \(p<0.0001\)) and decreasing afterwards (Trend\textsubscript{NTGD,post,base} = -0.2% incidence/month, \(p<0.0001\)). A different pattern was found for the sensitivity model. In this case, a decreasing pre-intervention period trend was detected (Trend\textsubscript{NTGD,pre,sens} = -0.8% incidence/month, \(p<0.0001\)), with a “blunting” of this decreasing trend seen post-PAF-ASP implementation (Trend\textsubscript{NTGD,post,sens} = -0.2% incidence/month, \(p<0.0001\)).
Table 5-4. Inferential statistics for rates of “non-targeted” (NTGD) antimicrobial use (AMU) for both the base-case and sensitivity model conditions.

Data presented includes relative reduction in post-intervention period use (Post-Period RRR\textsubscript{NTGD}), pre-intervention period trend (Trend\textsubscript{NTGD,pre}), and post-intervention period trend (Trend\textsubscript{NTGD,post}).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period RRR\textsubscript{NTGD}</th>
<th>Trend\textsubscript{NTGD,pre}</th>
<th>Trend\textsubscript{NTGD,post}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>Base-case NTGD AMU</td>
<td>7.1%</td>
<td>0.2163</td>
<td>+0.2%</td>
</tr>
<tr>
<td>Sensitivity NTGD AMU</td>
<td>0.6%</td>
<td>0.9216</td>
<td>-0.8%</td>
</tr>
</tbody>
</table>

*Values in black font represent no change; values in red font represent increases; values in green font represent decreases*
5.5.3.2 Total (TTL) Antibiotic Use

Table 5.5 summarizes the base-case and sensitivity model findings for TTL AMU. No statistically significant difference in the relative rate of TTL AMU was detected in the base-case or sensitivity model scenario (Post-Period RRR_{TTL,base} = 6.2% reduction/post-period, p=0.2219; Post-Period RRR_{TTL,sens} = -0.8% reduction/post-period, p=0.9040).

The Trend model $\beta_6$ parameter was statistically significant for the base-case model but not the sensitivity model. For the base-case model, a “pivot” in pre- to post-intervention trend of TTL use was detected. TTL use was found to be increasing prior to PAF-ASP implementation (Trend_{TTL,pre,base,} = +0.4% incidence/month, p<0.0001) and decreasing afterwards (Trend_{TTL,post,base,} = -0.3% incidence/month, p<0.0001). TTL trend for the sensitivity model was unaffected by the intervention and found to be decreasing by 0.3% use/month throughout the sensitivity model study period (Trend_{TTL,pre&post,sens} = -0.3% incidence/month, p<0.0001).
Table 5-5. Inferential statistics for rates of “total” (TTL) antimicrobial use (AMU) for both the base-case and sensitivity model conditions.
Data presented includes relative reduction in post-intervention period use (Post-Period RRR$\text{_{TTL}}$), pre-intervention period trend (Trend$\text{_{TTL,pre}}$), and post-intervention period trend (Trend$\text{_{TTL,post}}$).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Post-Period RRR$\text{_{TTL}}$</th>
<th>Trend$\text{_{TTL,pre}}$</th>
<th>Trend$\text{_{TTL,post}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>Base-case TTL AMU</td>
<td>6.2 %</td>
<td>0.2219</td>
<td>+0.4%</td>
</tr>
</tbody>
</table>
| Sensitivity TTL AMU | -0.8% | 0.9040 | -0.3% (<0.0001) | \\

*Values in black font represent no change; values in red font represent increases; values in green font represent decreases*
5.4 Discussion

This study used ITS Poisson regression models to evaluate the impact of the SHSC PAF-ASP on institutional rates of TGD, NTGD, and TTL AMU in the 7-year (84-month) period following PAF-ASP implementation. Although a statistically significant reduction in the overall consumption of TGD agents was not detected for the base-case scenario (Post-Period \( \text{RRR}_{\text{TGD,base}} = 2.1\% \) reduction/post-period, \( p=0.7288 \)), a significant 12.3% reduction was found when the sensitivity model conditions were applied (Post-Period \( \text{RRR}_{\text{TGD,sens}} = 12.3\% \) reduction/post-period, \( p=0.023 \)). In both scenarios, PAF-ASP implementation was associated with a significant improvement in the trend of use over time. In both scenarios, rates of TGD AMU were found to be increasing in the pre-intervention period (\( \text{Trend}_{\text{TGD,pre,base}} = +0.7\% \) incidence/month, \( p<0.0001 \); \( \text{Trend}_{\text{TGD,pre,sens}} = +0.2\% \) incidence/month, \( p=0.0007 \)), which "pivoted" to become decreasing trends in the post-intervention period (\( \text{Trend}_{\text{TGD,post,base}} = -0.02\% \) incidence/month, \( p<0.0001 \); \( \text{Trend}_{\text{TGD,post,sens}} = -0.2\% \) incidence/month, \( p<0.0001 \)).

The consistent PAF-ASP associated “pivot” in TGD AMU trend and the Post-Period \( \text{RRR}_{\text{TGD,sens}} \) findings are in keeping with the early-phase SHSC PAF-ASP assessments and existing body of literature. A 22% reduction in TGD agent use was found 12 months post-ICU Pilot implementation9, and a 21% reduction in TGD agent use was found among qualifying patients 12 months after the Ward Roll-Out program27. Furthermore, a meta-analysis of high quality quasi-experimental studies found ASP implementation was associated with a 27% decrease in TGD AMU (95% CI: 0.8% to 52% reduction)7, and a Cochrane meta-analysis of randomized controlled trials found antibiotic consumption dropped 25% following ASP implementation (95% CI: 13% to 37% reduction)4. The magnitude of TGD use reduction is smaller in this study, but this is potentially due to between-study differences in the antibiotics assessed, the scale of the assessment (i.e. institution-level change vs. unit-level change), the duration of follow-up, and the statistical methods applied to quantify effects (i.e. Poisson regression vs. linear regression vs. other).

Interpreting the non-significant Post-Period \( \text{RRR}_{\text{TGD,base}} \) is more challenging. Comparing the results of the base-case scenario to existing data was not possible as high-quality studies with pre-intervention periods greater than 3 years in length were not able to be identified. This problem was anticipated, and it was the reason the sensitivity model with an abbreviated 23-
month pre-intervention period were created. However, the significant “pivot” in TGD AMU trend seen in the base-case and sensitivity model scenarios strongly suggest that PAF-ASP implementation positively impacted TGD agent use. Therefore, a likely explanation for the absence of a base-case relative reduction in TGD AMU is that the pre-intervention increases and the post-intervention decreases mirrored each other very closely to produce a negligible “net” effect.

No change in relative consumption of NTGD agents or TTL AMU were found in the base-case and the sensitivity model scenarios (Post-Period RMR_{NTGD} range = 0.6% to 7.1% reduction/post-period, p-values 0.2163 to 0.9261; Post-Period RMR_{TTL} range = 6.2% to -0.8% reduction/post-period, p-values 0.2219 to 0.9040). This was anticipated as the SHSC PAF-ASP specifically intervenes on TGD agents. The absence of Post-Period RRR_{NTGD} and Post-Period RRR_{TTL} changes are positive finding since TGD and TTL AMU were included as balancing metrics for TGD use. The lack of change in overall NTGD AMU and TTL AMU incidence demonstrates that the PAF-ASP did not “squeeze the balloon”\(^2\) to increase prescribing of non-audited agents in a clinically significant manner. This further supports the beneficial role of the institutional PAF-ASP. Since NTGD AMU accounts for 50.37% of TTL AMU, and no change in overall NTGD AMU incidence was detected in either the base-case or sensitivity scenario, it is reasonable that no change in TTL AMU incidence was found in the base-case and sensitivity model scenario.

Results of the Trend analyses supported the incidence analyses and suggested that the PAF-ASP had either a positive and/or neutral effect on NTGD and TTL AMU. Base-case models (84-month pre-intervention period) suggested overall improvements with “pivots” in trend detected for all outcomes (Trend_{TGD,pre,base} = +0.7% incidence/month, Trend_{TGD,post,base} = -0.2% incidence/month, Trend_{NTGD,pre,base} = +0.2% incidence/month, Trend_{NTGD,post,base} = -0.2% incidence/month, Trend_{TTL,pre,base} = +0.4% incidence/month, and Trend_{TTL,post,base} = -0.3% incidence/month; p<0.0001 for all trends).

Sensitivity models (23-month pre-intervention period) detected a significant improvement in TGD AMU trend, a mild compensatory increase in NTGD AMU trend, and no change in TTL AMU trend. In these models, TGD AMU trend was increasing (Trend_{TGD,pre,sens.} = +0.2% incidence/month, p<0.0001) and NTGD AMU trend was decreasing (Trend_{NTGD,pre,sens.} = -0.8%
incidence/month, p<0.0001) during the pre-intervention period. This suggests that broad-spectrum agents were being preferentially prescribed over narrow spectrum agents in the 23-month period preceding PAF-ASP implementation. The sensitivity models detected a pivot in TGD AMU trend associated with PAF-ASP implementation (i.e. transition from increasing to decreasing trend; \(\text{Trend}_{\text{TGD,post,sens.}} = -0.2\% \text{ incidence/month, p}<0.0001\)), a “blunting” of the NTGD AMU decreasing trend (i.e. a transition to a slightly less negative trend; \(\text{Trend}_{\text{NTGD,post,sens.}} = -0.2\% \text{ incidence/month, p}<0.0001\)), and no change in TTL AMU trend (\(\text{Trend}_{\text{TTL,pre&post,sens.}} = -0.3\% \text{ incidence/month, p}<0.0001\)). These findings suggest that PAF-ASP implementation was associated with significant improvement in the use of TGD agents and a minor compensatory increase in NTGD use, but that this program successfully maintained decreasing rates of AMU for agents throughout the post-intervention period (i.e. TGD, NTGD, and TTL AMU).

To the best of this writer’s knowledge, this is one of the first studies to evaluate the long-term impact of an ASP on TGD antibiotic consumption (i.e. over 5 years post-implementation). The strengths of this study include the use of comprehensive ITS Poisson regression models, the use of practical aggregate outcome metrics, and the use of base-case and sensitivity conditions. The ITS is a robust quasi-experimental design ideal for assessing the effects of population-level interventions over time\textsuperscript{137}. The ITS design minimized threats to internal validity by incorporating historic control groups into the analyses and requiring multiple observations be taken in both the pre- and post-intervention periods\textsuperscript{142,143}. Poisson regression models are the most appropriate models for count-based data (i.e. \# DOT/month), and use of these models allowed us to characterize changes in both the trend and relative antibiotic consumption over time\textsuperscript{148}. The models also allowed us to control for the effect of multiple potential confounders and minimize the risk of bias (i.e. autocorrelation, seasonal variability in antibiotic consumption, hospital-occupancy). The use of sensitivity models allowed us to validate the results of this study against pre-existing data, and the concurrent assessment of balancing metrics (NTGD and TTL AMU) strengthens the validity of the primary outcome findings. Finally, the use of a composite primary outcome metric (i.e. hospital-wide consumption of TGD AMU measured in DOT/month) and data sets with over 100 time points ensured adequate fitting of the base-case and sensitivity models\textsuperscript{152}. 
The limitations of this study include its quasi-experimental design, the absence of an external control, and the generalizability of the results to other acute care PAF-ASP programs. Although the ITS is a robust longitudinal design, randomized controlled trials remain the gold standard for establishing causality. Like all retrospective designs, there remains some risk of unrecognized confounders biasing the results. For this reason, the results of this study do not definitively establish a cause-and-effect relationship between SHSC PAF-ASP implementation and the observed reductions in SHSC inpatient TGD AMU. However, the inclusion of known confounders in the models of this study, the consistency in TGD AMU findings for both the base-case and sensitivity model conditions, and the consistency between the findings of this study and the findings of the ICU Pilot and Ward-Roll Out assessments strengthen the likelihood of a causal relationship. We had hoped to evaluate changes in the trend and level of a non-antibiotic medication as an external control and increase the validity of the AMU findings. However, we were not able to identify an agent or class of agents for which prescribing practices remained constant across the 14-year study period, therefore the absence of an external control represents a study limitation.

The inability to assess compliance with PAF recommendations or the appropriateness of antibiotic therapy over the entire post-intervention period are additional limitations. Compliance rates were approximately 80% in the ICU Pilot and Ward Roll-Out studies, but process outcomes of this nature were not collected after April 2012. The inability to differentiate between PAF-specific effects and the effects of minor components of the SHSC ASP (i.e. changes to specific AMU or disease state management guidelines over the study time period) is another limitation. PAF consultations are inarguably the “backbone” of the SHSC ASP, but a variety of passive AS interventions were enhanced in the post-intervention period which may have enhanced the PAF effect (i.e. medical education, launch of the online SHSC Handbook App, etc.). Although it is not possible to disentangle PAF-specific changes in AMU from changes due to complementary passive strategies, it is generally agreed that active interventions (such as PAF) produce more significant and sustained effects on AMU compared to passive strategies. For this reason, it is reasonable to assume that PAF is driving the effects detected in this study.
A final limitation is the generalizability of the observed effect to centres with different ASP structures. No two hospitals have the exact same ASP in place, and few sites have a PAF component as comprehensive as the SHSC PAF-ASP; therefore, the changes in AMU seen with the SHSC ASP may not be transferrable to ASPs with different structures. Nonetheless, other centres hoping to reduce TGD AMU could use the findings of this study to justify implementation of PAF-ASPs similar to SHSC model. Alternatively, other sites might apply the robust methodology described in this study to evaluate the impact of their own ASPs on AMU. Although comparisons would be indirect, differences in the magnitude of observed effects might provide some information about the relative effectiveness of different ASP structures—such as the relative effectiveness of restriction-based ASPs, since restriction-based interventions have been shown to have a more profound “squeezing the balloon effect”\textsuperscript{129}.

5.5 Conclusion

The results of this study support the finding of the SHSC PAF-ASP ICU Pilot and Ward-Roll Out studies and confirm that implementation of the SHSC PAF-ASP has been accompanied by significant and sustained reductions in institutional TGD AMU. These results support the AMR findings discussed in Thesis Chapter 4 and confirm that the observed reductions in institutional AMR coincide with reductions in institutional AMU. Overall, these findings support the biological plausibility of the AS hypothesis.
Chapter 6
Trends in the Affiliated Long-term Care Facility in Relation to Acute Care Antimicrobial Stewardship Program Implementation
6 Resistance Trends in the Affiliated Long-term Care Facility in Relation to Acute Care Antimicrobial Stewardship Program Implementation

6.1 Preface

The previous chapter described the impact of the Sunnybrook Health Sciences Centre (SHSC) prospective audit-and-feedback (PAF) antimicrobial stewardship program (ASP) on rates of inpatient antimicrobial use (AMU) in the acute care facility by evaluating differences in the incidence and trend of targeted (TGD) AMU, non-targeted (NTGD) AMU, and total (TTL) AMU between the pre- and post-intervention periods.

This chapter describes the methods and findings of the study that was conducted to address the tertiary objective of this thesis research: Exploring the impact of the SHSC acute care ASP on the burden of antimicrobial resistance (AMR) in the geographically adjacent long-term care facility (LTCF). Differences in the incidence and trend of LTCF-acquired antibiotic-resistant organisms (LTCF-ARO) and LTCF-acquired multi-drug resistant organisms (LTCF-MDRO) between the years preceding and following ASP implementation were used to infer program impact.

6.2 Background

AMR is increasing worldwide and represents a serious threat to modern medicine. Antimicrobial stewardship (AS) has been proposed as a solution to reduce the burden of AMR. Despite an increasing body of evidence evaluating ASPs and initiatives, definitive evidence demonstrating the positive impact of these programs on the burden of AMR in healthcare facilities is lacking. This is true in both the acute care setting and LTCF setting.

SHSC implemented a multidisciplinary PAF-ASP at the Bayview Site acute care facility on October 1st, 2009. The PAF-ASP is an “active” intervention in which the AS team reviews acute care inpatient orders over 10 TGD antibiotic agents and provides suggestions to optimize therapy to the primary care team. However, the SHSC ASP also includes several “passive” components to guide antibiotic prescribing that complement the active PAF core, including antibiotic use
policies, educational initiatives, and online SHSC Antimicrobial Handbook with therapeutic guidelines, antibiotic monographs, and antibiograms.

Although the LTCF lacked a formal PAF-ASP, it shared personnel, policies, and educational resources with the adjoining acute care centre. Consequently, it is possible that LTCF prescribers were exposed to the passive and/or active elements of the acute care ASP, and that these elements positively influenced LTCF prescribing to improve LTCF antibiotic use (AMU) and LTCF AMR by way of an indirect or “trickle down” effect.

The presence of an indirect effect on LTCF outcomes cannot be presumed because the SHSC ASP was designed to influence acute care AMU and AMR. Trends in LTCF AMR before and after implementation of the SHSC PAF-ASP cannot be predicted with any degree of certainty due to the lack of existing data in this area. AMR is not routinely surveyed in LTCFs\textsuperscript{[138]}, and the need for ecologic and/or interventional studies describing the trends in LTCF AMR has been identified\textsuperscript{[139,140]}. For these reasons, an exploratory study describing the trends in AMR at the SHSC LTCF was warranted.

6.2.1 Objective and Hypothesis

This study sought to explore and characterize trends in SHSC LTCF AMR in relation to implementation of the SHSC acute care PAF-ASP, as measured by changes in incidence of LTCF-ARO and LTCF-MDRO. No hypothesis regarding the presence or direction of an effect was proposed given the exploratory nature of this study.

6.3 Methods

6.3.1 Study Design

Changes in the LTCF burden AMR in relation to implementation of the SHSC acute care PAF-ASP were assessed using retrospective interrupted time series (ITS) analyses. The ITS is a robust quasi-experimental design, and it is the most appropriate design for evaluating longitudinal effects of population-level interventions over time\textsuperscript{[137,142,143]}. Implementation of the acute care PAF-ASP on October 1\textsuperscript{st}, 2009 was the intervention for this study. Monthly incidences of LTCF-acquired resistant bacteria in the post-intervention period (i.e., in the presence of the PAF-ASP
and supportive activities) were compared to the monthly incidences of LTCF-acquired resistant bacteria in the pre-intervention period (i.e. in the absence of a PAF-ASP), such that the pre-intervention period served as a historic control. Identification of a relative reduction in the monthly rate of LTCF-acquired resistant bacteria from the pre- to post-intervention period (i.e. Post-Period Relative Rate Reduction, “Post-Period RRR”), and a difference in the pre- and post-intervention period incidence trends over time, were used to infer acute care facility PAF-ASP impact in the LTCF.

Pre- and post-intervention periods were each 84 months in duration (pre-intervention period October 2002 – September 2009; post-intervention period: October 2009 – September 2016). The decision to use an 84-month pre-intervention period for the base-case model was somewhat arbitrary; an 84-month post-intervention period was available for the PAF-ASP at the time of study design, and an 84-months pre-intervention period was selected to achieve pre- and post-intervention periods of symmetrical durations.

6.3.2 Study Setting and Population

SHSC is a multi-site academic health centre affiliated with the University of Toronto and located in Toronto, Ontario, Canada. The Bayview Site is home to a 627-bed acute care tertiary referral teaching hospital and a 530-bed long term care facility (LTCF).

All non-duplicate LTCF-acquired clinical isolates for target bacterial species isolated from patients admitted to the SHSC LTCF during the defined study period were included in this analysis. LTCF-acquired clinical isolate was defined as a positive bacterial culture grown from a LTCF-clinical specimen collected from a LTCF patron >48h after admission to the LTCF; this was in keeping with the standard definition of healthcare-acquired infection. LTCF-clinical specimen was defined as a specimen collected in the LTCF for the purpose of assisting with the diagnosis of an infection (i.e. blood, urine, sputum, etc.). Isolates grown from screening swabs, surveillance swabs, or other cultures sent for infection prevention and control (IPC) purposes were excluded from this analysis (i.e. nasal and rectal swabs).

Clinical isolates of the following common nosocomial pathogens were included in this analysis: *Escherichia coli*, *Klebsiella* spp., *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*,
Providencia spp., Serratia spp., Citrobacter spp., Enterobacter spp., Pseudomonas aeruginosa, Acinetobacter spp., Enterococcus spp., and Staphylococcus aureus. Duplicate isolates were removed from the data set to minimize bias. For the base-case data set, duplicate isolates were defined as same-species isolates with identical susceptibility profiles collected from the same patient within 14 days.

6.3.3 Outcomes

6.3.3.1 Primary Outcome

Changes in the monthly incidence of LTCF-ARO were assessed as the primary outcome (i.e. monthly LTCF-ARO incidence rate = number of LTCF-ARO identified in study month X standardized by the number of patient days (PD) in study month X for the entire LTCF facility). LTCF-ARO was defined as a LTCF-clinical isolate of any target bacterial species exhibiting resistance to at least one therapeutically active antibiotic agent. Isolates were classified as susceptible or resistant in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines active at the time of collection (i.e. as determined by the SHSC Microbiology Laboratory at the time of sensitivity testing). Isolates with intermediate susceptibility were considered resistant.

A PAF-ASP associated change in burden of LTCF-AMR was assessed by comparing the mean monthly LTCF-ARO incidence rate in the pre-intervention period to the mean monthly LTCF-ARO incidence rate in the post-intervention period. Differences were reported as the relative reduction in LTCF-ARO incidence in the post-intervention period (i.e. Post-Period Relative Rate Reduction, “Post-Period RRR_{LTCF-ARO}”, reported as % incidence reduction/post-period). The presence of a PAF-ASP associated change in LTCF-ARO incidence rate trend was also assessed, and pre- and post-intervention trend estimates were determined to further characterize PAF-ASP impact (“Trend_{LTCF-ARO,pre}” and “Trend_{LTCF-ARO,post}”, reported as Δ% incidence/month).

6.3.3.2 Secondary Outcome

Changes in the monthly incidence of LTCF-MDRO were assessed as the primary outcome (i.e. monthly LTCF-MDRO incidence rate = number of LTCF-MDRO identified in study month X standardized by the number of patient days (PD) in study month X for the entire LTCF facility).
MDRO was defined as a clinical isolate of any target bacterial species exhibiting resistance to three or more antibiotic classes\textsuperscript{146}. The definition for LTCF-isolate and the criteria used to classify isolates as susceptible or resistant described in Section 6.3.3.1 were applied.

A PAF-ASP associated change in burden of LTCF-AMR was assessed by comparing the mean monthly LTCF-MDRO incidence rate in the pre-intervention period to the mean monthly LTCF-ARO incidence rate in the post-intervention period. Differences were reported as the relative reduction in LTCF-MDRO incidence in the post-intervention period (i.e. Post-Period Relative Rate Reduction, “Post-Period RRR\textsubscript{LTCF-MDRO}”; reported as % incidence reduction/post-period). The presence of a PAF-ASP associated change in LTCF-MDRO incidence rate trend was also assessed, and pre- and post-intervention trend estimates were determined to further characterize PAF-ASP impact (“\text{\text{\text{\text{\text{Trend}_{LTCF-MDRO,pre}}} \text{Trend}_{LTCF-MDRO,post}}}}”; reported as \(\Delta\)\% incidence/month).

6.3.4 Data Collection and Preparation

6.3.4.1 Microbiology Data

Patient-level data for clinical isolates of target bacterial species collected from LTCF patrons from October 1\textsuperscript{st}, 2002 to September 30\textsuperscript{th}, 2016 were retrospectively extracted from the SHSC Microbiology Department Database into a Microsoft Excel spreadsheet. The following parameters were extracted for each clinical isolate: Patient identifier, patient age and sex, patient date of admission, date and location of culture collection (i.e. ward location), specimen type (blood, sputum, urine, wound, CSF, etc.), bacterial species (\textit{Escherichia coli}, \textit{Klebsiella} spp., \textit{Morganella morganii}, \textit{Proteus mirabilis}, \textit{Proteus vulgaris}, \textit{Providencia} spp., \textit{Serratia} spp., \textit{Citrobacter} spp., \textit{Enterobacter} spp., \textit{Pseudomonas aeruginosa}, \textit{Acinetobacter} spp., \textit{Staphylococcus aureus}, \textit{Enterococcus} spp.), and isolate susceptibility profile as tested and reported by the Microbiology Laboratory at the time of collection.

6.3.4.2 Administrative Data

PD data for the LTCF were retrospectively extracted from the SHSC Health Data Resources Database into a Microsoft Excel database. PD data was extracted as LTCF-wide aggregate count for each study month.
6.3.5 Statistical Analyses

6.3.5.1 Descriptive Statistics

The following descriptive statistics were reported for the study period: (a) patient count, (b) percentage of male patients, and (c) mean patient age. Standardized total counts (N*= total count/10 000 PD/period) and standardized mean monthly counts (μ*= monthly count/10 000 PD/period) were determined for various clinical isolate groups, LTCF-ARO, and LTCF-MDRO and reported for the complete study period, the pre-intervention period, and the post-intervention period. Pre- to post-intervention unadjusted relative rate reductions (unadjusted RRR = 100% – [μ*post/μ*pre]) and unadjusted absolute rate reductions (unadjusted ARR = μ*pre – μ*post) were reported for descriptive purposes. Total PD count and mean monthly PD were also reported for the complete study period, the pre-intervention period, and the post-intervention period.

6.3.5.2 Inferential Statistics

The presence of PAF-ASP associated changes in LTCF-ARO and LTCF-MDRO were tested using Poisson generalized linear mixed models. The presence of PAF-ASP associated reductions in LTCF-ARO and LTCF-MDRO incidence (i.e. Post-period RRR) were assessed using the “Relative Rate Reduction (RRR) Regression Model” described below. The presence of PAF-ASP associated changes in the trends of LTCF-ARO and LTCF-MDRO incidence, and estimates of the pre- and post-intervention period monthly trends (i.e. Trendpre and Trendpost), were assessed using the “Trend Regression Models” described below.\textsuperscript{148}

Relative Rate Reduction (RRR) Regression Model

Differences in the relative incidence of LTCF-ARO and LTCF-MDRO in the pre- and post-intervention periods were tested using Poisson regression models of the following form:

\[
\text{Ln (Monthly Count/Bed Occupancy)} = \beta_1(\text{Study Period}) + \beta_2(\text{Season})
\]

Monthly counts of ARO and MDRO (“Monthly Count”) standardized by institutional patient load (“Bed Occupancy” in PD) were the outcome variables. “Study Period” was included as fixed component and assessed as the main predictor (0 = pre-intervention period; 1= post-intervention period). “Season” was included as a fixed component to adjust for the effect of
season on AMU and therefore ARO and MDRO incidence (1 = March, April, May; 2 = June, July, August; 3 = September, October, November; 4 = December, January, February). Study month was treated as a random component and modelled from a distribution with an autoregressive correlation structure. The autoregressive correlation structure assumed that time points closer together were more similar than time points further apart.

β1 and β2 represent the model-adjusted estimates for the effects of Study Period and Season on ARO and MDRO incidence. A statistically significant difference in pre- and post-intervention period incidence was inferred when the p-value for the β1 parameter was equal or less than 0.05. The incidence rate ratio (IRR) for pre- to post-intervention period incidences of ARO and MDRO were obtained by exponentiating the β1 parameter (i.e. $e^{\beta_1} = \text{IRR} = \frac{\text{Rate}_{\text{post-period}}}{\text{Rate}_{\text{pre-period}}}$). The Post-Period RRR was obtained by taking the difference between the IRR and 100% (i.e. Post-Period RRR$_{\text{base}} = 100\% - \text{IRR}$) and reported as the percent reduction in post-period incidence (Post-Period RRR = % reduction/post-period). Post-Period RRR$_{\text{base}}$ greater than ±10% were considered clinically significant. β2 parameters and the impact of season on antibiotic were not evaluated or further discussed as they are not directly relevant to this study’s objective.

**Trend Regression Models**

PAF-ASP associated changes in the trajectories, or “trends”, of LTCF-ARO and LTCF-MDRO incidence were tested using interaction models of the following form:

$$\ln \left( \frac{\text{Monthly Count}}{\text{Bed Occupancy}} \right) = \beta_3(\text{Study Period}) + \beta_4(\text{Season}) + \beta_5(\text{Study Month}) + \beta_6(\text{Study Month}*\text{Study Period})$$

This model had four fixed components: “Study Period”, “Season”, “Study Month”, and “Study Month*Study Period”. Study Month was included as a fixed component because the month-to-month change in ARO and MDRO counts (i.e. “trends”) were being assessed. The interaction between Study Phase*Study Month was included as a fixed factor to specifically test for a difference between pre- and post-intervention period trends. A statistically significant difference in pre- and post-intervention period trend was inferred when the p-value for the β6 parameter was equal or less than 0.05.
When the $\beta_6$ parameter was statistically significant, pre- and post-intervention period trend estimates were characterized by running the follow-up model below:

**Study Phase 0:** \[ \ln (\text{Monthly Count//Bed Occupancy}) = \beta_7 (\text{Study Month}) \]

**Study Phase 1:** \[ \ln (\text{Monthly Count//Bed Occupancy}) = \beta_8 (\text{Study Month}) \]

A statistically significant pre-intervention period trend was inferred when the p-value for the $\beta_7$ parameter was equal or less than 0.05. Pre-intervention period trend estimates (i.e. “Trend$_{\text{pre,base}}$”) were obtained by exponentiating $\beta_7$ parameter (i.e. \(\text{Trend}_{\text{pre,base}} = e^{\beta_7}\)) and were reported as the percent change in incidence each month (\(\text{Trend}_{\text{pre,base}} = \% \Delta \text{ incidence/month}\)). Trend$_{\text{pre}}$ with p-values <0.05 were deemed statistically significant.

A statistically significant post-intervention period trend was inferred when the p-value for the $\beta_8$ parameter was equal or less than 0.05. Post-intervention period trend estimates (i.e. “Trend$_{\text{post}}$”) were obtained by exponentiating $\beta_8$ parameter (i.e. \(\text{Trend}_{\text{post,base}} = e^{\beta_8}\)) and were reported as the percent change in incidence use each month (\(\text{Trend}_{\text{post,base}} = \% \Delta \text{ incidence/month}\)). Trend$_{\text{post}}$ with p-values <0.05 were deemed statistically significant.

**6.3.5.3 Model Fitting**

It is suggested that time series data sets include at least 9 pre-intervention period time points and 9 post-intervention period time points to provide enough variability to fit the model$^{152}$. However, it is generally agreed that more time points are better. Another rule of thumb is that there should be at least 10 time points per fixed component (i.e. predictor variable) in a multi-variable model to avoid over-parameterization$^{148}$. In addition, it is encouraged that each time point have at least 100 observations to minimize the number of outliers and provide more stable estimates$^{152}$.

For this study, RRR models had 2 predictor variables (Study Period, Season) and Trend models had a maximum of 4 predictor variables (Study Period, Season, Study Month, Study Month*Study Period). The data set consisted of 168 time points. Therefore, even the model with the largest number of predictors (i.e. 4) had a time point-to-predictor ratio exceeding the 10:1 general rule of thumb. For this reason, adequate fitting of the models was anticipated.
6.4 Results

6.4.1 Descriptive Statistics

Over the 168-month (14-year) study period, 4,878 unique bacterial isolates were identified \( \left( n_{\text{LTCF-isolates}} = 4,878 \right) \). These isolates were collected from 2,753 inpatients (mean age = 88 years, 79% male). The majority of isolates were gram negative bacilli (GNB; \( n_{\text{GNB}} = 3,862 \), 79%). The majority of GNB isolates were *Enterobacteriaceae* \( \left( n_{\text{Enterobacteriaceae}} = 3,450 \right) \), and 52% of the *Enterobacteriaceae* were *E. coli* \( \left( n_{\text{E.coli}} = 1,796 \right) \). Standardized isolate counts and other descriptive statistics are provided in Table 6-1. Post-intervention period standardized isolate counts were higher than pre-intervention period standardized isolate counts for most groups; the exceptions were aerobic non-fermenting GNB (*P. aeruginosa* and *Acinetobacter* spp., unadjusted Post-Period RRR\(_{\text{aerobic non-fermenters}} = 19\% \) reduction/post-period) and *S. aureus* (unadjusted RRR\(_{S.\text{aureus}} = 38\% \) reduction/post-period). PD counts were lower in the post-intervention period counts (unadjusted RRR = 3% reduction/post-period).

Approximately 85% of isolates exhibited resistance to at least one therapeutically active antibiotic agent \( \left( n_{\text{AR0}} = 4,113 \right) \) with 31% classified as multidrug resistant \( \left( n_{\text{MDRO}} = 1,581 \right) \). Standardized counts \( \left( N^* \right) \) and mean monthly counts \( \left( \mu^* \right) \), unadjusted RRR, and unadjusted ARR for LTCF-ARO and LTCF-MDRO are summarized in Table 6-2. Unadjusted RRR and unadjusted ARR suggested increased prevalence of LTCF-ARO and LTCF-MDRO (unadjusted RRR\(_{\text{LTCF-ARO}} = -9\% \) reduction/post-period; unadjusted RRR\(_{\text{LTCF-MDRO}} = -13\% \) reduction/post-period; unadjusted ARR\(_{\text{LTCF-ARO}} = -1.5 \) isolates/10,000 PD; unadjusted ARR\(_{\text{LTCF-MDRO}} = -0.8 \) isolates/10,000 PD).

A visual representation of LTCF-ARO and LTCF-MDRO trends over time \( \left( n/10,000 \text{ PD/month} \right) \) is provided in Figure 6-1.

6.4.2 Primary Outcome Results – Long-term care facility-associated antibiotic resistant organisms (LTCF-ARO)

Results from the RRR and Trend Poisson regression analyses for LTCF-ARO are summarized in Table 6-3. No clinically or statistically significant change in overall LTCF-ARO incidence was detected (Post-Period RRR\(_{\text{LTCF-ARO}} = -7.0\% \) reduction/post-period, \( p=0.3023 \)).
The Trend model \( \beta_6 \) parameter was statistically significant for a change in pre- to post-intervention period trend. Accordingly, pre- and post-intervention period trends (\( \text{Trend}_{\text{pre}} \) and \( \text{Trend}_{\text{post}} \)) were characterized. LTCF-ARO trend was found to be increasing prior to PAF-ASP implementation (\( \text{Trend}_{\text{LTCF-ARO,pre}} = +0.5\% \) incidence/month, \( p<0.0001 \)), which stabilized to a flat trend rate (i.e. absence of a statistically significant monthly increase or decrease) in the post-intervention period (\( \text{Trend}_{\text{LTCF-ARO,post}} = -0.1\% \) incidence/month, \( p=0.1409 \)).

### 6.4.3 Secondary Outcome Results – Long-term care facility-associated multidrug-resistant organisms (LTCF-MDRO)

Results from the RRR and Trend Poisson regression analyses for LTCF-MDRO are summarized in Table 6-3. No clinically or statistically significant change in overall LTCF-MDRO incidence was detected (Post-Period \( \text{RRR}_{\text{LTCF-MDRO}} = -2.8\% \) reduction/post-period, \( p=0.8539 \)).

The Trend model \( \beta_6 \) parameter was statistically significant for a change in pre- to post-intervention period trend. Accordingly, pre- and post-intervention period trends (\( \text{Trend}_{\text{pre}} \) and \( \text{Trend}_{\text{post}} \)) were characterized. LTCF-MDRO trend was found to be increasing prior to PAF-ASP implementation (\( \text{Trend}_{\text{LTCF-MDRO,pre}} = +0.5\% \) incidence/month, \( p<0.0001 \)), which stabilized to a flat trend rate (i.e. absence of a statistically significant monthly increase or decrease) in the post-intervention period (\( \text{Trend}_{\text{LTCF-MDRO,post}} = -0.2\% \) incidence/month, \( p=0.1232 \)).
### Table 6-1. Descriptive data for clinical isolates and patient days in the long-term care facility (LTCF).

Standardized isolate counts (N*), standardized mean monthly isolate rates (μ*), and patient days (PD) are reported for the complete study period, the pre-intervention period, and the post-intervention period. Pre- to post-intervention unadjusted relative rate reductions (RRR) are reported as percentages (%). Pre- to post-intervention unadjusted absolute rate reductions (ARR) are reported as standardized mean rates (Δμ* = rate/10 000 PD).

<table>
<thead>
<tr>
<th></th>
<th>Complete Study Period</th>
<th>Pre-Intervention Period</th>
<th>Post-Intervention Period</th>
<th>Unadjusted RRR</th>
<th>Unadjusted ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>μ</strong></td>
<td><strong>N</strong>&lt;sub&gt;pre&lt;/sub&gt;</td>
<td><strong>μ</strong>&lt;sub&gt;pre&lt;/sub&gt;</td>
<td><strong>N</strong>&lt;sub&gt;post&lt;/sub&gt;</td>
<td><strong>μ</strong>&lt;sub&gt;post&lt;/sub&gt;</td>
</tr>
<tr>
<td>Clinical isolates</td>
<td>3216.9</td>
<td>19.1</td>
<td>1522.7</td>
<td>18.1</td>
<td>13.3</td>
</tr>
<tr>
<td>Gram Negative</td>
<td>2549.6</td>
<td>15.2</td>
<td>1116.6</td>
<td>13.3</td>
<td>1456.3</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>2279.1</td>
<td>13.6</td>
<td>966.9</td>
<td>11.5</td>
<td>1334.1</td>
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<tr>
<td><strong>E. coli</strong></td>
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<td>476.0</td>
<td>5.7</td>
<td>724.1</td>
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<tr>
<td>Klebsiella spp.</td>
<td>404.9</td>
<td>2.4</td>
<td>153.6</td>
<td>1.8</td>
<td>257.3</td>
</tr>
<tr>
<td>Other spp.&lt;sup&gt;1&lt;/sup&gt;</td>
<td>685.3</td>
<td>4.1</td>
<td>337.3</td>
<td>4.0</td>
<td>352.7</td>
</tr>
<tr>
<td>Aerobic Non-Fermenters&lt;sup&gt;2&lt;/sup&gt;</td>
<td>270.6</td>
<td>1.6</td>
<td>149.7</td>
<td>1.8</td>
<td>122.2</td>
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<tr>
<td>Gram Positive</td>
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<td>406.1</td>
<td>4.8</td>
<td>268.4</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td>651.7</td>
<td>3.9</td>
<td>402.8</td>
<td>4.8</td>
<td>256.2</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
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<td>0.1</td>
<td>3.3</td>
<td>0.0</td>
<td>12.2</td>
</tr>
<tr>
<td>Patient Days</td>
<td>2551574</td>
<td>15187.9</td>
<td>1295596</td>
<td>15423.8</td>
<td>1255978</td>
</tr>
</tbody>
</table>

* Standardized by 10 000 PD

<sup>1</sup> Proteus spp., Citrobacter spp., Enterobacter spp., M. morganii, Providencia spp., Serratia spp.;<sup>2</sup> P. aeruginosa, Acinetobacter spp.

Values in red font suggest increases; values in green font suggest decreases.
Table 6-2. Descriptive data for clinical isolates, antibiotic-resistant organisms (ARO), and multidrug-resistant organisms (MDRO) from the long-term care facility (LTCF).

Standardized counts (N*) and standardized mean monthly incidence rates (μ*) are reported for the complete study period, the pre-intervention period, and the post-intervention period. Counts and mean monthly incidence rates are standardized by 10 000 PD. Pre- to post-intervention unadjusted relative rate reductions (RRR) are reported as percentages (%). Pre- to post-intervention unadjusted absolute rate reductions (ARR) are reported as standardized mean rates (Δμ* = rate/10 000PD).

<table>
<thead>
<tr>
<th></th>
<th>Complete Study Period</th>
<th>Pre-Intervention Period</th>
<th>Post-Intervention Period</th>
<th>Unadjusted RRR</th>
<th>Unadjusted ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Isolates</td>
<td>N*</td>
<td>μ*</td>
<td>N*&lt;sub&gt;pre&lt;/sub&gt;</td>
<td>μ*&lt;sub&gt;pre&lt;/sub&gt;</td>
<td>N*&lt;sub&gt;post&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>3216.9</td>
<td>19.1</td>
<td>1522.7</td>
<td>18.1</td>
<td>13.3</td>
</tr>
<tr>
<td>LTCF-ARO</td>
<td>2713.8</td>
<td>16.2</td>
<td>1295.5</td>
<td>15.4</td>
<td>1446.1</td>
</tr>
<tr>
<td>LTCF-MDRO</td>
<td>1043.2</td>
<td>6.2</td>
<td>489.3</td>
<td>5.8</td>
<td>562.5</td>
</tr>
</tbody>
</table>

* Standardized by 10 000 PD
Values in red font suggest increases; values in green font suggest decreases
Figure 6-1. Trends in long-term care facility (LTCF)-acquired antibiotic-resistant organism (LTCF-ARO) and multidrug resistant organisms (LTCF-MDRO).

Monthly incidence of LTCF-ARO and LTCF-MDRO at the Sunnybrook Health Sciences Centre (SHSC) LTCF across the 14-year study period (84-month pre-intervention period; 84-month post-intervention period). Monthly incidence is measured as an aggregate count standardized by 10,000 patient days (# LTCF-ARO/10,000 PD; # LTCF-MDRO/10,000 PD). The stabilization of the LTCF-ARO trend and LTCF-MDRO trend coinciding with implementation of the SHSC antimicrobial stewardship program (ASP) (BLACK ARROW) suggest that PAF-ASP implementation was associated with improvements in the trajectory of resistance.
Table 6-3. Inferential statistics for clinical isolates, antibiotic-resistant organisms (ARO), and multidrug-resistant organisms (MDRO) from the long-term care facility (LTCF).

Data presented includes relative reduction in post-intervention period incidence (Post-Period $\text{RRR}_{\text{LTCF}}$), pre-intervention period trend (Trend$_{\text{LTCF,pre}}$) and post-intervention period trend (Trend$_{\text{LTCF,post}}$).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period $\text{RRR}_{\text{LTCF}}$</th>
<th>Trend$_{\text{LTCF,pre}}$</th>
<th>Trend$_{\text{LTCF,post}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>LTCF-ARO</td>
<td>-7.0%</td>
<td>0.3023</td>
<td>+0.5%</td>
</tr>
<tr>
<td>LTCF-MDRO</td>
<td>-2.8%</td>
<td>0.8539</td>
<td>+0.5%</td>
</tr>
</tbody>
</table>

*Values in black font indicate no change; values in red font indicate increases; values in green font indicate decreases*
6.5 Discussion

This study sought to explore and characterize trends in SHSC LTCF AMR across a 168-month time period and in relation to the implementation of the SHSC acute care ASP. Small increases in LTCF-ARO and LTCF-MDRO incidence were seen but were neither clinically or statistically significant (Post-Period RRR_{LTCF-ARO} = -7.0% reduction/post-period, \( p=0.3023 \); Post-Period RRR_{LTCF-MDRO} = -2.8% reduction/post-period, \( p=0.8539 \)). PAF-ASP associated improvements in the trends of LTCF-ARO and LTCF-MDRO incidence were detected. Monthly LTCF-ARO and LTCF-MDRO incidences exhibited positive trends in the pre-intervention period (\( \text{Trend}_{LTCF-ARO,\text{pre}} = +0.5\% \text{incidence/month}, p<0.0001; \text{Trend}_{LTCF-MDRO,\text{pre}} = +0.5\% \text{incidence/month}, p<0.0001 \)). This increasing baseline or “secular” trend suggests that the burden on LTCF AMR was increasing prior to ASP implementation (i.e. in the absence of any ASP). Implementation of the acute care ASP was associated with significant changes in the trajectories of these baseline trends, such that no positive or negative trends were detected in the post-intervention period (\( \text{Trend}_{LTCF-ARO,\text{post}} = -0.01\% \text{incidence/month}, p=0.1409; \text{Trend}_{LTCF-MDRO,\text{post}} = -0.02\% \text{incidence/month}, p=0.1232 \)). The transition from an increasing trend to the absence of a trend (i.e. flat trend) is in keeping with a PAF-ASP-associated improvement in LTCF AMR and a possible “trickle-down” effect of the acute care program. Significant increases in post-period LTCF-ARO and LTCF-MDRO burden were avoided due to stabilization of the pre-intervention period trend.

Although the core component of the SHSC ASP is an active PAF intervention that was not extended to the LTCF during the defined post-intervention period (October 1st 2009 to September 30th 2016), it is possible that LTCF prescribers were exposed to the passive and/or active elements of the acute care ASP due to the sharing of personnel, policies, and educational resources between facilities. It follows that antibiotic prescribing at the LTCF may have been positively influenced by exposure to acute care ASP policies and practices despite the absence of a dedicated LTCF PAF intervention (i.e. LTCF prescribing was positively influenced by the “SHSC ASP without PAF”), and that this exposure improved LTCF AMU and LTCF AMR by way of an indirect or “trickle down” effect.

Under this assumption, exposure to the SHSC ASP without PAF was associated with a stabilization, or elimination, of the increasing secular AMR trend but was not associated with a
significant change in collective incidence of LTCF-ARO or LTCF-MDRO. As described in Thesis Chapter 4, exposure to the full SHSC ASP (i.e. SHSC PAF-ASP or “SHSC ASP with PAF”) was associated with an inversion (or “pivot”) in AMR trend and clinically significant improvements in the collective incidence of HA-ARO and HA-MDRO (Post-Period RRR_{HA-ARO,base} = -9.3% reduction/post-period, p=0.0278; Post-Period RRR_{HA-MDRO,base} = -12.3% reduction/post-period, p=0.1319). The comparatively tempered effect on LTCF AMR outcomes (i.e. hypothetical exposure to the SHSC ASP without PAF), and the more pronounced effect on acute care AMR outcomes (i.e. with exposure to the SHSC ASP with PAF), is in keeping with the notion that passive ASP strategies and interventions (i.e. education, guidelines, etc.) are less effective than proactive interventions (i.e. PAF and pre-authorization (PRA)) for altering antibiotic prescribing behaviors and improving AMR\textsuperscript{2,3,74}.

To the best of this writer’s knowledge, this is the first study to assess trends in LTCF AMR over such a prolonged time period. This is also the first study to explore the possible indirect effect of an ASP implemented in a facility that shares ASP resources with the study site. These are major strengths of this exploratory study. Additional strengths include the use of comprehensive ITS Poisson regression models and innovative aggregate outcome metrics to describe the burden of AMR. The ITS is a robust quasi-experimental design endorsed by the Cochrane Effective Practice and Organisation of Care (EPOC) Group\textsuperscript{155}. It is ideal for assessing the effects of population-level interventions over time\textsuperscript{137}. The ITS minimizes threats to internal validity by utilizing historic controls as the basis for comparison and requiring multiple observations in both the pre- and post-intervention periods\textsuperscript{142,143}. Poisson regression models are the most appropriate models for count-based data (i.e. # ARO/month), and these models allowed us to characterize changes in both the trend and relative incidence of LTCF-ARO and LTCF-MDRO over time\textsuperscript{148}. The models also allowed us to control for the effect of multiple potential confounders such as autocorrelation, seasonal variability in ARO and MDRO prevalence, and LTCF bed-occupancy.

The use of innovative composite outcome metrics to characterize resistance across various clinically relevant pathogen-sensitivity profiles is another strength of this study (i.e. institutional ARO incidence-density; # ARO/10,000 PD). No standard metric to quantify the collective burden of AMR burden exists\textsuperscript{72,73}, and these novel metrics capture the overall institutional burden of AMR in a practical and easy to understand way. Consistent use of these aggregate
metrics in the acute care study (Thesis Chapter 4) and the current study facilitated indirect comparison of the relative effectiveness of different types of ASP interventions (i.e. SHSC with active PAF compared to SHSC ASP without PAF).

However, this exploratory study also has several limitations. Many of these limitations relate to its quasi-experimental design. Although the ITS is a robust longitudinal design, the results of this study do not definitively establish a causal relationship between the acute care SHSC PAF-ASP and the improvements in LTCF-ARO and LTCF-MDRO trends that were found. Significant improvements in these trends were detected, but attributing these improvements to the passive components of the acute care ASP is based on a number of unproven and untested assumptions.

The first assumption is that LTCF prescribers were aware of the acute ASP policies, practices, and resources and used them to inform the prescribing of antibiotics to LTCF patrons. Previous research by the SHSC AS group\textsuperscript{9,77} demonstrated improvements in prescribing process outcomes associated with the PAF component of the program (i.e. number of antibiotic prescriptions assessed by the AS pharmacist and recommendations to optimize therapy accepted by the most responsible physician), but this type of data does not exist for the passive elements of the SHSC ASP. Similarly, there is no data demonstrating that the ASP-associated improvement in LTCF-AMR trend is paralleled by an ASP-associated improvement in LTCF AMU. Paralleled improvements in acute care AMR and AMU (as described in Chapter 4 and Chapter 5) strengthen the causal inferences of the acute care findings. Demonstrating an ASP-associated improvement in LTCF AMU would have strengthened the LTCF AMR findings, but collecting and analyzing trends concurrent trends in LTCF AMU was outside the scope of this exploratory study. This remains an opportunity for future research.

Another assumption is that the resistance seen among “LTCF”-acquired pathogens is reflective of LTCF prescribing practices and LTCF AMU. LTCF-acquired isolates were defined as isolates collected from LTCF patrons greater than 48 hours after admission to the LTCF; however, the 48-hour cut-off is somewhat arbitrary and has been criticized as over-estimating rates of other healthcare-associated infections\textsuperscript{150,151}. LTCF patrons are transferred to the adjacent acute care centre when they develop more severe illnesses, and it is possible that post-intervention period improvements in LTCF-ARO and LTCF-MDRO trends are artifacts of PAF-attributable
reductions in antibiotic exposure during acute care admissions. Unfortunately, testing the effect of this potential confounding factor (i.e. admission to the acute care facility in the period immediately preceding isolate collection) would have required data extraction from an independent database and complex analytical procedures that were outside the scope of this exploratory study. Therefore, this potential confounding remains a major limitation of this study.

The risk of Infection Prevention and Control (IPC) interventions confounding the results is another limitation. Two IPC interventions were introduced to the LTCF during the defined study period: (a) Implementation of the SHSC Hand Hygiene (HH) Campaign in November 2007, and (b) the installation of Vernacare human waste management system in 2013. The current design does not control for the potential impact of these interventions. The 36% decrease in the post-intervention period *S. aureus* unadjusted RRR is a possible signal of a HH Campaign effect, as IPC interventions would be expected to impact the incidence and transmission of this species more than others. However, confounding related to HH campaign implementation was tested in the acute care AMR study (Thesis Chapter 4), and the HH campaign did not affect the direction of the effects. The exclusion of screening isolates (i.e. only non-duplicate clinical isolates were included in this analyses) and the low prevalence of gram-positive isolates (21%) also help guard against IPC intervention confounding to some degree (i.e. since the IPC interventions introduced were more likely to affect gram positives). Nonetheless, further investigation to characterize the resistance trends of individual species and/or groups of species would be an interesting avenue of future research.

Although confounder- and assumption-related bias remain possibilities, attempting to correct or control these factors was outside the scope of this exploratory study. Indeed, no hypothesis regarding the presence or direction of an ASP-associated effect was proposed given the exploratory nature of this study, and many confounders were identified after the analyses were complete and direction of the effect identified. This study detected improvement in LTCF-AMR trends associated with implementation of the acute care ASP, but threats to internal validity limit the degree of causal attribution. That being said, detecting a more tempered reduction in AMR in a population exposed to passive elements of an ASP, and a more pronounced reduction in AMR in a population exposed to both passive and active elements of the same ASP, is consistent with the notion that passive ASP strategies (i.e. education, guidelines, etc.) are less effective than
active ASP strategies (i.e. PAF) for altering antibiotic prescribing behaviors and improving AMU and AMR\textsuperscript{2,3,74}. Research is an iterative process, and the need for ecologic and/or interventional studies describing the trends in LTCF AMR has been described\textsuperscript{139,140}. Therefore, this study is an exciting first step and preliminary contribution to this field, and the results and limitations identified can be used to inform future research in this area and AS research overall.

6.6 Conclusion

Implementation of the acute care SHSC ASP was associated with significant improvements in the trends of ARO and MDRO in the adjoining LTCF, suggesting an indirect or “trickle-down” effect of the passive strategies of this ASP. The tempered effect on LTCF-AMR, compared to the more pronounced effect on acute care AMR outcomes, is consistent with the postulated effectiveness of passive versus active AS interventions for changing antibiotic prescribing behaviors and resultant rates of AMU and AMR. However, the exploratory design and presence of potential confounding factors limit the degree of causal inference.
Chapter 7
Discussion of Thesis Research Findings
7 Discussion of Thesis Research Findings

7.1 Preface

The preceding chapters discussed the methods and findings for the three studies conducted to evaluate the impact of the Sunnybrook Health Sciences Centre (SHSC) prospective audit-and-feedback (PAF) antimicrobial stewardship program (ASP) on the burden of antimicrobial resistance (AMR) in the acute care facility (Chapter 4; primary thesis objective), the use of systemic antibiotics in the acute care inpatient population (Chapter 5; secondary thesis objective), and burden of AMR in the adjoining long-term care facility (LTCF) (Chapter 6; tertiary thesis objective).

This chapter summarizes the main findings, discusses their collective significance, and describes the major strengths and limitations of this research.

7.2 Summary of Thesis Findings

SHSC implemented a multidisciplinary ASP in at the Bayview Site acute care facility on October 1st, 2009. The core activity of the ASP is an “active” PAF intervention, wherein the AS team independently reviews acute care inpatient orders for “targeted” (TGD) antibiotics and provides suggestions to optimize therapy to the primary care team. The program also has several “passive” elements that complement the active PAF core, including antibiotic use policies, educational initiatives, an online SHSC Antimicrobial Handbook App, and many other elements.

Interrupted time series (ITS) Poisson regression models were used to evaluate the changes in the rates of hospital-acquired (HA-) and community-acquired (CA-) resistant bacterial pathogens in the acute care facility, rates of antimicrobial use (AMU) in the acute care facility, and rates of LTCF-acquired resistant pathogens in the LTCF in relation to SHSC PAF-ASP implementation. The main findings for each study are summarized in Table 7-1. For the acute care AMR and AMU studies, results for the base-case model and the sensitivity model with the 23-month abbreviated pre-intervention period were included in Table 7-1 (i.e. “Sensitivity Model #5” for the acute care AMR study; “Sensitivity Model” for the acute care AMU study). Figure 7-1 provides a visual summary of the findings and includes the time series plots for each study.
Table 7-1. Inferential statistics for major study outcomes.
Data presented includes relative reduction in post-intervention period incidence (Post-Period RRR), pre-intervention period trend (Trend\textsubscript{pre}) and post-intervention period trend (Trend\textsubscript{post}).

<table>
<thead>
<tr>
<th></th>
<th>Post-Period RRR</th>
<th>Trend\textsubscript{pre}</th>
<th>Trend\textsubscript{post}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% reduction/post-period</td>
<td>p-value</td>
<td>%Δ incidence/month</td>
</tr>
<tr>
<td>HA-ARO\textsubscript{Base}</td>
<td>9.3%</td>
<td>0.0278</td>
<td>+0.5%</td>
</tr>
<tr>
<td>HA-ARO\textsubscript{sens5}</td>
<td>16.2%</td>
<td>0.0097</td>
<td>+1.2%</td>
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<tr>
<td>HA-MDRO\textsubscript{Base}</td>
<td>12.6%</td>
<td>0.1319</td>
<td>+1.0%</td>
</tr>
<tr>
<td>HA-MDRO\textsubscript{sens5}</td>
<td>25.3%</td>
<td>0.0089</td>
<td>+1.4%</td>
</tr>
<tr>
<td>CA-ARO\textsubscript{Base}</td>
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<td>&lt;0.0001</td>
<td>+0.4%</td>
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<tr>
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<td>3.3%</td>
<td>0.7573</td>
<td>+1.3%</td>
</tr>
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<td>CA-MDRO\textsubscript{Base}</td>
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<td>&lt;0.0001</td>
<td>+0.9%</td>
</tr>
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<td>CA-MDRO\textsubscript{sens5}</td>
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<td>&lt;0.0001</td>
<td>+2.3%</td>
</tr>
<tr>
<td>TGD use\textsubscript{Base}</td>
<td>2.1%</td>
<td>0.7288</td>
<td>+0.7%</td>
</tr>
<tr>
<td>TGD use\textsubscript{sens}</td>
<td>12.3%</td>
<td>0.023</td>
<td>+0.2%</td>
</tr>
<tr>
<td>NTGD use\textsubscript{Base}</td>
<td>7.1%</td>
<td>0.2163</td>
<td>+0.2%</td>
</tr>
<tr>
<td>NTGD use\textsubscript{sens}</td>
<td>0.6%</td>
<td>0.9220</td>
<td>-0.8%</td>
</tr>
<tr>
<td>TTL use\textsubscript{Base}</td>
<td>6.2%</td>
<td>0.2219</td>
<td>+0.4%</td>
</tr>
<tr>
<td>TTL use\textsubscript{sens}</td>
<td>-0.8%</td>
<td>0.9040</td>
<td>+0.3% (&lt;0.0001)</td>
</tr>
<tr>
<td>LTCF-ARO</td>
<td>-7.0%</td>
<td>0.3023</td>
<td>+0.5%</td>
</tr>
<tr>
<td>LTCF-MDRO</td>
<td>-2.8%</td>
<td>0.8539</td>
<td>+0.5%</td>
</tr>
</tbody>
</table>

Values in black font indicate no clinically or statistically significant change; values in red font indicate statistically significant increases; values in green font represent statistically significant decreases; values in blue font represent clinically significant decreases with p>0.05.
Figure 7-1. Trends in acute care antibiotic resistance, acute care antibiotic use, and long-term care antibiotic resistance at Sunnybrook Health Sciences Centre (SHSC).

**Panel A.** Trends in the monthly incidence of hospital-acquired antibiotic-resistant organism (HA-ARO, BLUE LINE) and community-acquired antibiotic-resistant organism (CA-ARO, RED LINE) at SHSC acute care facility across the 14-year base case study period (84-month pre-intervention period; 84-month post-intervention period). Monthly incidence is shown as an aggregate count standardized by 10,000 patient days (# ARO/10,000 PD). The pivots in HA-ARO trend coinciding with implementation of the SHSC prospective audit-and-feedback antimicrobial stewardship program (PAF-ASP) (BLACK ARROW) suggest that PAF-ASP implementation was associated with improvements in HA-ARO rates. The continued upward trajectory of CA-ARO post-PAF-ASP implementation suggests no PAF-ASP-associated improvement in CA-ARO rates.

**Panel B.** Trends in the monthly incidence of hospital-acquired multidrug-resistant organisms (HA-MDRO, GREEN LINE) and community-acquired multidrug-resistant organisms (CA-MDRO, ORANGE LINE) at SHSC acute care facility across the 14-year base case study period (84-month pre-intervention period; 84-month post-intervention period). Monthly incidence is shown as an aggregate count standardized by 10,000 patient days (# MDRO/10,000 PD). The pivots in HA-MDRO trend coinciding with implementation of the SHSC PAF-ASP (BLACK ARROW) suggest that PAF-ASP implementation was associated with improvements in HA-MDRO rates. The continued upward trajectory of CA-MDRO post-PAF-ASP implementation suggests no PAF-ASP-associated improvement in CA-MDRO rates.

**Panel C.** Trends in monthly targeted (TGD, GREEN LINE), non-targeted (NTGD, RED LINE), and total (TTL, BLUE LINE) antibiotic use at the SHSC acute care facility for the 14-year base case study period (84-month pre-intervention period; 84-month post-intervention period). Antibiotic use is shown in days of therapy standardized by 10,000 patient days (# DOT/10,000 PD). The pivots in TGD, NTGD, and TTL coinciding with implementation of the SHSC PAF-ASP (BLACK ARROW) suggest that PAF-ASP implementation was associated with improvements in the trend of inpatient antibiotic use.

**Panel D.** Trends in the monthly incidence of long-term care facility (LTCF)-acquired antibiotic-resistant organism (LTCF-ARO, BLUE LINE) and multidrug resistant organisms (LTCF-MDRO, GREEN LINE) at the SHSC LTCF across the 14-year study period (84-month pre-intervention period; 84-month post-intervention period). Monthly incidence is shown as an aggregate count standardized by 10,000 patient days (# LTCF-ARO/10,000 PD; # LTCF-MDRO/10,000 PD). The stabilization of the LTCF-ARO trend and LTCF-MDRO trend coinciding with implementation of the SHSC antimicrobial stewardship program (ASP) (BLACK ARROW) suggest that PAF-ASP implementation was associated with improvements in the trajectory of resistance.
7.2.1 Acute Care Facility Antimicrobial Resistance (AMR)

Over 54 thousand unique bacterial isolates were identified. Isolates were classified as antibiotic-resistant organisms (ARO) and multidrug-resistant organisms (MDRO) based on the susceptibility profile reported at the time of collection. Clinically and statistically significant improvements in the incidence and trend of HA-ARO were detected for all base-case and sensitivity model conditions (Post-Period RRR$_{HA-ARO}$ range = 9.3% to 16.2% reduction/post-period; p-value range = <0.0001 to 0.0377). Results from the Trend models supported these findings, and statistically significant “pivots” in HA-ARO trend associated with PAF-ASP implementation were found for all base-case and sensitivity scenarios. Monthly HA-ARO trends were consistently positive in all pre-intervention period models (Trend$_{HA-ARO,pre}$ range = +0.1% to +1.2% incidence/month; p-value range = <0.0001 to 0.0507), suggesting the monthly HA-ARO burden was increasing in the absence of a dedicated ASP. Monthly HA-ARO trends were consistently negative in all post-intervention period models (Trend$_{HA-ARO,post}$ range = -0.02% to -0.2% incidence/month; p-value <0.0001 for all scenarios), suggesting the monthly HA-ARO burden started to decrease with the PAF-ASP in place.

Clinically significant improvements in the incidence of HA-MDRO were detected in the majority of scenarios (i.e. Base-case, Sens2, Sens3, Sens5 models) (Post-Period RRR$_{HA-MDRO}$ range = 12.6% to 25.3% reduction/post-period; p-values 0.0089 to 0.1319), with a statistically significant improvement being detected in Sens5 model (Post-Period RRR$_{HA-MDRO,Sens5}$ = 25.3% reduction/post-period; p = 0.0089. The exception was Sens4 model. This model included 2 additional predictors in the regression equation (mean monthly length of stay (LOS), and monthly positive culture rate) and found no change in HA-MDRO incidence (RRR$_{HA-MDRO,Sens4}$ = -1.4% reduction/post-period, p=0.8877). However, all Trend models (including the Trend model for Sens4), detected statistically significant “pivots” in the trajectory of HA-MDRO from the pre- to the post-intervention period (Trend$_{HA-MDRO,pre}$ range = +0.1% to +1.4% incidence/month, p-values <0.0001 for all scenarios; Trend$_{HA-MDRO,post}$ range = -0.3% to -0.4% incidence/month, p-values <0.0001 for all scenarios). These pivots demonstrate that the PAF-ASP implementation was associated with a consistently positive effect on HA-MDRO and prevented increases that would have occurred had the pre-intervention period trend continued unopposed.
CA-ARO and CA-MDRO analyses evaluated changes in the burden AMR in a population completely unexposed to the SHSC acute care ASP. Results suggest that significant increases in AMR occurred in the absence of a dedicated ASP. Clinically and statistically significant increases in CA-ARO incidence (i.e. the control outcome for HA-ARO) were detected for the majority of scenarios (i.e. Base-case, Sens2, Sens3, Sens4) (Post-Period RRR\textsubscript{CA-ARO} range = -25.6% to -40.4% reduction/post-period; p<0.0001 for all). The exception was the Sens5 model. This model utilized an abbreviated 23-month pre-intervention period and found no change in CA-ARO incidence (RRR\textsubscript{CA-ARO,Sens5} = 3.3% reduction/post-period, p=0.7573). However, all HA-ARO exhibited the largest decrease in the Sens5 scenario. Furthermore, all CA-ARO Trend analyses confirmed increasing rates of CA-ARO in both the pre- and post-intervention periods, suggesting the monthly CA-ARO burden continued to increase in the absence of a dedicated PAF-ASP (\text{Trend\textsubscript{CA-ARO,pre}} range = +0.4% incidence/month to +1.3% incidence/month, p-values <0.001 for all conditions; \text{Trend\textsubscript{CA-ARO,post}} = +0.5% incidence/month, p<0.0001 for all conditions). The findings for CA-MDRO (i.e. the control outcome for HA-MDRO) were similar to CA-ARO: CA-MDRO incidence increased significantly in the post-intervention period of all convergent models (i.e. Base-case, Sens5) (Post-Period RRR\textsubscript{CA-MDRO} range = -41.1% to -68.7% reduction/post-period, p<0.0001 for all), and CA-MDRO trend continued on an upward trajectory throughout the post-intervention period in all scenarios (\text{Trend\textsubscript{CA-MDRO,post}} = +0.4% to +0.5% incidence/month, p<0.0001 for all conditions).

7.2.2 Acute Care Facility Antimicrobial Use (AMU)

Data was extracted for over 1 million individual antibiotic days of therapy (DOT). These DOT were classified as TGD or “non-targeted” (NTGD) AMU. TGD agents were audited by the AS team. NTGD agents were not directly audited by the AS team. Total (TTL) AMU was the sum TGD and NTGD AMU. Implementation of the SHSC PAF-ASP was consistently associated with significant improvement in the trend of TGD AMU in both the base-case and sensitivity model conditions: Rates of TGD AMU were found to be increasing in the pre-intervention period (\text{Trend\textsubscript{TGD,pre}} range = +0.2% to +0.7% incidence/month, p<0.0001 to 0.0007), which “pivoted” to become decreasing trends in the post-intervention period (\text{Trend\textsubscript{TGD,post}} = -0.02% incidence/month with p<0.0001 for all cases). A statistically significant 12.3% reduction in post-period TGD AMU incidence was found in the sensitivity model (Post-Period RRR\textsubscript{TGD,sens} =

12.3% reduction/post-period, p=0.0296). This sensitivity model utilized a 23-month pre-intervention period (as opposed to the base-case 84-month pre-intervention period) to be more consistent with the pre-intervention periods used in existing literature. No change in TGD AMU incidence was found in the base-case model (Post-Period RRR_{TGD,base} = 2.1% reduction/post-period, p=0.7288), but the “pivot” in TGD AMU trend strongly suggests that PAF-ASP implementation positively impacted overall use. An explanation for this finding is that pre-intervention increases and post-intervention decreases in TGD AMU mirrored each other very closely to produce a negligible “net” effect.

No PAF-ASP associated changes in the incidence of NTGD AMU or total (TTL) AMU were detected (Post-Period RMR_{NTGD} range = 0.6% to 7.1% reduction/post-period, p-values 0.2163 to 0.9261; Post-Period RMR_{TTL} range = 6.2% to -0.8% reduction/post-period, p-values 0.2219 to 0.9040). This was anticipated as the SHSC PAF-ASP specifically intervenes on TGD agents. The absence of Post-Period RRR_{NTGD} and Post-Period RRR_{TTL} changes are positive finding since TGD and TTL AMU were included as balancing metrics for TGD use. The lack of change in overall NTGD AMU and TTL AMU incidence demonstrates that the PAF-ASP did not “squeeze the balloon” to increase prescribing of non-audited agents in a significant manner. This further supports the beneficial role of the institutional PAF-ASP.

Results of the Trend analyses supported the incidence analyses and suggested that the PAF-ASP had either a positive or neutral effect on NTGD and TTL AMU.

7.2.3 Long-term Care Facility (LTCF) Antimicrobial Resistance (AMR)

Approximately five thousand unique bacterial isolates were identified and classified as LTCF-acquired ARO and MDRO based on the susceptibility profile reported at the time of collection. No statistically significant differences in the overall incidence of LTCF-ARO and LTCF-MDRO were detected (Post-Period RRR_{LTCF-ARO} = -7.0% reduction/post-period, p=0.3023; Post-Period RRR_{LTCF-MDRO} = -2.8% reduction/post-period, p=0.8539). However, statistically significant improvements in the trends of LTCF-ARO and LTCF-MDRO relative to SHSC PAF-ASP implementation were found. Positive baseline or secular trends in monthly LTCF-ARO and LTCF-MDRO rates were detected in the pre-intervention period (Trend_{LTCF-ARO,pre} = +0.5% incidence/month, p<0.0001; Trend_{LTCF-MDRO,pre} = +0.5% incidence/month, p<0.0001), suggesting
that the burden of AMR in the LTCF was increasing prior to PAF-ASP implementation. Implementation of the acute care PAF-ASP was associated with a stabilization or elimination of the pre-intervention period trend, such that no positive or negative trends were detected in the post-intervention period (\(\text{Trend}_{\text{LTCF-ARO,post}} = -0.01\% \text{ incidence/month, p}=0.1409; \text{Trend}_{\text{LTCF-ARO,post}} = -0.02\% \text{ incidence/month, p}=0.1232\)). The transition from an increasing trend to the absence of a trend (i.e. flat trend) is consistent with an acute care facility PAF-ASP-associated improvement in the LTCF AMR and a possible indirect or “trickle-down” effect of the acute care program.

Although the core component of the SHSC PAF-ASP—active post-prescription review antibiotic orders by a dedicated stewardship pharmacist—was restricted to the acute care facility during the defined study period, it is possible that LTCF prescribers were exposed to the passive elements and/or activities associated with the acute care ASP, and that this exposure positively influenced prescribing, AMU, and AMR in the LTCF. The tempered effect on LTCF AMR outcomes (i.e. elimination of increasing secular trend without any change in overall incidence) and the more pronounced effect on acute care AMR outcomes (pivoting of trend and reductions in overall incidence) is in keeping with the postulated effectiveness of passive versus active AS interventions (i.e. active AS strategies being more effective for changing antibiotic prescribing behaviors, and resultant rates of AMU and AMR). However, the exploratory design and presence of potential confounding factors limits the strength of the causal inferences drawn from LTCF findings.

7.3 Strengths and Significance of Thesis Findings

Reducing AMR is a major incentive for ASPs. However, there remains a paucity of high quality data describing the impact ASPs on hospital AMR, and the lack of high-quality AMR outcome data has been cited as a barrier to program support\(^{136}\). To the best of this writer’s knowledge, this thesis is the first research to evaluate the impact of an acute care ASP on the institutional burden of AMR using robust methodology. Strengths of this research include the use of comprehensive ITS Poisson regression models and the prolonged 14-year study period. The ITS is an EPOC-approved study design able to infer causality\(^{81}\). It is particularly well-suited for assessing the effects of population-level interventions over time and is commonly applied in situations where a
randomized trial is not practical or feasible. Therefore, the ITS design was well-suited for the objective and nature of this thesis research. The ITS design minimizes threats to internal validity by incorporating a historic control group into the analysis (i.e. pre-intervention period) and requiring multiple observations be reported for both the pre- and post-intervention period groups\textsuperscript{142}. The extended 14-year (168-month) study period provided a sufficient number of observations to characterize baseline data trends, to control for potentially confounding systematic variation, and to examine the sustainability of PAF-ASP intervention effects.

Additional strengths of this thesis research include its large and complete dataset, the concurrent assessment of AMR and AMU outcomes, the assessment of possible confounders, and the multiple relevant sensitivity analyses conducted. Confirming that the observed reductions in institutional HA-AMR coincided with reductions in institutional AMU enhanced the validity of the HA-AMR findings. A significant amount of effort was put forth to control for potential confounders, including autocorrelation, hospital bed-occupancy, seasonal variations, patient length of stay, culture requisition rate, and outcome definition assumptions. This is the first study to consider many of these factors and incorporate them into the analyses. The consistency in the direction of base-case and sensitivity model effects strengthens the validity of the primary research findings.

This research was designed to meet the Cochrane Effective Practice, Organisation of Care (EPOC) Group high quality standards outlined in Appendices 1-4, which include the EPOC minimum study design criteria\textsuperscript{81}, the Cochrane methodological risk bias criteria\textsuperscript{89}, and the EPOC microbial risk of bias criteria\textsuperscript{4,5}. The use of an ITS design meets the study design criteria\textsuperscript{81}. As per this writer’s assessment, the HA-ARO and HA-MDRO findings are at low risk of microbial and methodological bias. The HA-AMR study scored “low risk” on all 7 items on the methodological risk of bias criteria\textsuperscript{89}: (1) the intervention occurred independently of other changes; (2) the point of analysis is the point of intervention; (3) the intervention was unlikely to affect data collection; (4) the outcomes were objective; (5) there is no missing data that could potentially bias the results; (6) there is no evidence of selective outcome reporting; and (7) other potential sources of bias were addressed to minimize the risk of confounding. Additional details regarding the application of the methodological risk of bias criteria to the HA-AMR study are provided in Table 7.2. Furthermore, the HA-AMR study also scored “low risk” on all 3 items on
the microbial risk of bias criteria\textsuperscript{4,5}: (1) a clear case definition was provided; (2) the intervention assessed was a planned intervention; and (3) there were no changes in practice coincident with PAF implementation. Additional details regarding the application of the microbial risk of bias criteria to the HA-AMR study are provided in Table 7.3. The AMU outcomes for the acute care facility have similarly low risk of methodological bias. The CA-AMR findings are at somewhat higher risk of bias given the reduced certainty regarding confounding exposures. The LTCF-AMR study has a higher risk of bias given the reduced certainty regarding the extent of intervention exposure, outcome metric validity, and reduced control of potential confounders.

Two other studies have reported ASP-mediated AMR effects with low risk of methodological and microbiologic bias\textsuperscript{82,83}. However, these studies reported on a narrow spectrum of resistance profiles (i.e. MRSA\textsuperscript{82} and \textit{E.coli} resistance to ciprofloxacin, cefuroxime, ceftazidime, trimethoprim-sulfamethoxazole, and tobramycin\textsuperscript{83}) over a relatively short time period (i.e. 1-2 years post-ASP implementation). Additionally, these studies failed to address potential confounders (i.e. seasonality) and did not validate their findings in control populations unexposed to the ASP intervention. This detailed body of thesis research was designed to avoid these limitations. This thesis research used novel composite AMR metrics to examine the impact of the SHSC PAF-ASP on the collective susceptibility of over 15 bacterial pathogens to over 15 antimicrobial agents. The effect of underlying assumptions and potential confounders were tested in various sensitivity analyses. AMU, CA-AMR, and LTCF-AMR outcomes were concurrently assessed to increase the internal validity of the primary HA-AMR findings, and use of an extended post-intervention period (84-month) shows the sustainability of any PAF-ASP mediated effects.
Table 7-2. Application of the interrupted time series risk of methodological bias tool to the hospital-acquired antibiotic resistant organism (HA-ARO) and hospital-acquired multidrug-resistant organism (HA-MDRO) outcomes

<table>
<thead>
<tr>
<th>Item</th>
<th>Criteria described in the Cochrane Effective Practice and Organisation of Care (EPOC) Resources for Review Authors website(^a)</th>
<th>Score</th>
<th>Score Justification</th>
</tr>
</thead>
</table>
| Intervention independent of other changes | • Score “Low risk” if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. If Events/variables identified, note what they are  
  • Score “High risk” if reported that intervention was not independent of other changes in time. | Low risk    | • The intervention occurred independently of other changes (i.e. no major changes to Infection Prevention and Control (IPC) or Antibiotic Stewardship policies and procedures occurring identified within 22 months of PAF implementation were identified by the IPC team)  
  • Implementation of the Hand Hygiene program in November 2007 addressed in sensitivity analyses; internal data indicates rates of Hand Hygiene compliance stable from November 2007 to September 2016 |
| Shape of the intervention effect pre-specified | • Score “Low risk” if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention.  
  • Score “High risk” if it is clear that the condition above is not met | Low risk    | • The point of analysis (October 2009) is the point of intervention (October 2009)                                                                                                                                 |
| Intervention unlikely to affect data collection | • Score “Low risk” if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention)  
  • Score “High risk” if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported) | Low risk    | • The intervention was unlikely to affect data collection as all data was retrospective in nature and was extracted from the Microbiology Database                                                                 |
| Knowledge of the allocated interventions adequately prevented during the study | • Score “Low risk” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors  
  • Score “High risk” if the outcomes were not assessed blindly.  
  • Score “Unclear risk” if not specified in the paper | Low risk    | • The outcomes were objective (i.e. count of resistant bacteria isolated each month; resistance determined by Microbiology Laboratory)                                                                                   |
### Table 7-2 (continued). Application of the interrupted time series risk of methodological bias tool to the hospital-acquired antibiotic resistant organism (HA-ARO) and hospital-acquired multidrug-resistant organism (HA-MDRO) outcomes

<table>
<thead>
<tr>
<th>Item</th>
<th>Criteria described in the Cochrane Effective Practice and Organisation of Care (EPOC) Resources for Review Authors website[^9]</th>
<th>Score</th>
<th>Score Justification</th>
</tr>
</thead>
</table>
| Incomplete outcome data adequately | • Score “Low risk” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result)  
  • Score “High risk” if missing outcome data was likely to bias the results.  
  • Score “Unclear risk” if not specified in the paper (Do not assume 100% follow up unless stated explicitly) | Low risk | • The robust, retrospective data extraction process makes it extremely unlikely that isolates meeting ARO or MDRO criteria were “missed” (i.e. data for all clinical isolates for all target species that were isolated in the Microbiology lab between October 2002 and September 2016 were extracted from the Microbiology Database)  
  • Emergently resistant bacteria not captured by the study ARO and MDRO definitions would have been equally “missed” in both the pre- and post-intervention periods, and are therefore unlikely to bias the results |
| Selective outcome reporting       | • Score “Low risk” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section)  
  • Score “High risk” if some important outcomes are subsequently omitted from the results  
  • Score “Unclear risk” if not specified in the paper. | Low risk | • There is no evidence of selective outcome reporting (i.e. outcomes reported in this thesis were consistent with the outcomes identified in the Research Ethics Board submission) |
| Other risks of bias               | • Score “Low risk” if there is no evidence of other risk of biases. E.g. should consider if seasonality is an issue (i.e. if January to June comprises the pre-intervention period and July to December the post, could the “seasons’ have caused a spurious effect) | Low risk | • Other potential sources of bias were addressed to minimize the risk of confounding (i.e. bed-occupancy, seasonality, Infection Prevention and Control interventions, etc.). |
Table 7-3. Application of the risk of microbial bias criteria to the hospital-acquired antibiotic resistant organism (HA-ARO) and hospital-acquired multidrug-resistant organism (HA-MDRO) outcomes

<table>
<thead>
<tr>
<th>Item</th>
<th>Criteria as described in the 2017 Cochrane Effective Practice and Organisation of Care (EPOC) systematic review on antimicrobial stewardship programs⁴,⁵</th>
<th>Score</th>
<th>Score Justification</th>
</tr>
</thead>
</table>
| Case definition             | • Score as ‘low’ if there is a clear definition either of infection or of colonisation and there were no major changes in laboratory diagnostic methods during the study period | Low risk | • Clear case definition that specified specimen type (clinical isolates), bacterial species, and criteria for ARO and MDRO classification  
• Specific agents tested on antibiotic panels and MICs changed during the study period; however, the Microbiology Team did not identify any major changes in laboratory diagnostic methods that would have affected case classification over the study period (i.e. AROs were consistently classified as isolates resistant to at least one therapeutically active antibiotic agent as per CLSI guidelines active at the time of testing; MDROs were consistently classified as isolates resistant to at least three therapeutically active antibiotic classes as per CLSI guidelines active at the time of testing) |
| Planned intervention        | • Score as ‘low’ if the intervention was planned to reduce endemic rates of colonisation or infection and was not implemented in response to an outbreak. Regression to the mean following an outbreak is an important risk of bias for estimates of the effect of interventions in ITS studies of infection. | Low risk | • The intervention assessed was a planned intervention to determine the effectiveness and feasibility of using a PAF strategy to improve inpatient antibiotic use                                                                                                                                                                                              |
| Other infection control measures | • Score as ‘low’ if infection control practices (IPC; hand hygiene, gowning, or other personal protection) and isolation or cohorting policies are described and there were no changes coincident with the intervention to change antibiotic prescribing | Low risk | • No changes in IPC practice coincident with PAF implementation were identified by the IPC Team  
• The IPC Team identified implementation of the Hand Hygiene program in November 2007 as potential confounder (which was addressed in sensitivity analyses), but were not able to definitively identify or provide reliable data or implementation dates for any other potential changes (i.e. i.e. no dates or details regarding any major changes in personal protection, environmental cleaning, or other IPC policies or procedures were identified). Therefore, it was not possible to address such changes in the analyses.  
• A thorough description of IPC practices across the 14-year study period was not provided as no changes in practice coincident with PAF implementation were identified |
Exposure to the comprehensive SHSC PAF-ASP was associated with significant and sustained improvements in acute care facility AMR. In the 84-month period following PAF-ASP implementation, the burden of HA-ARO and HA-MDRO decreased by 9.3% (p=0.0278) and 12.6% (p=0.1319), respectively. Differences equal or greater than 10% were deemed clinically significant. The consistent “pivot” in HA-ARO and HA-MDRO trends, and the concordant improvement in acute care inpatient TGD AMU, enhance the validity of the AMR findings and support the biological plausibility of the AS hypothesis (i.e. ASP-associated reductions in AMU remove the selective pressure favouring the persistence of ARO and incur reductions in ARO prevalence).

The causal inference of the SHSC acute care PAF-ASP curbing development of HA-AMR is strengthened by the significant increases that were detected in corresponding CA-AMR outcomes (i.e. 40.4% increase in CA-ARO post-period burden, p<0.0001; 68.7% increase in CA-MDRO post-period burden, p<0.0001), and attenuated effects in corresponding LTCF-AMR outcomes (i.e. 7.0% non-significant increase in LTCF-ARO post-period burden, p=0.3023; 2.8% non-significant increase in LTCF-MDRO post-period burden, p=0.8539). The CA-ARO and CA-MDRO findings can be used to infer the AMR change that occurred in the absence of a dedicated ASP (i.e. the complete absence of the SHSC PAF-ASP resulted in a significant increase in the overall post-period burden of resistance). The LTCF-ARO and LTCF-MDRO findings can be used to infer the change in AMR attributable to the passive elements of the SHSC ASP (i.e. the SHSC ASP without PAF curbed any statistically significant increase in AMR but was not able reduce the pre-existing burden). Based on these findings, it is reasonable to conclude that the PAF intervention is driving the reductions in HA-AMR.

The number of HA-ARO and HA-MDRO infections prevented by the SHC PAF-ASP in the 2016-2017 fiscal year can be estimated by multiplying the unadjusted ARR_{HA-ARO} (10/10 000 PD) and unadjusted ARR_{HA-MDRO} (7/10 000 PD) rates provided in Thesis Section 4.5.1 by the SHSC annual bed occupancy rate (219 817 PD\textsuperscript{10}). These calculations suggest that 220 HA-ARO infections and 154 HA-MDRO infections were avoided. Maslikowska et al\textsuperscript{156} used SHSC data to compare the differences in healthcare costs and risk of mortality between MDRO and non-MDRO infections. MDRO infections incurred an additional $3,416 CAD (p=0.04) in healthcare costs and a 12% increase in the risk of mortality (17% mortality rate for MDRO infections vs.
5% mortality rate for non-MDRO infections; p= 0.04). Accordingly, the estimated 154 HA-MDRO infections prevented in the 2016-2017 fiscal year is associated with a cost avoidance of $526,064 CAD and saved approximately 18 lives. The limitations of these estimates are discussed in Thesis Section 7.4.

The absence of credible ASP outcome data and the operational costs associated with running more comprehensive ASPs are often cited as barriers to ASP implementation and reasons why many institution-based ASPs remain underdeveloped. Demonstrating economic feasibility and benefits to patient-care are prerequisites to leadership buy-in and the provision of ASP financial support. This research provides clear and direct evidence that SHSC PAF-ASP implementation was associated with significant and sustained improvements in the clinical burden of AMR. The estimated 18 deaths prevented and $526 064 CAD annual cost avoidance further demonstrate the benefit of this program. Other sites could use these figures to justify implementation of a PAF-ASP like the SHSC model. This research also provides evidence for which types of AS programming work best to accomplish AMR reductions, which was another limitation of AS research identified in the literature. The findings of this thesis research suggest that the SHSC PAF intervention is superior to the PRA policies and other passive AS interventions implemented at SHSC. PRA was the dominant AS strategy at SHSC prior to PAF implementation, and acute care rates of AMR and AMU increased across the pre-intervention period despite the presence of these restrictive policies. However, acute care rates of AMR and AMU decreased once the PAF-ASP was in place. Also, AMR was reduced in the acute care facility (i.e., facility exposed to the SHSC ASP with PAF), but remained static in the LTCF (i.e., facility exposed to the SHSC ASP without PAF). This suggests that PAF exposure was integral for AMR reductions to occur; however, the extent of LTCF exposure to the non-PAF ASP elements is unclear.

7.4 Limitations of Thesis Research

As previously mentioned, the quasi-experimental and retrospective nature of this research is an important limitation. Although the ITS is a robust longitudinal design, randomized controlled trials remain the gold standard for establishing causality. Like all the retrospective designs, there remains some risk of unrecognized confounders biasing the results. For this reason, the results of
this study do not definitively establish a cause-and-effect relationship between SHSC PAF-ASP implementation and the observed reductions in HA-ARO and HA-MDRO burden. However, the consistent improvements in HA-AMR, the efforts made to minimize confounding, and the direction and magnitude of CA- and LTCF-AMR effects all strengthen the likelihood of a causal relationship. Furthermore, prospective randomized controlled trials of this scale are unlikely to be conducted given the complex nature of ASP interventions, so ITS evidence provides valuable insight to the effectiveness of these programs. It is possible that changes in ARO screening policies, compliance with contact precautions, environmental cleaning practices, or microbiology lab procedures occurred during the post-intervention period and favourably biased AMR results. However, IPC and microbiology laboratory team members were not able to definitively identify any such changes or provide reliable data or implementation dates for any potential changes. Therefore, it was not possible to address such changes in the analyses.

The inability to differentiate between PAF-specific effects and the effects of supportive AS strategies introduced in the post-intervention period to compliment PAF (i.e. medical education, launch of the online SHSC Handbook App, etc.) is another limitation. However, proactive strategies (such as PAF) are known to be more effective than passive strategies for producing behavior changes\(^2,74\), and attenuated AMR effects were found in the population of ARO and MDRO collected from patients presumably exposed to the passive elements of the acute care ASP, but not PAF (i.e. LTCF patrons possibly exposed to the SHSC ASP without PAF). These findings suggest that PAF is driving the observed reductions in AMR seen in the acute care facility. Moreover, SHSC lifted the PRA restrictions on ciprofloxacin and levofloxacin use during the post-intervention period. These PRA policies had been in place for over a decade and were introduced prior October 1\(^{\text{st}}\), 2002 (i.e. the start of the pre-intervention period). Previous studies have shown that lifting PRA policies results in compensatory increases in AMU up to 399\(^\%\).\(^4\) The fact that AMU and AMR reductions were detected in the post-intervention period in spite of lifting these PRA policies further demonstrates the effectiveness of the SHSC PAF intervention.

Additional limitations have been well described in previous chapters and include the proportional nature of the Poisson regression output, the lack of information on the ASP-associated effects on ARO and AMU subgroups, and the generalizability of the results to other sites. Although
Poisson regression is the most appropriate technique for assessing changes in count-based data (i.e. number of AROs or DOTs), the effects are calculated as proportions, and, therefore, unadjusted data must be used to approximate “absolute” effects. Unadjusted ARR were used to infer that the program prevented 154 HA-MDRO infections, prevented 18 HA-MDRO-related deaths, and avoided $526,064 CAD in excess expenditures in the 2016-2017 fiscal year. Unfortunately, the precision of these estimates are limited due to the reliance on unadjusted ARR values and various other assumptions, including that the excess costs and mortality attributable to HA-MDRO are equivalent to the costs and mortality risk reported by Maslikowska et al. and that all HA-MDRO identified represent causative pathogens in active infections. Indeed, the case definitions applied for ARO and MDRO likely overestimate the rates of ARO and MDRO infections since clinical isolates from non-sterile sites were included (i.e. potentially reflecting asymptomatic colonization or carriage). In turn, since all cases of ARO and MDRO colonization and carriage are not captured, it is also likely that the aggregate AMR metrics employed in this research underestimate the total true number of emergently resistant bacteria.

Additional limitations of the AMR metrics include that the HA- and CA- criteria have not been validated for determining the time of organism acquisition, do not account for recent healthcare exposure, and do not address the possibility of prolonged ARO or MDRO carriage. Factors that limit the validity of AMU metrics and outcomes include the inability to identify and evaluate changes in the level and trend of a non-antibiotic medication as an external control, the inability to assess the appropriateness of antibiotic therapy, and the inability to assess compliance with PAF recommendations over the entire post-intervention period. Compliance rates were approximately 80% in the ICU Pilot and Ward Roll-Out studies, but process outcomes of this nature were not collected after April 2012.

Although the use of composite endpoints were strengths of this research in that they provided the power necessary to detect statistically significant differences in AMR outcomes and characterized the macro-level effects of the ASP, a limitation of this strategy was the lack of information regarding the effects on specific ARO and AMU subgroups (i.e. genus and/or species-level changes or changes in the consumption of specific antibiotic agents). However, examining the collective changes was the objective of this research, and investigating the micro-
level effects within this data set will be an exciting avenue for future research now that global positive effects have been established.

Finally, institutional differences in ASP programming may limit the generalizability of these thesis research findings. Although the IDSA and SHEA guidelines\textsuperscript{2-3} recommend specific classes of interventions over others (i.e. PAF and/or PRA over others), there is little practical guidance on how to best structure or operationalize these interventions. Accreditation Canada’s Antimicrobial Stewardship Required Organizational Practice criteria are also purposefully general on ASP structure\textsuperscript{71}, and the result is that no two hospitals have exactly the same ASP in place. Few sites have a PAF program as comprehensive as that at SHSC, and for this reason the transferability of the SHSC PAF-ASP findings may be limited. Nonetheless, other centres hoping to reduce AMU and AMR could use these thesis research findings to justify implementation of PAF-ASPs similar to the SHSC model. Other researchers could also apply the robust yet feasible methodology described in this report to examine the impact of ASPs with different programming on AMR and AMU and generate data about the relative effectiveness of various ASP structures.

7.5 Future Research Directions

Potential directions for future research that have been discussed in previous sections of this thesis include the following: (a) characterizing the impact of the PAF-ASP on specific ARO subgroups (i.e. genus and/or species-level changes) or specific bug-drug sensitivity profiles, (b) characterizing the impact of the PAF-ASP on specific antibiotic agents or classes of agents, (c) cross-correlating trends in specific AMR profiles to trends in antibiotic use, and (d) characterizing the impact of the ASPs implemented in other acute care facilities to generate data about the relative effectiveness of different ASP structures. Subgroup analyses examining the impact of the SHSC PAF-ASP on isolates by specimen types (i.e. blood, urine, etc) is another opportunity. An analysis of isolates from sterile sites isolates would remove cases representing colonization from the dataset and provide a more accurate representation of the impact of the program on active ARO and MDRO infections.
Chapter 8
Conclusion
8 Conclusion

Antimicrobial resistance (AMR) is a serious global public health problem projected to claim 10 million lives by the year 2050 and cost the world economy $100 trillion USD\(^\text{35}\). Excessive and inappropriate antimicrobial use (AMU) has been a key driver of the AMR problem; therefore, promoting responsible AMU via the practice of antimicrobial stewardship (AS) was one of five fundamental strategies identified in the global action plan to combat AMR adopted by the World Health Assembly in May 2015\(^1\). AMR is particularly problematic in institutional settings; accordingly, implementation of institutional antimicrobial stewardship programs (ASPs) has been identified as a method to reduce inappropriate AMU and contain the global AMR problem\(^2\)–\(^4\).

Available evidence for institutional ASPs demonstrated positive impacts on prescribing behaviors, antimicrobial use (AMU), and drug-acquisition costs\(^4\)–\(^7\), but the effect on nosocomial AMR remained unclear. Despite an increasing body of evidence evaluating ASP initiatives, a paucity of high quality data describing the impact ASPs on resistance in hospital acquired pathogens remained\(^4\),\(^5\),\(^8\). The lack of high-quality AMR outcome data has been cited as a barrier to ASP support\(^1\)\(^36\).

This research used robust interrupted time series (ITS) models to evaluate the impact of the Sunnybrook Health Sciences Centre (SHSC) acute care prospective audit-and-feedback (PAF) ASP on institutional rates of AMR and AMU. Implementation of the SHSC PAF-ASP was associated with clinically significant and sustained reductions in the burden of AMR in the acute care facility, as measured by the 9.3% and 12.6% decreases in the incidence of hospital-acquired (HA-) antibiotic resistant organism (ARO) and HA-multidrug-resistant organisms (HA-MDRO), respectively. Concordant improvements in acute care inpatient AMU, significant increases in community-AMR, and attenuated effects on AMR the geographically adjacent long-term care facility (LTCF), were also detected. These findings support the biological plausibility of the AS hypothesis and strengthen the causal inference of the SHSC acute care PAF-ASP curbing development of HA-AMR.

This research provides high certainty evidence demonstrating the effectiveness of a comprehensive PAF-ASP for reducing institutional AMR and fills a gap in the literature. The
findings could be used to inform AS policies and guide AS best practice, and the robust yet practical methodology could be applied to future research projects to increase the body of ASP-AMR literature, validate AS theory, and further AS science.
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Appendices
# Appendix 1. Studies to be considered for inclusion in EPOC reviews

The following text is quoted from the Cochrane Effective Practice and Organisation of Care (EPOC) *Resources for Review Authors* website and describes the four study designs acceptable for inclusion in an EPOC review in their reviews (i.e. randomised trials (RT), non-randomized trials (NRT), controlled before-after (CBA), and interrupted time series (ITS)):

Randomised trials are often not available to address questions about the effects of health system interventions and implementation strategies. Consequently it is often, but not always appropriate to include a broader range of study designs in EPOC reviews.

Consideration should generally be given to four types of study designs:

- Randomised trials
- Non-randomised trials
- Controlled before-after studies
- Interrupted time series studies and repeated measures studies

There may be good reasons for not including all of these study designs. For example, controlled before-after and interrupted time series studies may add little to what is known when sufficient evidence is available from randomised trials. However, there may sometimes be compelling reasons for including study designs other than those listed above; for example, cohort studies, regression discontinuity designs, or higher order interaction designs. Inclusion of uncontrolled before-after studies or cross sectional studies is strongly discouraged. It is difficult, if not impossible to attribute causation from such studies.

Review authors should consider their specific review question in deciding which study designs to include and provide a compelling justification or rationale for this decision in the review proposal form and protocol. Where review authors propose including study designs other than randomised trials, they also need to show: that there is likely to be added value by including these other study designs; that the review team has the technical expertise to deal with any additional types of studies; and that such studies exist in relation to their review question (examples of such studies should be cited in the review proposal form and protocol). Review authors should be aware that increasing the range of study designs included in a review is likely to add considerable time to the review and that they need to have sufficient resources available to manage this additional work. The final decision on whether to include additional study designs rests with the EPOC editors.

## Randomised trials

Randomisation ensures that participants in each comparison group should differ only in their exposure to the intervention. All other factors that might affect the outcomes of interest should be distributed equally, provided there is a large enough sample size – whether they are known and measured or not.

Randomisation of individual recipients of care is not appropriate if the intervention is targeted at health care providers or groups of people. Under these circumstances, providers or clusters (groups) of people should be randomised. Trials where groups of people are allocated (or where individual health professionals are randomised and outcomes are measured in patients) are called cluster randomised trials. In these trials, the assumption of independence is violated; because people within any one cluster are more likely to respond in a similar manner (e.g. treatment of patients by a single physician is likely to be more consistent than treatment by several physicians). This lack of independence means larger sample sizes are required to adjust for the clustering effect and analysis should be undertaken at the cluster level or using special analytic techniques. In addition, when relatively few clusters are randomised other factors that might affect the outcomes of interest may not be distributed equally. This should be taken into consideration when assessing the risk of bias. Consequently, we suggest including criteria to assess whether baseline outcome measurements were similar and whether baseline characteristics were similar. (See Suggested risk of bias criteria for EPOC reviews)

## Non-randomised trials

These are trials where the investigators allocated participants to the different groups that are being compared using a method that is not random. These studies have a greater risk of bias than randomised trials (See Cochrane Handbook for Systematic Reviews of Interventions, Section 8.9.1.)

## Controlled before-after studies

In controlled before-after studies, decisions about allocation to the different comparison groups are not made by the investigators. Outcomes of interest are measured in both intervention and control groups before the intervention is introduced and again after the intervention has been introduced. These studies have a high risk of bias because there
may be unidentified differences between the intervention and control groups that may affect changes in the outcome measure.

**Interrupted time series studies**

Interrupted time series studies can provide a method of measuring the effect of an intervention when randomisation or identification of a control group are impractical. Multiple data points are collected before and after the intervention and the intervention effect is measured against the preintervention trend. There is no way to assess the impact of any concurrent events on the outcomes of interest.

**Terminology and exclusions**

We suggest using consistent terminology for different types of studies in EPOC reviews to avoid confusion and to help to ensure clear definitions and understanding. We also suggest excluding controlled studies with only one intervention or control site and ITS studies that do not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention. These suggestions are summarised in the table below.

<table>
<thead>
<tr>
<th>Suggested terminology and exclusions</th>
<th>Definition</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised trial</strong></td>
<td>An experimental study in which people are allocated to different interventions using methods that are random.</td>
<td>Studies with only one intervention or control site. For cluster randomised trials, non-randomised cluster trials, and controlled before-after studies.</td>
</tr>
<tr>
<td><strong>Non-randomised trial</strong></td>
<td>An experimental study in which people are allocated to different interventions using methods that are not random.</td>
<td>Exclusion recommend only including studies with two intervention sites and two control sites. In studies with only one intervention or control site, the intervention (or comparison) is completely confounded by study site making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables.</td>
</tr>
<tr>
<td><strong>Controlled before-after study</strong></td>
<td>A study in which observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not</td>
<td>Studies in which data collection is not contemporaneous in study and control sites during the pre- and post-intervention periods of the study and/or does not use identical methods of measurement.</td>
</tr>
<tr>
<td><strong>Interrupted time series study</strong></td>
<td>A study that uses observations at multiple time points before and after an intervention (the ‘interruption’). The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time.</td>
<td>Studies that do not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention.</td>
</tr>
</tbody>
</table>
### Appendix 2. Risk of bias tool for studies with a separate control group

The following text is quoted from the Cochrane Effective Practice and Organisation of Care (EPOC) Resources for Review Authors website and provides the suggested criteria for assessing the methodological risk of bias for randomised trials, non-randomized trials, and controlled before-after (CBA) studies (i.e. studies with a separate control group):89

Nine standard criteria are suggested for all randomised trials, non-randomised trials and controlled before-after studies. Further information can be obtained from Chapter 8: Assessing risk of bias in included studies of the Cochrane handbook.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>Unclear Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random sequence generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score “Low risk” if a random component in the sequence generation process is described (e.g. Referring to a random number table). Score “High risk” when a nonrandom method is used (e.g. performed by date of admission). Non-randomised trials and controlled before-after studies should be scored “High risk”. Score “Unclear risk” if not specified in the paper.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Allocation concealment</strong></td>
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<tr>
<td>Score “Low risk” if the unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study; or if the unit of allocation was by patient or episode of care and there was some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes were used. Controlled before-after studies should be scored “High risk”. Score “Unclear risk” if not specified in the paper.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline outcome measurements similar</strong> [1,2]</td>
<td></td>
<td></td>
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<tr>
<td>Score “Low risk” if performance or patient outcomes were measured prior to the intervention, and no important differences were present across study groups. In randomised trials, score “Low risk” if imbalanced but appropriate adjusted analysis was performed (e.g. Analysis of covariance). Score “High risk” if important differences were present and not adjusted for in analysis. If randomised trials have no baseline measure of outcome, score “Unclear risk”.</td>
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<tr>
<td><strong>Baseline characteristics similar</strong></td>
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<tr>
<td>Score “Low risk” if baseline characteristics of the study and control providers are reported and similar. Score “Unclear risk” if it is not clear in the paper (e.g. characteristics are mentioned in text but no data were presented). Score “High risk” if there is no report of characteristics in text or tables or if there are differences between control and intervention providers. Note that in some cases imbalance in patient characteristics may be due to recruitment bias whereby the provider was responsible for recruiting patients into the trial.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incomplete outcome data</strong> [1]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score “Low risk” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the intervention and control groups or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score “High risk” if missing outcome data was likely to bias the results. Score “Unclear risk” if not specified in the paper (Do not assume 100% follow up unless stated explicitly).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Knowledge of the allocated interventions adequately prevented during the study</strong> [1,3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score “Low risk” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score “High risk” if the outcomes were not assessed blindly. Score “Unclear risk” if not specified in the paper.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protection against contamination</strong></td>
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</tr>
<tr>
<td>Score “Low risk” if allocation was by community, institution or practice and it is unlikely that the control group received the intervention. Score “High risk” if it is likely that the control group received the intervention (e.g. if patients rather than professionals were randomised). Score “Unclear risk” if professionals were allocated within a clinic or practice and it is possible that communication between intervention and control professionals could have occurred (e.g. physicians within practices were allocated to intervention or control)</td>
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<tr>
<td><strong>Selective outcome reporting</strong></td>
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<tr>
<td>Score “Low risk” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score “High risk” if some important outcomes are subsequently omitted from the results. Score “Unclear risk” if not specified in the paper.</td>
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</tbody>
</table>
**Other risks of bias**

Score “Low risk” if there is no evidence of other risk of biases.

[1] If some primary outcomes were imbalanced at baseline, assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.

[2] If “Unclear risk” or “High risk”, but there is sufficient data in the paper to do an adjusted analysis (e.g. Baseline adjustment analysis or Intention to treat analysis) the criteria should be re scored as “Low risk”.

[3] This refers to blinding of participants and personnel and blinding of outcome assessment.

[4] If some primary outcomes were assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.
Appendix 3. Risk of bias tool for interrupted time series

The following text is quoted from the Cochrane Effective Practice and Organisation of Care (EPOC) Resources for Review Authors website and provides the suggested criteria for assessing the methodological risk of bias for interrupted time series studies:

Seven standard criteria are used for all interrupted time series studies. Further information can be obtained from Chapter 8: Assessing risk of bias in included studies of the Cochrane handbook.

Note: If the interrupted time series study has ignored secular (trend) changes and performed a simple t-test of the pre versus post intervention periods without further justification, the study should not be included in the review unless reanalysis is possible.

Intervention independent of other changes
Score “Low risk” if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. If Events/variables identified, note what they are. Score “High risk” if reported that intervention was not independent of other changes in time.

Shape of the intervention effect pre-specified
Score “Low risk” if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention. Score “High risk” if it is clear that the condition above is not met.

Intervention unlikely to affect data collection
Score “Low risk” if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention); Score “High risk” if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).

Knowledge of the allocated interventions adequately prevented during the study [3,4]
Score “Low risk” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score “High risk” if the outcomes were not assessed blindly. Score “Unclear risk” if not specified in the paper.

Incomplete outcome data adequately [4]
Score “Low risk” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score “High risk” if missing outcome data was likely to bias the results. Score “Unclear risk” if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

Selective outcome reporting
Score “Low risk” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score “High risk” if some important outcomes are subsequently omitted from the results. Score “Unclear risk” if not specified in the paper.

Other risks of bias
Score “Low risk” if there is no evidence of other risk of biases. E.g. should consider if seasonality is an issue (i.e. if January to June comprises the pre-intervention period and July to December the post, could the “seasons’ have caused a spurious effect).

[1] If some primary outcomes were imbalanced at baseline, assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.
[2] If “Unclear risk” or “High risk”, but there is sufficient data in the paper to do an adjusted analysis (e.g. Baseline adjustment analysis or Intention to treat analysis) the criteria should be re-scored as “Low risk”.
[3] This refers to blinding of participants and personnel and blinding of outcome assessment.
[4] If some primary outcomes were assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.
## Appendix 4. Tool to assess microbial risk of bias

The following text is quoted from the 2017 Cochrane Effective Practice and Organisation of Care (EPOC) systematic review on antimicrobial stewardship⁴ and provides the suggested criteria for assessing the microbiologic risk of bias for studies reporting microbial outcomes:

1. **Case definition**: score as 'low' if there is a clear definition either of infection or of colonisation and there were no major changes in laboratory diagnostic methods during the study period.

2. **Planned intervention**: score as 'low' if the intervention was planned to reduce endemic rates of colonisation or infection and was not implemented in response to an outbreak. Regression to the mean following an outbreak is an important risk of bias for estimates of the effect of interventions in ITS studies of infection.

3. **Other infection control measures**: score as 'low' if infection control practices (hand hygiene, gowning, or other personal protection) and isolation or cohorting policies are described and there were no changes coincident with the intervention to change antibiotic prescribing.⁴