Healthcare-associated bloodstream infections (HABSI) in Quebec after the establishment of BACTOT, a hospital-wide provincial HABSI surveillance program.

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November 2018

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of

Master of Science

Acknowledgements

This thesis would not have been possible without Dr. Caroline Quach's continuous and constructive guidance. Her expertise in the fields was invaluable. She created an environment that encouraged critical and creative thinking that fueled my work. I am continually inspired by her steadfastness and incredible work ethic.

Sincere thanks to Dr. Élise Fortin for her support from beginning to end. The opportunities she has made available to me were integral to the development of this thesis. Her advice, both academic and personal, has made my direction in this journey clearer, and her kind, encouraging words were always appreciated.

Warm thanks to Dr. Alexandra Schmidt, who has inspired me from our first encounter in her regression class. Her enthusiasm and engagement in this project were invaluable. Even when things were not going as planned, I always left her company cheerful and hopeful.

I thank SPIN and the SPIN Working Group, whose members are listed below, for collecting the data and providing clinical feedback. Without them none of this work would have been possible.

Finally, I would like to thank my parents and brothers for their love, encouragement, and support. It goes without saying that none of this would have been possible if it were not for them. They were the light at the end of the tunnel and my gratitude towards them knows no bounds.

Abstract

Background. We described the secular trends of HABSI incidence rates (IRs) in Quebec between April 1st, 2007 and March 31st, 2017 in eligible hospitals that have participated in BACTOT since its inception. We then evaluated the HABSI trend over surveillance year in eligible hospitals that have participated in BACTOT for at least 3 years without interruption, regardless of their date of entry.

Methods. HABSI IRs over calendar time were analysed by fitting Poisson regression models using Generalized Estimating Equations and were stratified by infection source. For analysis over surveillance time, we used a Bayesian framework to fit multilevel Poisson regression to HABSI and its most common subtypes to decompose their mean rates into a surveillance year effect, periodic effect, and hospital effect. Cohort-level risk of surveillance years 2 to 10 relative to year 1 were calculated. A subgroup analysis was performed by fitting the same Bayesian models to hospitals that participated for less than 10 years to exclude hospitals that may have been conducting surveillance prior to participation.

Results. In calendar years, HABSI rates did not exhibit statistically significant changes from year to year. Non-catheter-associated-primary BSIs were the only HABSI type that exhibited a sustained change across the 10 years, increasing from 0.69/10,000 patient-days (95% CI: 0.59-0.80) in 2007-08 to 1.42/10,000 patient-days (95% CI: 1.27-1.58) in 2016-17. For HABSI, CA-BSI, and BSI-UTI, there was no difference between the estimated risks of surveillance years 2 to 10 compared to surveillance year 1. As for NCA-BSI, the risk of the 10th year of surveillance was 29% (95% CI: 1-89%) higher than the risk in the first year. In the subgroup analysis, no differences in risks were detected between the years for HABSI and all analysed subtypes.

Conclusion. Despite ongoing surveillance, HABSI rates have not decreased over either calendar time or over surveillance time. While surveillance may continue for data collection and documentation purposes, for improvements in rates, targeted interventions must be employed and evaluated.

Résumé

Contexte. Nous avons décrit les tendances séculaires des taux d'incidence des bactériémies au Québec entre le 1er avril 2007 et le 31 mars 2017 dans les hôpitaux éligibles ayant participé à BACTOT depuis ses débuts. Ensuite, nous avons évalué la tendance des bactériémies au cours des années de surveillance dans les hôpitaux éligibles qui ont participé sans interruption à BACTOT pendant au moins 3 ans, quelle que soit leur date d'entrée.

Méthodes. Les taux d'incidence séculaires des bactériémies ont été analysés à l'aide de modèles de régression de Poisson (utilisant des équations d'estimation généralisées), et ont été stratifiés par source d'infection. Pour l'analyse en fonction du temps de surveillance, nous avons utilisé un cadre Bayésien pour adapter la régression de Poisson multi-niveaux aux bactériémies globales et ses sous-types les plus communs en décomposant les taux moyens en un effet de l'année de surveillance, un effet périodique et un effet hospitalier. Le risque de cohorte des années de surveillance 2 à 10 par rapport à l'année 1 a été calculé. Une analyse de sous-groupe a été réalisée en adaptant les mêmes modèles bayésiens aux hôpitaux qui participaient depuis moins de 10 ans afin d'exclure les hôpitaux qui auraient pu avoir débuté une surveillance avant l'entrée dans BACTOT.

Résultats. Les taux annuels de bactériémies n'ont pas présenté de changements statistiquement significatifs au cours du temps (années de calendrier). Les bactériémies primaires non associées à un cathéter étaient le seul type de bactériémies à avoir subi un changement soutenu au cours des 10 années, passant de 0,69 / 10 000 jours- présence (IC à 95%: 0,59-0,80) en 2007-2008 à 1,42 / 10 000 jours- présence (IC à 95%: 1,27-1,58) en 2016-2017. Pour les bactériémies globales, les bactériémies sur cathéter et les bactériémies secondaires à une infection urinaire, il n'y avait pas

de différence entre les risques estimés des années de surveillance 2 à 10 par rapport à la 1re année de surveillance. Quant aux bactériémies primaires non associées au cathéter, le risque de la 10e année de surveillance était de 29% (IC 95%: 1-89%) plus haut que la risque de la première année. Dans l'analyse de sous-groupe, aucune différence dans les risques n'a été détectée au cours des années pour les bactériémies globales et tous les sous-types analysés.

Conclusion. Malgré la surveillance continue, les taux d'HABSI n'ont pas diminué, que ce soit selon les années calendrier ou de surveillance. Alors que la surveillance peut se poursuivre à des fins de collecte de données et de documentation, pour une baisse des taux, des interventions ciblées devront être implémentées et évaluées.

Contributions of Authors

I (Iman Fakih) am the primary co-author of the two manuscripts in this thesis. I contributed to study design, data analysis, and the writing of the first drafts of both manuscripts and their subsequent revisions.

Dr. Caroline Quach was the supervisor for this thesis work and co-author on both manuscripts. She provided me with the opportunity to collaborate with SPIN-BACTOT and guided me through all the processes that lead to the production of this thesis. This included the advice on the process of research, interpretation of results, preparation of the manuscripts and their submission, as well as the revision of the thesis.

Dr. Élise Fortin was the co-supervisor for this thesis work and co-author of both manuscripts. She mediated the process of acquiring the data, prepared it for analysis, provided the foundation of the study designs used in both manuscripts, gave statistical guidance for the first, contributed to the preparation of the manuscripts, and the revision of the thesis.

Dr. Alexandra Schmidt was co-author for the second manuscript and was integral in the intellectual process of devising a suitable statistical method that addressed its objective and matched its study design. She provided the program code used to model the data, advised on the statistical interpretation of the results, and was involved in the revision of the manuscript.

For both manuscripts, data BACTOT data collection was performed by the SPIN-BACTOT working group, which constitutes of Élise Fortin, Charles Frenette, Lise-Andrée Galarneau, Sylvie Latreille, Danielle Moisan, Muleka Ngenda-Muadi, Noémie Savard, Marc-André Smith, Claude Tremblay, Mélissa Trudeau, Jasmin Villeneuve. Charles Frenette, Marc-

André Smith, Claude Tremblay, and Jasmin Villeneuve also contributed valuable insight in the revisions of the first manuscript. Permission to reproduce both manuscripts has been obtained by all co-authors.

Dr. Gilles Paradis was the liaison with McGill University that allowed me to remain under the supervision of Dr. Caroline Quach after her move to Université de Montréal.

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List of Abbreviations

BACC-USI	*Surveillance des bactériémies nosocomiales sur cathéters centraux aux soins intensifs* (Nosocomial central-line associated bloodstream infection surveillance in intensive care units)
BACTOT	*Surveillance des bactériémies nosocomiales panhospitalières* (Hospital-wide surveillance of nosocomial bloodstream infections)
BSI	Bloodstream infection
BSI-ABDO	Bloodstream infection secondary to an intra-abdominal infection
BSI-BONE	Bloodstream infection secondary to a bone and joint infection
BSI-Other	Bloodstream infection secondary to a non-specified primary infection
BSI-PULM	Bloodstream infection secondary to a pulmonary infection
BSI-SSI	Bloodstream infection secondary to a surgical site infection
BSI-SST	Bloodstream infection secondary to a skin and soft tissue infection
BSI-UTI	Bloodstream infection secondary to a urinary infection
CA-BSI	Catheter-asscoiated bloodstream infection
CoNS	Coagulase-negative *Staphylococci*
CLABSI	Central-line associated bloodstream infection
CDC	Centre of Disease Control
DALY	Disability-adjusted life year
HABSI	Healthcare-associated bloodstream infection
HAI	Healthcare-associted infection
ICU	Intensive care unit
INSPQ	*Institut National de Santé Publique du Québec* (Quebec National Public Health Insitute)
IR	Incidence rate
KISS	Krankenhaus-Infektions-Surveillance System (German national nosocomial infection surveillance system)
SENIC	Study on the Efficacy of Nosocomial Infection Control
SIRO	Finnish Hospital Infection Program
SPIN	*Surveillance provinciale des infections nosocomiales* (Provincial surveillance of nosocmial infections)
SSI	Surgical site infection
MCMC	Markov Chain Monte Carlo
MDR	Multi-drug resistant
MRSA	Methicillin resistant Staphylococcus aureus
NCA-BSI	Non-catheter-associated primary bloodstream infection
NHSN	National Healthcare Safety Network, USA
NINNS	Nosocomial Infection National Surveillance Scheme, England
NNIS	National Nosocomial Infections Surveillance System, USA
NSIH	National Surveillance of Infections in Hospitals, Belgium
UTI	Urinary tract infection
VRE	Vancomycin resistant *Enterococci*

Preface

My thesis primarily focuses on Quebec's provincial hospital-wide surveillance program which monitors healthcare-associated bloodstream infections (HABSI), BACTOT. Reports on such a program are rare in the literature and even though it has been running for more than ten years, detailed peer-reviewed publication on its findings and effects are limited to a single article focused on bloodstream infections secondary to urinary infections.

The first chapter of this thesis introduces, in the form of a literature review, the topic of healthcare associated infections (HAI) and then focuses on HABSI as an especially morbid and fatal subset. I then present public health surveillance as a preventive measure that can be used to reduce HAI incidence. The handful of existing HABSI surveillance programs are described followed by an overview of BACTOT. The chapter closes with the objectives of the thesis.

Chapter 2 is a brief presentation of the methods used in the manuscripts that form the body of the thesis. It is followed by Chapter 3, the first manuscript titled, *A ten-year review of healthcare-associated bloodstream infections from 40 hospitals in Quebec, Canada,* which is a descriptive presentation of HABSI and its secular trends seen between 2007-08 and 2016-17. It is the first peer-reviewed article that details the HABSI epidemiology collected through BACTOT surveillance over its ten-year operation. This manuscript has already been accepted for publication. Chapter 4 is the second manuscript titled, *Healthcare-associated bloodstream infection rate trends under a provincial surveillance program independent of entry year*, which is an evaluation of HABSI trends across time of BACTOT surveillance. Under a Bayesian framework, HABSI risk from the first year of surveillance is used as a baseline to compare risk of subsequent surveillance years using hospitals with different participation times. The

manuscript uses a novel method to decompose risk and to deal with different length of participation. Chapter 5 is the Discussion wherein I bring together the findings of the two manuscripts and examines their methodological strengths and weaknesses. I follow this by discussing the implications of the results on BACTOT's operation and end with suggestions for further inquiry that can be made using BACTOT's databases.

Chapter 1: Introduction

1.1 Literature review

1.1.1 Healthcare-associated infections

Healthcare-associated infections (HAI) are one of the most common adverse events in healthcare, affecting at least 12 patients for every 100 admissions in Canada.[1] Furthermore, they are the primary cause of preventable disability among hospitalized patients.[2] A recent study estimated that the 6 most morbid HAIs had a combined annual burden of 501 disability-adjusted life years (DALYs) per 100,000 of the European general population. This number exceeded the total burden of all other communicable diseases.[3] The majority of HAI DALYs is explained by the associated increased risk of dying, which has been estimated to range between 30%-80%.[4] In addition to the cost of life, HAI pose an unnecessary financial burden on the health care system. It is estimated that one case of HAI can cost Canadian taxpayers an excess of $2,265 to $22,400 due to prolonged lengths of stay, treatments, and long-term disabilities.[5]

The Centers for Disease Control and Prevention (CDC) formally define a health care-associated infection (HAI) as "a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) [with] no evidence that the infection was present or incubating at the time of admission to the acute care setting."[6] The microorganisms that cause HAI differ widely in complexity and pathogenicity. The CDC characterised the most common offenders as *Staphylococcus aureus, Escherichia coli*, coagulase-negative staphylococci, and *Klebsiella* species.[7] Over the last decades, HAI microorganisms have exhibited a dramatic increase in antimicrobial resistance and increased pathogenicity, driven largely by the

indiscriminate use of antibiotics.[8] Methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococci* are leading examples of this. Antibiotic resistant pathogens are associated with treatment failures and increased morbidity and mortality.[9]

The infectious agents that cause HAI have either endogenous or exogenous sources. Endogenous sources are body sites, such as the skin, gastrointestinal tract, and vagina, that are typically colonised by microorganisms. Exogenous sources are those external to the patient.[10] Agents from exogenous sources can be transmitted to the patients directly or indirectly. Direct transmission takes place by physical contact between the infected and uninfected hosts or by droplets from the infected host to a close uninfected one. Indirect transmission is either vehicle-borne, airborne, or vector-borne, all of which require an intermediate source between the infected and uninfected.[11]

While contact with the infectious agent is necessary for a patient to develop a HAI, it is not sufficient. The agent may multiply and colonise the patient without invoking an immune response. If infection does take place and the patient mounts an immune response, it can remain subclinical. Once a measurable response occurs and symptoms become apparent, the diagnosis of the infection is possible and the ascertainment as healthcare-associated can be done. The development from contact to colonisation to infection depends on multiple factors related to the infectious agent, the patient, and the environment around them.[11]

HAI overall pose a serious threat to patient health, and as a result can be a useful measure of healthcare performance and safety. However, for purposes of treatment and prevention, HAI sub-categories are used. They are most frequently classified by the primary organ or source of infection but may also be grouped based on the infectious agent and its susceptibility profile, or

the source of infection.[12] A recent review identified more than 80% of HAI, excluding *Clostridium difficile* infections, comprise of urinary tract infections (UTIs), pneumonia, surgical site infections (SSIs), and bloodstream infections (BSIs).[12] UTIs are often the most frequent, representing 20-30% of HAI, but carry the lowest mortality and cost.[5] SSIs tend to follow second in frequency with similar cost.[1,5,13-15] Pneumonia and BSIs are less common but are associated with high mortality rates, doubling the risk of death in infected patients.[16-18]Additionally, they represent a considerable financial burden on the healthcare system as a case of either is associated with up to an additional $30,000, increasing to ranges between $50,000 and $65,000 if the case arises in the ICU.[8]

1.1.2 Healthcare-associated bloodstream infections

Bloodstream infections (BSIs) occur when one or more viable microorganism invades the normally sterile bloodstream. For the infection to be deemed healthcare-associated it must develop at least 48 hours after a patient's admission. The infection is further classified as primary or secondary. When the isolated microorganism originates from an infection at another body site, the BSI is secondary. Conversely, a primary BSI indicates that the isolated microorganism has no recognizable focus of infection elsewhere in the body, and also includes BSIs resulting from intravascular catheters.[19] This granularity in HABSI classification is owed to its clinical utility in preventing and treating the BSI, given the underlying pathophysiology.

Risk factors

Factors that predispose patients to HABSI include their age, underlying disease, and therapeutic procedures, all of which are generally related to perturbations to the normal functioning of the immune system. Neonates and elderly are generally more prone to HAI because of their weaker immune systems, but also because they have longer lengths of stays and thus are more exposed.[16,20] Diseases most associated with increased BSI risk are diabetes (due to vascular insufficiency or induced leukocyte defects), renal and hepatic failure (due to increased intestinal patency), hematological malignancies, immuno-developmental diseases, [16,19]. Patient's treatment for an underlying disease can also increase BSI risk: cancer patients receiving immunosuppressive and cytotoxic therapies, placement of central venous catheters, urinary catheters and other indwelling devices, or endoscopic procedures.[16,17] Risk factors for developing fungal HABSI are total parenteral nutrition, as glucose-containing solutions and lipid emulsions favor the formation of *Candida* biofilms within catheters used, as well as antibiotic administration which reduces the bacterial microbiome that usually prevents *Candida* overgrowth and consequent BSI.[16]

Signs and symptoms

While HABSI is easily diagnosed if a blood culture is positive, indications for a blood culture are not as clear and sensitivity of the blood culture is not 100%. Patients with BSI generally present with non-specific symptoms, including fever, weakness, anorexia, malaise, or confusion, which could also be manifestations of the underlying condition for which the patient was initially hospitalised.[16] Additionally, fever, the most common sign of a serious BSI, can be absent in certain patient populations such as neonates and elderly, immunocompromised hosts, and persons with end-stage renal disease.[19] This may prevent clinicians from recognising the development of a BSI

and delay necessary treatment.[6] Instead, symptoms such as changes in mental status or functional status are indications of BSI in elderly patients or in patients with renal dysfunction.[21,22] In neonates, BSI present with lethargy, feeding intolerance, apnea, cholestasis, and temperature instability rather than fever.[23,24] Once a BSI is suspected, blood is drawn from the patient and cultured for the identification of the microorganism responsible for the BSI and treatment is initiated.

Microbial etiology

HABSI can be caused by a variety of microorganisms. Isolated pathogens differ depending on the environment (hospital and ward type), focal source of the infection, and patient medical history.[25-27] While overall, Gram-positive bacteria represent the majority of HABSI cases, *Escherichia coli* has been the leading species to cause HABSI, followed by *Staphylococcus aureus*, and coagulase-negative staphylococci (CoNS).[25,26,28] BSIs acquired in the healthcare setting differ in etiology from those acquired in the community. A higher proportion of HABSI tend to be caused by *S. aureus*, *Pseudomonas aeruginosa*, and are more often polymicrobial. On the other hand, community-acquired BSIs show higher proportions of *E. coli*, *Streptococcus pneumoniae* and hemolytic streptococci.[25,26]

HABSI are associated with almost 3 folds higher incidence of antibiotic resistance compared to community-acquired BSIs.[29,30] Leading resistant causes are methicillin resistant staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE), but other resistant pathogens such as ESBL producing *Enterobacteriaceae*, *Acinetobacter baumannii*, and *P.*

aeruginosa carry heavy burdens as well. Their rates differ substantially across hospitals depending on the patient population and whether the microorganisms have become endemic pathogens in the facility.[17]

A problem that clinicians and microbiologists often face is how to differentiate between a true positive blood culture and one that is contaminated by microorganisms commonly found on human skin, mainly CoNS, such as *Staphylococcus epidermidis* and *Staphylococcus haemolyticus.*[16] To make an informed diagnosis, clinicians need to be familiar with the microbiology of their clinical setting, in order to avoid writing off a true BSI as a contamination or letting a patient undergo unnecessary treatment.[11] However, even with this knowledge, differentiating between true infection and contamination requires a detailed clinical picture of the patient and clear definition to abide by for diagnosis.

Treatment and prognosis

HABSI is mainly treated with antimicrobial therapy, management of complications, and source control (i.e., removing the probable source of infection). Empiric antimicrobial therapy against the most probable pathogens is recommended pending blood culture results, which can take between 36 and 48 hours using traditional culturing techniques.[16] The choice of therapy should be guided by the patient's characteristics, medical history, suspected source of infection and the microbial epidemiology of the hospital/ward where the BSI developed.[16,31] These are especially important if the patient has been previously infected/colonised by multi-drug resistant

(MDR) organisms or if the hospital is endemic for MDR organisms. Once blood culture results become available, empiric therapy is reassessed and may be de-escalated to a tailored regimen.[16]

While appropriate antimicrobial therapy initiated early reduces mortality in patients with BSI, wrong choices of empiric therapy occur in around 30% of HABSI cases, more frequently when the pathogen is MDR.[17,32-34] This contributes to the high case-fatality of HABSI, which is estimated between 12% and 31%.[33,35-37] A tenth of HABSI patients die within 1 week of the positive blood culture result and 16% within a month.[38] Associated factors are age, severity of the patient's underlying disease, patient's host response to the BSI, the BSI being secondary, polymicrobial, or caused by difficult to treat pathogens such as *Pseudomonas*, *Acinetobacter*, or *Serratia* species.[17,31] While all these may contribute to a more fatal infection, it is also the case that HABSI are associated with higher risk of death than community-acquired BSIs.[17,39]

Sources of HABSI

Appropriate treatment of HABSI is highly dependent on the discernment of its source, both to establish the most likely causative pathogen for appropriate antimicrobial therapy, and to treat the source.[17] One of the most common sources of HABSI are catheter-associated BSIs (CABSI) or, as more commonly known, central-line-associated BSIs (CLABSI).[39-41] Central lines are long catheters inserted into a large vein leading to the heart mainly used to administer drugs that cannot be given by mouth or via a conventional needle in the arm, when such administration is frequent and long term, or to measure central venous pressure.[42] Central venous access is necessary to manage and treat a large proportion of critically ill patients, and so central lines are used

ubiquitously in healthcare settings.[2] The catheter's material is susceptible to colonisation with BSI-causing micro-organisms, such as *S. aureus* and *S. epidermidis*, when installed for long periods of time and because catheters offer direct entry for microorganisms into the bloodstream they tend to be associated with high risk of BSI.[43] CLABSI are considered primary HABSI, as the infectious agent is not present elsewhere in the body. US national rates of CLABSI range between 0.8 and 5.5 CLABSI per 1,000 central-line days, depending on the ward.[43] As with most HAI, CLABSI rates in ICUs are at least double the rates in other acute care wards.[17,44] Due to their frequency, associated morbidity and mortality, and relative preventability, CLABSI tend to be the most targeted HABSI and have consequently been exhibiting rate reductions in the past decade.[2,8,43]

Patients with primary infections tend to develop secondary BSIs when they exhibit the earlier discussed risk factors that predispose patients to BSI. Prominent sources of secondary BSIs are UTIs, SSIs, pulmonary infections, and intra-abdominal infections.[39] UTIs tend to be the most common source, as they are prevalent in healthcare settings. It has been reported that around 21% of all HABSI are secondary to a urinary focus (BSI-UTI) [45] with a 33% case fatality rate.[46] SSIs, in particular deep SSIs or those involving an organ/space, can develop into HABSI if the purulent source is not adequately controlled.[47] The most morbid source of HABSI is considered to be pulmonary infections, particularly pneumonia, as the primary infection itself is associated with the highest disability and death among HAI.[2,3] The high mortality can partly be explained by the presence of the highly pathogenic and often multi-drug resistant *Pseudomonas aeruginosa* and severe underlying conditions in many cases.[48] While in theory any body site can act as a primary focus to HABSI, other sites are studied less extensively because they occur at relatively infrequent rates.[39] When a primary focus of infection cannot be identified, the HABSI is often classified as

primary that is not catheter-associated (NCA-BSI). These infections usually occur after surgeries without an associated SSI and other clinical procedures (e.g., prostate biopsy).[39] Around 20% of HABSI tend to be NCA-BSI. [39-41]

Prevention and Control of HABSI

It is in the interest of all stakeholders to reduce HAI rates, especially those of HABSI, whose targeting would potentially allow the prevention of the highest number of deaths among all HAI. As such, several measures have been introduced in the clinical setting to do so.

The simplest, most cost-effective prevention practice is hand hygiene.[8,49] However, compliance with hand-hygiene standards and guidelines is typically poor with adherence levels between 16% and 81%.[50] Doebbeling et al. showed that an increase in handwashing frequency (with a higher volume of use of antiseptic soap) resulted in a substantial 22% reduction in the incidence rate of HABSI and could reduce MRSA infections by 35% in ICUs.[49,51,52]

More specifically, prevention measures can directly target possible sources of infection. Those with the highest potential for prevention tend to be catheter- and device- associated HABSI because of the alterability of the circumstances.[9] Common methods include reductions in unnecessary use, employment of proper practices of insertion, and careful maintenance.[19] Interventional studies using the best available techniques to prevent catheter-associated infections reduced rates by 56% in all adult patients and 66% in ICU patients.[9,53] As the number of unnecessary catheters drop, promising technologies in materials and device design have been providing gains in device-associated HAI prevention and control.[8]

Antimicrobial stewardship plays a significant role in reduction of HABSI, especially those caused by resistant pathogens, by limiting unnecessary or inappropriate antibiotic use, without compromising the quality of care.[52] The main ways to do so is by de-escalating initial therapy and shortening its duration. De-escalation after blood culture results is necessary if initial therapy was broad-spectrum to decrease antibiotic selection pressure, curtail emergence of resistance and prevent resistant strains from becoming endemic in hospitals.[16,31] Duration of antimicrobial therapy must be shortened when possible especially when the identified pathogen is susceptible, and the infection source is properly controlled. The shortening must be guided by close monitoring of a patient's status and by biomarker testing.[31] Sustained reduction in antibiotic use has been shown to decrease rates of HABSI, especially those arising from MDR pathogens.[52,54,55] Sustained reduction in antibiotic use reduced rates of candidemia and MRSA infections, and associated mortality rates.[54] Decreasing antimicrobial therapy use by half reduced the incidence of drug resistant bacteria by 70% in neonates and sustained the reduction for one year.[55]

However, it must be noted that not all HABSI are preventable. Most prevention measures target reasons for infection exogenous to the patient, such as catheter-removal and prudent antibiotic use. There remain reasons intrinsic to the patients themselves that cannot be controlled under realistic conditions, such as the patients' age, immune status, and comorbid conditions.[9] In such circumstances, efforts should be focused on alleviating the severity of the infection and reducing associated mortality.

1.1.3 Surveillance

In addition to clinical measures, surveillance has been promoted since the 1970s as an essential step in HAI prevention and control. The CDC defines surveillance as, "the ongoing systematic collection, analysis, and interpretation of health-related data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know."[56] They identified the final link of the surveillance chain to be the application of this data to prevention and control. The CDC was one of the first to set up a national surveillance system, the National Nosocomial Infections Surveillance System (NNIS) in 1970, to monitor HAI.[57]

To reach the final goal of HAI prevention and control, more specific objectives are set. The most common one is the need to establish endemic baseline rates in order to inform further prevention and control strategies.[58] Once the endemic rates are established, deviations from the baseline, intended through interventions and employment of control measures, or unintended like regional outbreaks, can be identified.[59] Similarly, surveillance results allow a healthcare facility to compare its HAI rates with rates of other facilities, allowing them to identify weaknesses and areas that are most in need of improvement. Such comparisons, however, require accurate data and appropriate adjustment of underlying risk differences.[59]

Good surveillance programs share several characteristics. First, the data collected must be accurate and consistent. Accurate data results from sensitive and specific case definitions and the use of appropriate denominator data. Consistency is derived from the uniform application of surveillance methods, data sources, and case definitions over time and space.[59] Otherwise, surveillance would result in wasted efforts and may cause the deployment of inappropriate and possibly harmful interventions. Finally, surveillance programs must be useful and practical, spent

on actionable issues that have room for validated methods of improvement, while respecting the limited resources of those conducting it.

HAI surveillance was first popularised as a facility-wide activity, monitoring all HAI arising in all wards in a facility. Slowly, targeted surveillance became more common, as it was seen as a more efficient use of facilities' resources, while facility-wide surveillance is time consuming and labour intensive, and not feasible for many facilities.[59] The targeting of the surveillance can be site-directed or unit directed. Site-directed surveillance focuses on HAI types, such as HABSI and methicillin-resistant *S. aureus*, among all admitted patients while unit-directed surveillance targets certain patient populations with highest risks of HAI, such as ICU patients or neonates.[59] The NNIS began as a voluntary facility-wide surveillance program in 1970 but added the choice of targeted surveillance in 1986 when the number of participating hospitals decreased steadily.[57] Eventually, in 1990, the facility-wide component was discontinued due to limited participation.[19]

In addition to specifying what data is collected, how it is collected is equally important. There are two temporal methods of surveillance: prospective and retrospective. Prospective HAI surveillance means monitoring patients throughout their hospital stay to identify the infection as it develops. Retrospective surveillance involves looking back at past patients to identify the infections after they occur, often after patients' discharge. For circumstances with a need for intervention, prospective surveillance is appropriate for the quick identification of infection clusters prompting opportune investigation and response to deal with cases and prevent the development of new ones.[59] Retrospective surveillance requires less resources than prospective

surveillance but is best suited for issues that are not time-sensitive and do not require intervention.[60]

The method of investigation to identify HAI during surveillance can be passive or active. In passive surveillance, non-specialised individuals routinely report an infection when it is suspected. Because the person doing the reporting is more preoccupied with patient care than surveillance, problems like misclassification and underreporting often occur.[59] Active surveillance involves search for HAI by specially trained infection control personnel.[61] Current with surveillance case definition, they seek various data sources and methods to determine whether an infection has occurred. While active surveillance requires more resources than passive, it has been shown to be more accurate and comprehensive and increases the visibility and importance of surveillance in the facility.[62,63]

Regardless of the scope of surveillance, the monitoring can focus on new cases only, called incidence-based surveillance or both new and existing cases, called prevalence-based surveillance. Point prevalence can be calculated by performing surveillance on a single day, and period prevalence can be calculated over several days. The main disadvantage of using prevalence-based surveillance is that prevalence overestimates disease burden, as existing cases with longer lengths of stay are overrepresented.[64,65] Hospitals with typically longer lengths of stay will exhibit higher prevalence than those with shorter lengths of stay.[18] This bias limits the usefulness of prevalence-based surveillance in comparisons across space and time.[66] Hence, the use of prevalence is best restricted to single surveys that inform specific concerns and to determine the need for further infection control and prevention measures.[59] Incidence-based surveillance provides more accurate estimates better suited for long-term, routine monitoring and for any comparative needs. To avoid

time-dependent bias, incidence estimates must also adjust for length-of-stay by using patient-time denominators.

Surveillance effect

While surveillance is viewed as a first step in infection prevention and control, it has also been shown that it alone, without the employment of further interventions, can reduce HAI rates. The CDC's SENIC Project (Study on the Efficacy of Nosocomial Infection Control) was the first study to demonstrate this phenomenon, termed the surveillance effect.[61] The Project analysed rates of nosocomial UTI, SSI, pneumonia, and BSI between 1970 and 1975-1976 in 3,599 NNIS participating hospitals. After adjusting for differences between hospitals and their patient populations, hospitals with effective, facility-wide surveillance programs showed a 32% reduction in HAI compared to a 18% increase in hospitals without such programs. Very effective surveillance required the establishment of two important components; 1) a strong infection surveillance and control activities, or at least having a hospital epidemiologist, and 2) at least one full-time-equivalent infection control nurse per 250 occupied beds. Establishing only one of the two components resulted in a moderately effective program. Less than 7% of the followed hospitals ran very effective programs, and showed 40.5% reduction in SSIs, 41.2% in UTIs, 27.4% in pneumonia, and 35.1% in BSIs. Percent of hospitals that ran moderately effective programs varied with infection type and ranged between 0% (for UTIs) and 51.1% (for SSIs). These programs showed an average 19.1% reduction in SSIs, 12.8% in surgical pneumonia, and 15.1% in BSIs. Programs at the remaining hospitals where either non-existent or completely ineffective

and showed increases in all recorded HAI; 18.1% in SSIs, 27% in UTIs, 8% in pneumonia, and 21.6% in BSIs.[63]

The promising results of the SENIC project encouraged other countries to set up HAI surveillance networks. Over the years, several studies assessing trends reported by such networks have been published in the peer-reviewed literature. A survey of notable multi-centre studies is shown in Table 1 below. The majority of studies report reduction in risk or rates of the infection monitored by the surveillance system, including BSI, UTI, ventilator-associated pneumonia (VAP), and SSI.[67-72] None of the listed studies reported the employment of interventions additional to active surveillance. The most commonly monitored infections were SSIs, and they tended to exhibit the greatest reductions. Only a minority of studies conducted hospital-wide surveillance.

Two studies report increases in rates following surveillance. Ronveaux et al. described a rise in HABSI from 6.5 to 7.3 cases/10,000 patient-days between 1992 and 1996.[73] However, initiation of surveillance established new protocols for BSI investigation and increased the frequency of blood cultures, suggesting that the rise in infections was a function of increased detection, as opposed to increased incidence. Les Saux et al. reported an increase in *C. difficile* infections from 3.2 to 5.2/10,000 patient days in paediatric hospitals between 2007 and 2011.[74] The objective of the surveillance conducted was to determine incidence and characteristics of infection strains. The considerable difficulty in controlling *C. difficile* infections and limiting its communicability could explain the difference between its response to monitoring compared to other nosocomial infections.[75]

Table 1 Summary of results from multicentre studies on HAI surveillance in the peer-reviewed literature.

Article	Population	Period	Infection	Surveillance effect
Ronveaux et al. 1998[73]	117 acute care hospitals in Belgium	1992–1996	BSI	Incidence increased from 6.5 to 7.3 cases/10,000 patient-days
Gaynes et al. 2001[67]	ICUs of 285 acute care hospitals in USA	1990-1999	BSI, UTI, ventilator-associated pneumonia	31-44% reduction in BSI, 40-59% reduction in UTI, 26-56% reduction in VAP, depending on ICU type
Zuschneid et al. 2003[68]	212 ICUs in Germany	1997-2001	CA-BSI	Incidence decreased by 25.7%
Gastmeier et al. 2005[69]	21 acute care hospitals in Germany	1997 earliest, at least 3 years of participation	Orthopaedic wound infections	Risk decreased by 46% in third year compared to first year
Geubbels et al. 2006[70]	38 hospitals in the Netherlands	1996 to 2000	SSI	Relative to first surveillance year, 31% risk reduction in fourth year, 57% risk reduction in fifth year. No statistically significant difference in second and third year.
Brandt et al. 2006[71]	130 surgical departments in Germany	1997-2004	SSI	Relative to surveillance year 1, risk decreased by 16% in year 2, 25% in year 3, and no statistically significant change in year 4.
Schwab et al. 2007[72]	24 NICUs in Germany	3 years of participation	BSI, pneumonia	Relative to surveillance year 1, BSI risk decreased by 23% in year 3 and no statistically significant change in pneumonia.
Zuschneid et al. 2007[76]	71 ICUs in Germany	1999 earliest, 3 years of participation	Ventilator-associated pneumonia	Relative to year 1, rate decreased by 19% in year 2, and by 24% in year 3.
Gastmeier et al. 2009[77]	Hospitals in Germany: 267 ICUs for CA-BSIs, 150 ICUs for VAP, 113 surgical departments for SSI	Between 1997 to 2008, 3 years of participation	CA-BSI, VAP, SSI	Relative to year 1, year 3 showed 20% reduction in VAP, 17% reduction in CA-BSI, and 44% for SSI.

Marchi et al. 2014[78]	355 surgical wards in Italy	2009-2011	SSI	Relative to year 1, 29% lower risk in the subsequent 2 years
Worth et al. 2014[79]	123 hospitals in Victoria, Australia	2010-2012	*S. aureus* bloodstream infections	Incidence decreased from 1.4 to 0.7/10,000 patient-days
Le Saux et al. 2015[74]	8 stand alone paediatric hospitals in Canada	2007-2011	*C. difficile* infection	Incidence increased from 3.2 to 5.2/10,000 patient days

1.1.4 HABSI surveillance

Despite the high morbidity and mortality associated with HABSI relative to other HAI, surveillance program dedicated to them are rare. Networks more commonly perform targeted surveillance, favouring the monitoring of certain HABSI, or limit surveillance to certain wards. CLABSI is the most monitored HABSI worldwide and is prioritised because of its high incidence compared to other HABSI subtypes and because of its preventability.[80-82] However, surveillance limited to CLABSI would miss 70-80% of HABSI cases,[39] most of which would be secondary infections that are often more morbid with higher case-fatality than primary infections.[83] Additionally, CLABSI have relatively low rates compared to other HAI and these have been decreasing worldwide as a result of targeted efforts in infection prevention.[10] While this is a welcome improvement, it limits CLABSI's power when attempting to follow hospitals' rates across time or when comparing rates across hospitals.[83]

Similarly, some surveillance programs limit their HABSI monitoring to ICUs,[72,80,84] as ICU patients account for a disproportional share of HAI in general, and HABSI in particular. Despite only making up 5% to 10% of all hospital beds, a US survey of 49 hospitals found 51% of all HABSIs occurred in the ICU.[29] A large multicenter study in France noted the risk of HABSI to be 12-fold greater in ICU patients than in ward patients.[85] Surveillance limited to ICUs would miss infections arising in acute care wards which represent around 40% of incident HABSI and probably have a better likelihood of prevention because they arise in less vulnerable patients.[44]

Although it is reasonable that institutions with limited resources focus their attention on the most frequent subtypes or the most vulnerable patients, such methods have impeded a more complete understanding of HABSI and have hindered a potentially more extensive reduction in

preventable cases. Surveillance programs at the level of jurisdictions may benefit more from monitoring HABSI as a single entity. To our knowledge, the handful of existing HABSI surveillance programs have been established in Belgium,[73,86] England,[38,87] Finland,[88] and in Quebec, Canada.[45]

National HABSI surveillance programs

Belgium. The earliest documented HABSI surveillance system was established in Belgium in 1992. The National Surveillance of Infections in Hospitals (NSIH) is an active, prospective, hospital-wide HABSI surveillance conducted in acute care hospitals. Participation was voluntary at first but became mandatory in 2014. The minimum period of participation is 3 months per year. Numerator data is collected from medical records. BSIs are classified as primary, secondary or of unknown origin. Denominator data is obtained from administrative sources, and consist of number of admissions, hospitalisation-days for the entire hospital and for ICU. Data is sent back, analysed and returned confidentially to the hospital, along with national figures from other participating hospitals.[73] NSIH has been publishing annual reports since 2013.[89] However, recent peer-review articles are focused on CLABSI,[90,91] and the last article on HABSI was published in 2010.[86]

Finland. In Finland, the Finnish Hospital Infection Program, SIRO, was established in 1998,[92] with a most recent English-language characterisation published in 2002.[88] Participation is voluntary and surveillance is active, prospective, and hospital-wide, covering all departments offering acute care. Patient-days and discharge data are obtained from the information

technology department of each participating hospital. Local infection-control nurses collect case data by regularly reviewing the hospital's laboratory database for positive blood-cultures which fit the CDC's definitions. BSIs are then divided into primary and secondary infections. The patient's clinical information and microbiological data are also reported.

England. The Nosocomial Infection National Surveillance Scheme (NINNS) was established in England in 1996. It covered HABSI, SSI and CA-UTI. Hospitals could participate in as many modules as they chose to, but the minimum duration of participation was 3 months. Surveillance was active, prospective, and hospital-wide. Numerator data, i.e. case data, was collected by the hospital's already existing Infection Control Team, while denominator data was obtained from the hospital's information department. Results from individual hospitals are only known to those hospitals and NINNS staff involved in their production. Hospitals receive quarterly and annual reports of their own results and aggregated data from hospitals participating in the HABSI module. Results are not disseminated elsewhere. The most recent peer-reviewed articles describing NINNS were published in 2000 and 2001.[38,87] Since then, Public Health England has limited national HABSI surveillance to bacteremia caused by MRSA, Methicillin-susceptible *S. aureus*, *E. coli*, *Klebsiella* spp., and *P. aeruginosa*, and has made participation mandatory for all hospitals.[93]

France. In 2002, France established *Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales*, RAISIN, a national HAI surveillance system with a HABSI module.[94] Surveillance was prospective, active. Positive blood cultures were reviewed weekly by an infection control physician, identified HABSI based on standardised definitions, and, with the ward physician, investigated the source of infection and reported case information. Denominator

data was not collected. Annual reports were expected to be presented to the institutional infection control committee and personalised reports to be shared at the ward-level more frequently. RAISIN discontinued the HABSI module in 2006, but some individual hospitals continue to perform surveillance.[94,95]

The programs are strong notably because they all perform active, prospective surveillance. More particular strengths include the employment of specialised infection control personnel to lead the surveillance process, as is the case with all programs with exception of Belgium's NSIH. The quarterly dissemination of results by England's NINNS is a strong suit because it keeps the matter of HAI control on the minds of the personnel and encourages them to take action towards improving the reported rates. Similarly, RAISIN's personalised reports throughout the year are a chance for infection control specialists to provide frequent and catered advice for potential improvements.

Several aspects of the HABSI programs can reduce their effectiveness. Participation for a minimum of 3 months per year produces results that are not necessarily representative of the entire year, especially when potential seasonality in certain HABSI sources such as pulmonary infections is considered. Limiting HABSI identification to medical records, as done in NSIH, reduces sensitivity of case measurement and the accuracy of the consequent estimates. The absence of denominator data in the instance of RAISIN almost renders the entire surveillance operation of limited usefulness. Unless the number of admissions and patient-days remains constant within a hospital over time, data can only be used to study the distribution of cases by source or pathogen. Estimates cannot be compared across hospitals because of unadjusted, differing patient populations.

1.1.5 BACTOT surveillance

In the Province of Quebec, the *Surveillance provinciale des infections nosocomiales* (SPIN; Provincial Nosocomial Infection Surveillance) committee, under the authority of the *Institut national de santé publique du Québec* (INSPQ; Quebec Institute of Public Health), oversees the monitoring of select HAIs in addition to antibiotic resistant microbes.

HABSI captured the attention of SPIN following two pilot surveys in 1998 (SPIN-1) and 2000-2001 (SPIN-2).[96,97] SPIN-1 recorded a hospital wide HABSI incidence of 6.7 HABSI/10,000 patient-days, a rate which quadrupled in ICUs.[96] As much as 88% of HABSI were recorded in ICUs. SPIN-2 found that 13.7% of HABSI in ICU were associated with death.[97] With such a high burden of HABSI in ICUs, SPIN initiated the surveillance of CLABSI in ICUs through the *Surveillance des bactériémies nosocomiales sur cathéters centraux aux soins intensifs* (BACC-USI) program in October 2003.[98]

After witnessing reductions through BACC-USI and developing its surveillance experience, SPIN introduced facility-wide HABSI surveillance in April 2007 though the *Surveillance des bactériémies nosocomiales panhospitalières* (BACTOT) program. HABSI surveillance was deemed a priority because it is associated with the highest morbidity and mortality among HAI. BACTOT would be more inclusive of the already existing BACC-USI, capturing the overlooked burden in smaller hospitals without ICUs. As HABSI frequency is often in proportion to the number of hospital admissions, lower resource hospitals which tend to be on the smaller side, are not overburdened with the monitoring and investigation of arising cases.

SPIN set the following objectives for BACTOT[98]:

1. Document the incidence of nosocomial bacteremia, outbreaks, geographical regions and changes over time according to different criteria.
2. Identify the etiological agents associated with these bacteremias.
3. Document morbidity and mortality at 30 days following nosocomial bacteremia.
4. Document the proportion of nosocomial bacteremia due to multi-resistant microorganisms.
5. Create a database to benchmark the rates of bacteraemia found in the various hospitals in Quebec and monitor these rates in a benchmarking way, thus allowing the facilities to compare their infection rate with the rates of infection of other facilities in Quebec.
6. Assist facilities to minimize the incidence of bacteremia and to identify hatching situations.
7. Consolidate the provincial surveillance network for nosocomial infections by providing a relevant monitoring menu for each facility.

BACTOT participation was initially voluntary for all hospitals with more than 1000 acute care admissions per year and became mandatory in April 2013. SPIN requires all participating hospitals to perform active surveillance for HABSI in their facility. Data collected from each facility are analysed annually, and reports are published on the INSPQ website for each administrative year. The main indicator calculated is the HABSI incidence rate per 10,000 patient-days for each facility. Rates are compared across facilities to benchmark a facility's relative performance. The proportions of each infection subtype are reported, in addition to the patterns of microorganism isolates and key antibiotic resistances. Although BACTOT was initiated in 2007 and achieved near full participation from eligible hospitals in 2014, only one peer-reviewed article

so far has shared its results. The published article focused on HABSI secondary to a urinary focus,[45] describing the proportion of HABSIs that were secondary to UTIs and some facility characteristics associated with their acquisition.

1.2 Objectives

The overarching objective of my thesis was to explore Québec HABSI rates longitudinally. The first objective was to describe the changes in HABSI rates over calendar time, from BACTOT inception to its tenth year of operation. While SPIN-BACTOT has been publishing its rate annually for the 10 years, it has not yet looked at the long-term secular trend over this period.

My second objective was to demonstrate an association between BACTOT surveillance and hospitals' HABSI rates. In this case, the time variable refers to the time a hospital has been participating in BACTOT, regardless of the calendar date of its entry. This will allow us to evaluate whether the consecutive years of surveillance participation show a reduction in HABSI rates relative to the first year of participation.

Chapter 2: Methods

2.1 Data source

Data used for both objectives of this thesis was obtained directly from SPIN-BACTOT. The process of data collection is described, and the case definitions employed for surveillance purposes are listed below.

2.1.1 BACTOT data collection

Participating hospitals perform facility-wide, active surveillance of HABSI, excluding psychiatric wards, long term care, and nurseries. The following information is collected for all participating hospitals: health region, teaching status, number of beds and ICU beds, and proportion of patients 65 years and older. For every administrative 4-week period, hospitals submit denominator and HABSI case data. Denominator data are total patient-days recorded, ICU-specific patient-days, and total admissions. Case data include patient demographics, date of diagnosis, unit in which the case arose, type of infection, microorganisms involved with antibiotic susceptibility profile, recent invasive procedures, risk factors for infection, suspected origin of acquisition, and complications resulting from the infection.

On April 1st, 2013 participation in BACTOT became mandatory province-wide for all acute care hospitals with more than 1,000 annual admissions. On the same date, a new online data entry platform was implemented (Nosokos®, Nosotech, QC, Canada).

2.1.2 BACTOT case definitions

BSI episodes are identified using the National Healthcare Safety Network (NHSN) criteria.[6] Cases must meet one of the following criteria (1) a patient with a recognized pathogen cultured from one or more blood cultures, not related to an infection at another site (primary BSI); or (2) a patient with a recognized pathogen cultured from one or more blood cultures related to an infection at another site (secondary BSI); or (3) a patient with a common skin contaminant cultured from 2 or more blood cultures less than one day apart with one or more of the following signs or symptoms: fever greater than 38°C, chills, hypotension or hypothermia less than 37°C, apnea, or bradycardia (also primary BSI). BSIs are deemed healthcare-associated (HABSI) if they occur 2 calendars days after admission, unless they resulted from a preceding admission or procedure.[6] Primary BSIs are subtyped as BSIs associated with a venous catheter (CA-BSI, either central or peripheral), and non-catheter-associated primary BSIs (NCA-BSI). Secondary BSIs are subtyped as secondary to surgical site infections (BSI-SSI), urinary tract infections (BSI-UTI), pulmonary infections (BSI-PULM), intra-abdominal infections (BSI-ABDO), skin-and-soft-tissues infections (BSI-SST), bone-and-joint infections (BSI-BONE) or any other primary focus (BSI-Other). Dialysis-associated primary BSIs are also followed by BACTOT but were not included in the obtained data as they predominantly occur in ambulatory settings and are the object of a separate surveillance.

Major changes in definitions over the 10-year period include the following: between April 1st, 2011 and March 31st, 2013, primary BSIs following invasive procedures (here classified under

NCA-BSI) were defined as cases occurring within 2 calendar days following the procedure. Before 2011 and after 2013, the window of causality was of 7 calendar days.

Ethics approval was obtained for both studies from the Institutional Review Board at McGill University. Data access was provided by the INSPQ's Immunisation and Nosocomial Infection scientific unit. INSPQ approved the use of BACTOT data for this project, as it was in line with its mandate to document determinants of incidence rates of healthcare-associated infections.[99]

2.2 Methodological considerations

As the two objectives of this thesis deal with longitudinal data collected from numerous hospitals, a major statistical challenge faced in the two manuscripts is the correlation between observations arising from the same hospitals. Numerous factors associated with the outcome are closely related to the hospital in which outcome arises. This includes management, infection and prevention control culture, geographical location, patient population, the types of wards it accommodates and so on. The correlation of observations from the same hospital arises because most of these factors remain relatively constant across time, causing the outcome to similarly behave.

Correlation becomes problematic when classical regressions are employed to capture changes in the outcome as a function of other covariates, as a main underlying assumption to these regressions is that the errors are independent. A residual plot generated from a classical regression model fitted to correlated data will reveal this correlation and confirm that it is not capturing the

true structure of variance. A violation of the assumption can lead to the inaccurate estimation of error in the data and may result in misleading inferences.[100]

To circumvent this problem, one can resort to fitting separate regressions for each hospital, but this prevents researchers from making inferences at the cohort-level, which is often the interest in such studies. Fortunately, a degree of sophistication has been reached in both statistical ingenuity and computational power to allow us to deal with correlated data appropriately. Generalised Estimating Equations and multilevel Bayesian modelling are employed to address my first and second objectives, respectively.

Chapter 3: Manuscript 1

A ten-year review of healthcare-associated bloodstream infections from 40 hospitals in Quebec, Canada. (Published in Infection Control and Hospital Epidemiology in the September 2018 issue)

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Abstract

Objective. Healthcare-associated bloodstream infections (HABSI) are a significant cause of morbidity and mortality worldwide. In Quebec, Canada, HABSI arising from acute care hospitals have been monitored since April 2007 through the BACTOT program, but this is its first detailed description of HABSI epidemiology.

Methods. This retrospective, descriptive study was conducted using BACTOT surveillance data from hospitals that participated continuously between April 1st, 2007 and March 31st, 2017. HABSI cases and rates were stratified by hospital type and/or infection source. Temporal trends of rates were analysed by fitting Generalized Estimating Equation Poisson models, and were stratified by infection source.

Results. For 40 hospitals, 13,024 HABSI cases and 23,313,959 patient-days were recorded, for an overall rate of 5.59/10,000 patient-days (95% C.I.: 5.54-5.63). The most common infection sources were catheter-associated BSIs (23.0%), BSIs secondary to a urinary focus (21.5%), and non-catheter-associated primary BSIs (18.1%). Teaching hospitals and non-teaching hospitals with ICUs often had rates higher than non-teaching hospitals without ICUs. Annual HABSI rates did not exhibit statistically significant changes from year to year. Non-catheter-associated-primary BSIs were the only HABSI type that exhibited a sustained change across the 10 years, increasing from 0.69/10,000 patient-days (95% CI: 0.59-0.80) in 2007-08 to 1.42/10,000 patient-days (95% CI: 1.27-1.58) in 2016-17.

Conclusion. Despite ongoing surveillance, overall HABSI rates have not decreased. The effect of BACTOT participation should be more closely investigated and targeted interventions along

with alternative surveillance modalities should be considered, prioritising high burden and potentially preventable BSI types.

Background

Healthcare-associated bloodstream infections (HABSI) are a significant cause of morbidity and mortality worldwide. Recent multi-center studies in Europe, the United States, and Australia report HABSI incidence rates (IRs) for acute care inpatients ranging between 6 and 21 cases per 10,000 patient-days,[101-103] with case fatality rates between 12% and 31%.[35,36] Estimates from Canada are limited to point prevalence studies,[1,30] which are subject to seasonality and time-dependent bias as they assume the population at risk is at a steady state and oversample sicker patients with longer lengths of stay.[64,65,104] Accurate estimates of HABSI are necessary to assess disease burden, benchmark and cross-comparison across facilities and jurisdictions, and ultimately to improve patient care and safety.

In the Province of Quebec, Canada, HABSIs have been monitored in acute care hospitals since April 1st, 2007, by the *Surveillance provinciale des infections nosocomiales* (SPIN; Provincial Nosocomial Infection Surveillance) through the *Surveillance des bactériémies nosocomiales panhospitalières* (BACTOT) program. BACTOT differs from most HABSI surveillance programs by monitoring all acute care HABSI, regardless of infection source or ward type. March 31st, 2017 marked the completion of 10 years of BACTOT surveillance. Only one peer-reviewed article focusing on HABSI secondary to a urinary focus has published its results so far.[45] This paper is a descriptive epidemiological presentation of BACTOT

surveillance data from hospitals that have participated continuously for10 years., describing the overall and source-specific IRs of HABSI, and temporal changes in them.

Methods

Data collection

Beginning on April 1st, 2007, SPIN required all voluntarily participating hospitals to perform active facility-wide surveillance of HABSI, excluding psychiatric wards, long term care, and nurseries. On April 1st, 2013, participation in BACTOT became mandatory province-wide for all hospitals with more than 1,000 admissions per year, and a new online data entry platform was implemented to streamline data collection (Nosokos®, Nosotech, QC, Canada). The following information was collected for all participating facilities: health region, teaching status, number of beds and ICU beds, and proportion of patients of 65 years and older. Facilities submitted overall and ICU specific inpatient-days denominators for every administrative 4-week period. SPIN also gathered pre-specified relevant variables for each HABSI case identified including: patient demographics, date of diagnosis, unit in which the case arose, type of infection, microorganisms involved with antibiotic susceptibility profile, recent invasive procedures, risk factors for infection, suspected origin of acquisition, and complications resulting from the infection.

Case definitions

BSI episodes were identified using the National Healthcare Safety Network (NHSN) criteria.[6] Cases had to meet one of the following criteria: (1) a patient with a recognized pathogen cultured from one or more blood cultures not related to an infection at another site (primary BSI); or (2) a patient with a recognized pathogen cultured from one or more blood cultures related to an infection at another site (secondary BSI); or (3) a patient with a common skin contaminant cultured from 2 or more blood cultures less than one day apart with one or more of the following signs or symptoms: fever greater than 38°C, chills, hypotension or hypothermia less than 37°C, apnea, or bradycardia (also primary BSI). Prior to April 1st, 2010, a primary catheter-related BSI with a common skin contaminant only required one positive blood culture, as long as the treating physician had initiated treatment. The data used here was corrected retrospectively to reject BSIs with less than 1 blood culture. BSIs were deemed healthcare-associated (HABSI) if they occurred more than 2 calendar days after admission, unless they resulted from a preceding admission or procedure.[6] Primary BSIs were subtyped as BSIs associated with a venous catheter (CA-BSI), either central or peripheral, and non-catheter-associated primary BSIs (NCA-BSI). Secondary BSIs were subtyped as secondary to surgical site infections (BSI-SSI), urinary tract infections (BSI-UTI), pulmonary infections (BSI-PULM), intra-abdominal infections (BSI-ABDOs), skin-and-soft-tissues infections (BSI-SST), bone-and-joint infections (BSI-BONE) or any other primary focus (BSI-Other). Between April 1st, 2011 and March 31st, 2013, primary BSIs following invasive procedures (classified under NCA-BSI) were defined as cases occurring within 2 calendar days following the procedure. After 2013, the window of causality was returned to 7 calendar days. Dialysis-associated primary BSIs are also followed by BACTOT but were not analysed in this study as they predominantly occur in ambulatory care.

Study design and analysis

This is a retrospective, descriptive study conducted using BACTOT surveillance data from a closed cohort of eligible hospitals participating for at least 11 of 13 administrative periods annually from April 1st, 2007 to March 31st, 2017. Data pooled by hospital and administrative period was obtained directly from SPIN. Ethics approval was obtained from the Institutional Review Board at McGill University.

Numerators: All incident HABSI cases among admitted patients were pooled by hospital and year, and stratified by type of infection, and/or hospital type (NT no ICU: non-teaching without an ICU; NT with ICU: non-teaching with an ICU; Teaching).

Denominators: Patient-days were pooled by hospital and year and stratified by hospital type. Every day spent at a participating hospital by a patient was counted as one patient-day. Days of admission and discharge were each counted as half a day.

Descriptive analyses: The characteristics of hospitals that met the inclusion criteria were described. A logistic regression was fitted to investigate any difference in the characteristics between included and excluded hospitals. The frequency distribution of HABSI subtypes over the 10-year period was reported. Annual and ten-year IRs were calculated, by dividing the number of incident cases from each period by the total number of patient-days of the same period and reported per 10,000 patient-days. Based on INSPQ standard practice, ninety-five percent confidence intervals for these rates were calculated using the normal approximation method further transformed to account for over-dispersion using the following formulas:

lower bound $= IR/\exp(1.96\sqrt{cases})$; upper bound = $IR \times \exp(1.96\sqrt{cases})$

Generalised Estimating Equations (GEE): GEE Poisson regression models with exchangeable correlation structures were fitted for all HABSI and each subtype. The variables in each model were administrative year, coded as a categorical variable with 10 levels (year 1 as reference), and hospital type, coded as a categorical variable with 3 levels (NT no ICU as reference, NT with ICU, and T). The incidence rate ratios (IRR) are reported.

All analyses were conducted using R version 3.4.1 with RStudio version 1.0.143 (RStudio Team, Boston, MA).

Results

Cohort description

Forty of the ninety (44%) acute care hospitals eligible to participate in BACTOT met the inclusion criteria. Between April 1st, 2007 and March 31st, 2017, a total of 13,024 HABSI cases were reported for 23,313,959 patient-days (Table 1). The included hospitals contributed 47% of all BACTOT recorded patient-days in Y10 (2016-2017).[105] Thirty-six of the included hospitals participated in all 130 administrative periods, while the remaining 4 contributed 129 periods each. Thirty percent of the cohort (n=12) were teaching hospitals, all of which had ICUs. NT with ICU hospitals formed 48% (n=19) of the cohort, while NT no ICU hospitals represented 23% (n=9). Hospitals' sizes varied between 29 and 549 beds, with a median of 188.5, totalling

8488 beds. In hospitals with ICUs, the number of ICU beds ranged from 3 to 75, with a median of 10. Only one hospital was exclusively paediatric. The proportion of a given hospital's patient population 65 years or older ranged between 30% and 57%, with a median of 47%. There was no statistically significant difference between the included and excluded hospitals in the aforementioned characteristics.

HABSI types

Of all reported cases, 41% were primary BSIs (23% CA-BSI and 18.2% NCA-BSI). The most common secondary HABSI was BSI-UTI (21.5%), followed by BSI-SSI (12.7%), BSI-PULM (11.2%) and BSI-ABDO (7.2%). BSI-SST represented 3.2% of all cases, BSI-Other 2.6% and BSI-BONE 0.5%.

Ten-year rates

The 10-year HABSI IR for the cohort was 5.59/10,000 patient-days (95% CI: 5.54 – 5.63) (Table 1). On average, NT with ICU hospitals had annual rates 1.47 (95% CI: 1.08-2.02) times higher than NT no ICU, while teaching hospitals had rates 3.10 (95% CI: 2.06-4.65) times higher than NT no ICU hospitals (Table 3).

Primary BSI: CA-BSI's 10-year rate was 1.29/10,000 patient-days (95% CI: 1.24-1.34). It was the most frequent HABSI in teaching hospitals. NCA-BSI's 10-year rate was 1.01/10,000 patient-days (95% CI: 0.97-1.05). Both types were significantly higher in teaching hospitals compared to NT no ICU hospitals (Table 3).

Secondary BSI: BSI-UTI had a 10-year rate of 1.2/10,000 patient-days (95% CI: 1.16-1.25) and was the most frequent HABSI in NT hospitals. BSI-SSI had a relatively lower 10-year of

0.71/10,000 patient-days (95% CI: 0.68-0.75). The 10-year rate for BSI-PULM was 0.62/10,000 patient-days (95% CI: 0.59-0.65) and was 0.4/10,000 patient-days (95% CI: 0.38-0.43) for BSI-ABDO. BSI-SST, BSI-Other, and BSI-BONE were relatively infrequent (Table 2).For all secondary HABSI except BSI-BONE, teaching hospitals had significantly higher rates than NT no ICU, while only BSI-UTI and BSI-SSI rates were significantly higher in NT with ICU (Table 3).

Time trends

The HABSI rate in Y1 was 5.63/10,000 patient-days (95% CI: 5.34-5.79) and showed minimal fluctuation until Y10 in which the rate was 5.61/10,000 patient-days (95% CI: 5.31-5.77) (Figure 1). GEE analyses showed no statistically significant effect of year on the IRs for the cohort (Table 4).

Primary BSI: In Y1, annual CA-BSI rate was 1.47/10,000 patient-days (95% CI: 1.32-1.63) and appeared to decrease consistently until Y8 (Figure 2). However, only Y8 showed a statistically significant 42% (95% CI: 26%-55%) drop relative to Y1, but the rate rebounded in the last two years (Table 2). NCA-BSI began with a rate of 0.69/10,000 patient-days (95% CI: 0.59-0.8), almost half the rate of CA-BSI in Y1. Rates showed a steep increase in Y7 where the rate was 1.13/10,000 patient-days (95% CI: 1.01-1.28), a 67% (95% CI: 20%-133%) increase from Y1. In Y8, the NCA-BSI rate of 1.32/10,000 patient-days (95% CI: 1.18-1.48) surpassed the CA-BSI rate. This rise was sustained until Y10, ending with a rate 110% (95% CI: 60%-176%) higher than Y1.

Secondary BSI: Annual BSI-UTI rates showed little year-to-year change (Table 2). Only in Y10 did the rates drop to 0.98/10,000 patient-days (95% CI: 0.86-1.12), a 25% (95% CI: 2%-43%) reduction from the Y1 rate. BSI-SSI rate was 0.81/10,000 patient-days (95% CI: 0.70-0.93) in Y1 and dropped by 26% (95% CI: 9%-39%) in Y3 but this decrease was not sustained in the following years. BSI-SST annual rates showed a statistically significant bump in Y4 with a 52% (95% CI: 4%-123%) increase compared to Y1. Similarly, BSI-Other showed unsustained increases in Y5 and Y6 of 60% (95% CI: 19%-116%) and 108% (95% CI: 25%-244%), respectively. Annual BSI-PULM, BSI-ABDO, and BSI-BONE rates showed no statistically significant changes.

Discussion

Our study is one of the largest published reports on HABSI epidemiology describing a large population surveyed over a full decade with a high case number. It adds substantial knowledge to the scarce literature, especially from North America. We reported an overall HABSI rate of 5.59 HABSI cases/10,000 patient-days, similar to 6.0/10,000 patient-days reported by the only recent high-coverage (24 hospitals), multi-center study in Queensland, Australia during a period overlapping ours.[101] A smaller study in Denmark reported a rate of 6.4/10,000 patient-days and another in the United States reported a range between 11.2 and 6.7 per 10,000 patient-days.[102,103]

HABSI rates were consistently higher in teaching hospitals and often higher in non-teaching hospitals with ICUs compared to non-teaching hospitals without ICUs. It is common for HAI rates to be higher in teaching hospitals as they often receive sicker patients given their mission to provide specialised care for severely-ill patients who are more vulnerable to

HABSI.[25,106-108] Higher HABSI rates in hospitals with ICUs can be explained by the usually higher rates in ICUs compared to wards outside the ICU.[29]

The longitudinal nature of surveillance data collection allowed us to analyse temporal trends in rates. We found no significant changes in annual HABSI rates at the cohort level. While there were no province-wide interventions that targeted HABSI as a whole, a campaign targeting multi-drug resistant HABSI, CLABSI, SSI, and ventilator-associated pneumonia was implemented in 2014 (Y7-Y8).[109] The degree to which hospitals complied with the campaign guidelines and its subsequent effects on our results are unknown. Other multi-centre studies have reported variable temporal trends in HABSI rates. Some exhibited decreases,[26,103] others increases,[110] and some no consistent trend.[20,102,111] It is difficult to compare our reported temporal trends because time periods did not overlap,[20,26,111] studied hospitals had characteristics different to ours,[102,103] or denominators used were population-based, not hospital-based.[110,111]

Owing to BACTOT's data collection procedure we were able to analyse HABSI cases and rates by infection source. The leading sources of cases were CA-BSI which include central-line associated BSI (CLABSI), the most targeted subset of HABSI in infection prevention and control, BSI-UTI, and NCA-BSI. Relatively similar proportions were reported by Valles et al.[39]

CA-BSI rates began as the highest subtype in Y1 and showed a statistically significant drop in rates in Y8 (2014-2015) that was not sustained. A 2014 drop was also seen in a recent study by Li et al. on another SPIN surveillance program (SPIN-BACC) that targets CLABSI in ICUs and may be explained by bundled practices introduced in the beginning of Y3.[112] While this may have contributed to the results seen here, our study includes an overall insubstantial

number (6.4%) of patient-days spent in ICUs compared to Li's study which was limited to CLABSI in the ICU.

NCA-BSI rates exhibited a sustained statistically significant increase in Y7 (2013-2014) and overtook other subtypes to become the most frequent in Y8-Y10. The rise coincides with returning the window of causality for BSIs following invasive procedures from 2 days to 7 days. However, if the rise was a result of the definition change, an equal reduction must have been seen in Y5 when the window was reduced to 2 days, which is not the case. Y7 was also the year the new data entry platform for BACTOT data collection was implemented in participating hospitals. As this was suspected to cause artefactual changes in rates, SPIN validated the platform and concluded that new data entry rules contributed to some cases being miscategorised or erroneously rejected and corrections were subsequently made. As our analyses utilize the corrected data, it is plausible that the persistent increase in NCA-BSI reported here is a true one. A possible cause for it could be an increase in the number of procedures performed.

Among secondary HABSI, BSI-UTI was consistently the most frequent. This is often the case in hospitals due to extensive use of urinary catheters, the main contributing cause of urinary tract infections and consequent BSI-UTI.[39,45] A considerable amount of HABSI were BSI-PULM, BSI-ABDO and BSI-SSI, but their rates did not exhibit any lasting changes in the 10 years. BSI-SST, BSI-BONE and BSI-Other occurred at relatively negligible rates.

The absence of a sustained change in HABSI rates is concerning but not necessarily an indication of ineffective surveillance. The observed trend may be a function of demographic changes and hospital performance developments masking the true effect of BACTOT participation on HABSI rates. For instance, the aging Canadian population results in more

elderly patients in hospitals. A 13.5% increase in patient-days contributed by patients ≥65 years from 2007-2008 to 2016-2017 indicates that more patients have become vulnerable to potentially non-preventable HABSI.[113] Additionally, lengths-of-stay are reportedly decreasing following efforts to reduce unnecessary healthcare utilisation. In Quebec, average length-of-stay decreased from 8.4 days in 2007-2008 to 7.8 in 2016-2017.[113] While this is a welcome improvement in hospital performance, it can result in inflated HABSI rates.

Nevertheless, it is not our objective to infer a causal mechanism of the observed trend. Our study's goal is to report the cohort-level trend as it occurred, which it does with several strengths. It covers 44% of all acute care hospitals in Quebec, capturing 47% of all patient-days in 2016-2017.[105] Hospitals included in the study did not exhibit statisticallysignificant differences in reported characteristics from excluded ones, suggesting the cohort is representative of all eligible hospitals, as does the substantial overlap between our Y10 (2016-2017) HABSI rate (5.30, 95% CI: 5.22-5.64) and that published by SPIN-BACTOT (5.61,95% CI: 5.31-5.77).[105] The study produces precise estimates of endemic rates not skewed to a particular type of hospital because of the diversity of included hospitals; therefore these rates can be used for benchmarking, informing future prevention measures, and as a baseline for further evaluations. Rates were calculated using patient-days, avoiding time-dependent bias common in point-prevalence studies, and reducing confounding due to exposure duration when comparing rates across time or populations, a limitation of population-based denominators. The 10-year period covered by our study allowed the exploration of time trends in HABSI rates, which is a rarity in recently published literature. Finally, it was possible to stratify incidence based on the primary source of infection because HABSI clinical diagnoses were systematically reported. To our

knowledge, this stratification has only been done once before and not to the granularity reported here.[39]

While our study estimates HABSI rates and subtype characterisations comparable to those reported by other recent HABSI studies, the lack of an overall reduction in HABSI rates over the prolonged period of time is concerning, especially given the amount of resources employed by SPIN and the participating hospitals. For this reason, we recommend a more detailed exploration of the effect of BACTOT surveillance on HABSI to evaluate whether current surveillance measures are meeting its pre-set objectives. Alternative surveillance modalities should be considered, including less frequent HABSI reporting and prioritisation of high burden BSI types. Aside from surveillance, interventions targeting potentially preventable BSI types are needed to see substantial reductions in rates.

Acknowledgements

We are grateful to all the infection control practitioners and infectious disease physicians/medical microbiologists who participate in the SPIN program. SPIN-BACTOT working group members: Élise Fortin, Charles Frenette, Lise-Andrée Galarneau, Sylvie Latreille, Danielle Moisan, Muleka Ngenda-Muadi, Noémie Savard, Marc-André Smith, Claude Tremblay, Mélissa Trudeau, Jasmin Villeneuve.

Financial support. This work was supported by SPIN, a program from the Quebec Institute of Public Health, funded by the Quebec Ministère de la Santé et des services sociaux (Ministry of

Health). Dr. Quach is supported through an external salary award (FRQ-S merit, grant # 252775). Dr. Alex Carignan is supported through an external salary award (FRQ-S junior 1).

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Tables and Figures

Table 1. Healthcare-Associated Bloodstream Infection (HABSI) Incidence Rates and Patient-days Reported for the Cohort Between 2007-08 and 2016-17, per Administrative Year, Stratified by Hospital Type.

Admin-istrative year	Calendar year	All hospitals (n=40)		NT no ICU (n=9)		NT with ICU (n=19)		Teaching (n=12)	
		Patient-days	Incidence rate* (95% CI)	Patient-days	Incidence rate* (95% CI)	Patient-days	Incidence rate* (95% CI)	Patient-days	Incidence rate* (95% CI)
Y1	**2007-08**	2,331,317	5.63 (5.34 - 5.79)	162,697	2.21 (1.60 - 2.61)	1,021,084	3.79 (3.43 - 3.99)	1,147,536	7.76 (7.26 - 8.02)
Y2	**2008-09**	2,373,262	5.97 (5.67 - 6.14)	163,424	2.45 (1.80 - 2.87)	1,049,740	4.41 (4.03 - 4.62)	1,160,098	7.89 (7.39 - 8.15)
Y3	**2009-10**	2,338,975	5.29 (5.01 - 5.45)	158,339	1.89 (1.32 - 2.27)	1,023,917	4.19 (3.81 - 4.40)	1,156,719	6.73 (6.28 - 6.98)
Y4	**2010-11**	2,348,932	5.77 (5.47 - 5.93)	157,138	2.61 (1.92 - 3.05)	1,020,489	3.86 (3.50 - 4.06)	1,171,305	7.85 (7.36 - 8.12)
Y5	**2011-12**	2,365,971	5.55 (5.25 - 5.70)	157,230	3.37 (2.58 - 3.87)	1,033,398	4.13 (3.76 - 4.34)	1,175,343	7.08 (6.61 - 7.33)
Y6	**2012-13**	2,366,943	5.60 (5.30 - 5.75)	151,936	2.24 (1.60 - 2.66)	1,048,827	3.99 (3.62 - 4.19)	1,166,180	7.49 (7.01 - 7.74)
Y7	**2013-14**	2,336,491	5.71 (5.42 - 5.87)	151,099	2.25 (1.61 - 2.67)	1,048,302	4.14 (3.77 - 4.34)	1,137,090	7.62 (7.13 - 7.89)
Y8	**2014-15**	2,310,355	5.25 (4.96 - 5.40)	149,219	1.88 (1.30 - 2.27)	1,053,187	4.03 (3.66 - 4.23)	1,107,949	6.86 (6.39 - 7.11)
Y9	**2015-16**	2,270,953	5.46 (5.17 - 5.62)	143,671	2.58 (1.87 - 3.04)	1,049,712	3.82 (3.46 - 4.02)	1,077,570	7.45 (6.95 - 7.72)
Y10	**2016-17**	2,270,760	5.61 (5.31 - 5.77)	138,363	2.17 (1.52 - 2.60)	1,059,695	3.99 (3.63 - 4.19)	1,072,702	7.66 (7.16 - 7.93)
Overall		23,313,959	5.59 (5.49 - 5.64)	1,533,116	2.37 (2.14 - 2.50)	10,408,351	4.04 (3.92 - 4.10)	11,372,492	7.44 (7.28 - 7.52)

NT no ICU: non-teaching hospitals without an ICU; NT with ICU: non-teaching hospitals with an ICU; Teaching: teaching hospitals; CI: confidence interval.

* Rates and confidence intervals are reported per 10,000 patient-days.

N.B. Between Y4 and Y6, BSIs following invasive procedures were considered primary NCA-BSI if they occurred 2 days after the procedure. Outside this time period, the window of causality was 7 days.

Table 2. Source-Specific Healthcare-Associated Bloodstream Infection (HABSI) Incidence Rates for the Cohort from 2007-2017.

Admin-istrative year	Incidence rate* (95% CI)								
	CA-BSI	**NCA-BSI**	**BSI-UTI**	**BSI-PULM**	**BSI-SSI**	**BSI-ABDO**	**BSI-SST**	**BSI-BONE**	**BSI-Other**
Y1	1.47 (1.32 - 1.63)	0.69 (0.59 - 0.8)	1.32 (1.18 - 1.47)	0.60 (0.50 - 0.70)	0.81 (0.70 - 0.93)	0.47 (0.39 - 0.57)	0.16 (0.11 - 0.22)	0.03 (0.01 - 0.06)	0.10 (0.07 - 0.15)
Y2	1.57 (1.42 - 1.74)	0.75 (0.65 - 0.87)	1.31 (1.17 - 1.46)	0.62 (0.53 - 0.73)	0.87 (0.76 - 1.00)	0.51 (0.43 - 0.61)	0.20 (0.15 - 0.27)	0.02 (0.01 - 0.04)	0.12 0.08 - 0.18)
Y3	1.38 (1.24 - 1.54)	0.81 (0.70 - 0.94)	1.11 (0.98 - 1.26)	0.67 (0.57 - 0.78)	0.60 (0.51 - 0.71)	0.41 (0.34 - 0.50)	0.14 (0.10 - 0.20)	0.02 (0.01 - 0.05)	0.15 0.10 - 0.20)
Y4	1.56 (1.41 - 1.73)	0.95 (0.83 - 1.08)	1.18 (1.05 - 1.33)	0.65 (0.55 - 0.76)	0.63 (0.54 - 0.74)	0.37 (0.30 - 0.46)	0.24 (0.19 - 0.31)	0.04 (0.02 - 0.07)	0.15 (0.11 - 0.21)
Y5	1.23 (1.09 - 1.38)	0.92 (0.81 - 1.05)	1.31 (1.17 - 1.46)	0.63 (0.54 - 0.74)	0.68 (0.58 - 0.79)	0.42 (0.34 - 0.51)	0.19 (0.14 - 0.25)	0.02 (0.01 - 0.05)	0.16 (0.11 - 0.22)
Y6	1.20 (1.06 - 1.34)	0.85 (0.74 - 0.98)	1.32 (1.18 - 1.47)	0.71 (0.61 - 0.83)	0.68 (0.58 - 0.79)	0.40 (0.33 - 0.49)	0.21 (0.16 - 0.28)	0.03 (0.01 - 0.06)	0.20 (0.15 - 0.27)
Y7	1.27 (1.13 - 1.42)	1.13 (1.01 - 1.28)	1.29 (1.15 - 1.45)	0.60 (0.51 - 0.71)	0.73 (0.63 - 0.85)	0.33 (0.27 - 0.42)	0.16 (0.12 - 0.22)	0.04 (0.02 - 0.07)	0.15 (0.11 - 0.21)
Y8	0.81 (0.70 - 0.93)	1.32 (1.18 - 1.48)	1.18 (1.05 - 1.33)	0.59 (0.50 - 0.70)	0.63 (0.54 - 0.74)	0.36 (0.29 - 0.45)	0.16 (0.11 - 0.22)	0.05 (0.03 - 0.09)	0.14 (0.10 - 0.20)
Y9	1.23 (1.10 - 1.39)	1.33 (1.18 - 1.48)	0.99 (0.87 - 1.13)	0.60 (0.51 - 0.71)	0.68 (0.58 - 0.8)	0.34 (0.27 - 0.42)	0.14 (0.10 - 0.19)	0.01 (0.00 - 0.04)	0.15 (0.10 - 0.20)
Y10	1.15 (1.02 - 1.3)	1.42 (1.27 - 1.58)	0.98 (0.86 - 1.12)	0.57 (0.48 - 0.68)	0.75 (0.64 - 0.87)	0.38 (0.31 - 0.47)	0.19 (0.14 - 0.26)	0.01 (0.00 - 0.04)	0.16 (0.12 - 0.22)
Overall	1.29 (1.24 - 1.34)	1.01 (0.97 - 1.05)	1.20 (1.16 - 1.25)	0.62 (0.59 - 0.65)	0.71 (0.68 - 0.75)	0.40 (0.38 - 0.43)	0.18 (0.16 - 0.20)	0.03 (0.02 - 0.04)	0.15 (0.13 - 0.17)

NT no ICU: non-teaching hospitals without an ICU; NT with ICU: non-teaching hospitals with an ICU; Teaching: teaching hospitals; HABSI, healthcare-associated bloodstream infection; CA-BSI, catheter-associated primary bloodstream infection (BSI); NCA-BSI, non-catheter-associated primary BSI; BSI-UTI, BSI secondary to urinary tract infections; BSI-PULM, BSI secondary to pulmonary infections; BSI-SSI, BSI secondary to surgical site infections; BSI-ABDO, BSI secondary to intra-abdominal infections; ; BSI-SST, BSI secondary to skin-and-soft-tissue infections; BSI-BONE, BSI secondary to bone-and-joint infections; BSI-Other, BSI secondary to any other primary focus; CI: confidence interval.

* Rates and confidence intervals are reported per 10,000 patient-days. N.B. Between Y4 and Y6, BSIs following invasive procedures were considered primary NCA-BSI if they occurred 2 days after the procedure. Outside this time period, the window of causality was 7 days.

Table 3. The Effect of Hospital Type on Overall Healthcare-Associated Bloodstream Infections (HABSI) and Source-Specific Incidence Rates.

Hospital type	IRR in comparison to NT no ICU (95% CI)									
	HABSI	**CA-BSI**	**NCA-BSI**	**BSI-UTI**	**BSI-PULM**	**BSI-SSI**	**BSI-ABDO**	**BSI-SST**	**BSI-BONE**	**BSI-Other**
NT with ICU	1.47 (1.08-2.02)	1.75 (0.85-3.64)	1.41 (0.83-2.39)	2.25 (1.62 - 3.14)	1.19 (0.78-1.80)	2.30 (1.38 - 3.84)	0.98 (0.48-2.01)	1.29 (0.59-2.80)	4.05 (0.57-28.73)	1.76 (0.75-4.14)
Teaching	3.10 (2.06-4.64)	5.27 (2.25 - 12.36)	3.27 (2.07 - 5.16)	2.39 (1.58 - 3.60)	2.22 (1.34 - 3.65)	5.85 (3.54 - 9.69)	2.37 (1.06 - 5.29)	2.69 (1.11 - 6.49)	4.09 (0.55-30.24)	2.39 (1.14-5.01)

IRR, incidence rate ratio as estimated using Generalized Estimating Equations; NT no ICU, non-teaching hospitals without an ICU; NT with ICU, non-teaching hospitals with an ICU; Teaching, teaching hospitals; HABSI, healthcare-associated bloodstream infection; CA-BSI, catheter-associated primary bloodstream infection (BSI); NCA-BSI, non-catheter-associated primary BSI; BSI-UTI, BSI secondary to urinary tract infections; BSI-PULM, BSI secondary to pulmonary infections; BSI-SSI, BSI secondary to surgical site infections; BSI-ABDO, BSI secondary to intra-abdominal infections; BSI-SST, BSI secondary to skin-and-soft-tissue infections; BSI-BONE, BSI secondary to bone-and-joint infections; BSI-Other, BSI secondary to any other primary focus; CI, confidence interval.

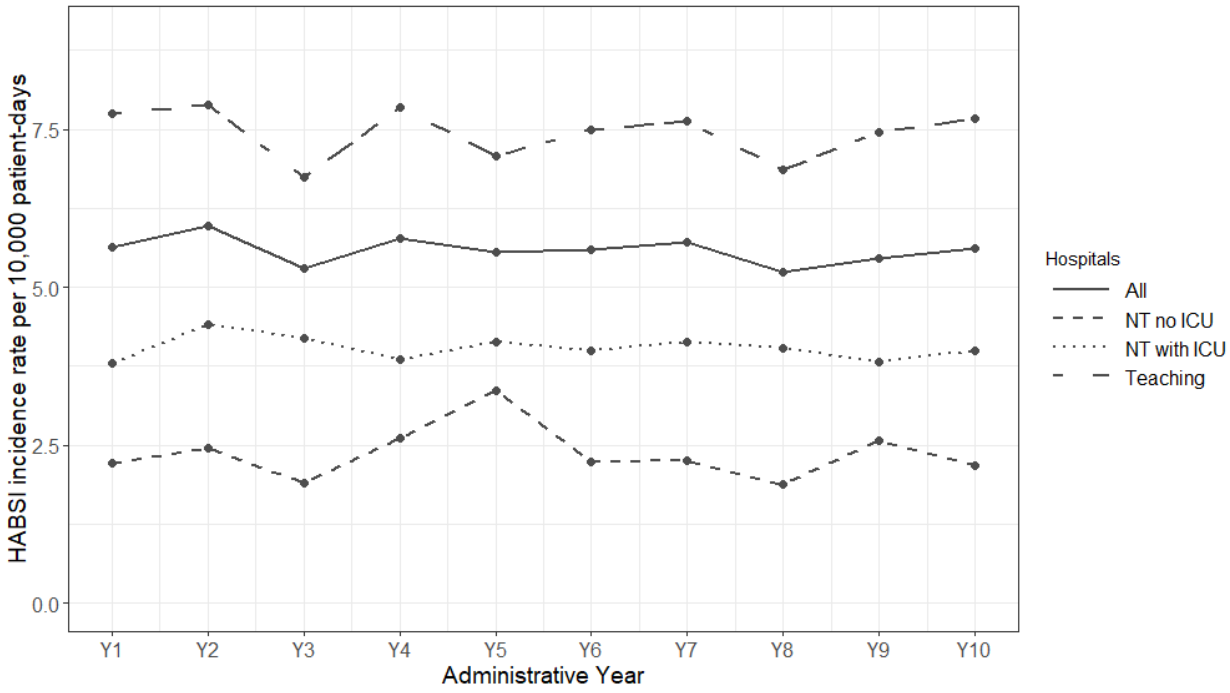

Figure 1. Annual incidence rates of all healthcare-associated bloodstream infections (HABSI) in hospitals that have participated in the Quebec HABSI surveillance program (BACTOT) from 2007-08 (Y1) to 2016-17 (Y10), stratified by hospital type.

NT with ICU, non-teaching hospitals with an intensive care unit; NT no ICU, non-teaching hospital without an intensive care unit; Teaching: teaching hospitals. N.B. Between Y4 and Y6, BSIs following invasive procedures were considered primary NCA-BSI if they occurred 2 days after the procedure. Outside this time period, the window of causality was 7 days.

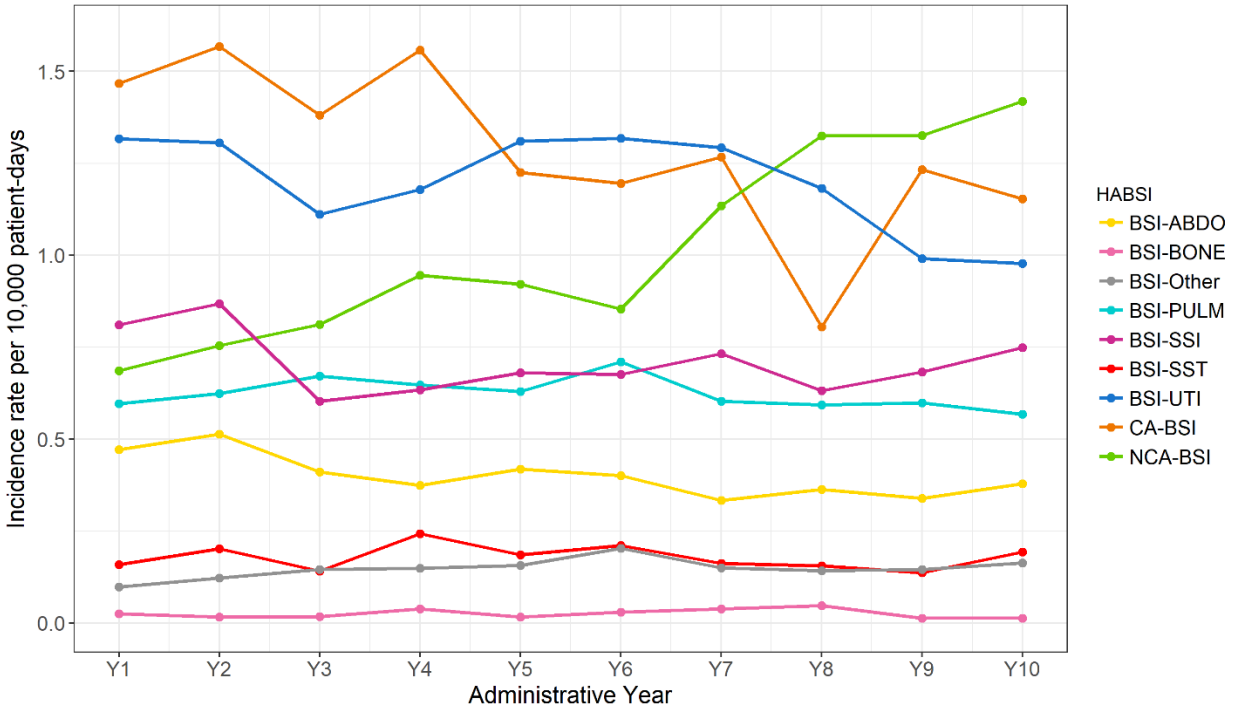

Figure 2. Annual incidence rates of healthcare-associated bloodstream infections (HABSI) in hospitals that have participated in the Quebec HABSI surveillance program (BACTOT) from 2007-08 (Y1) to 2016-17 (Y10), stratified by infection source.

BSI-ABDO, bloodstream infection (BSI) secondary to intra-abdominal infections; BSI-BONE, BSI secondary to bone-and-joint infections; BSI-PULM, BSI secondary to pulmonary infections; BSI-SSI, BSI secondary to surgical site infections; BSI-SST, BSI secondary to skin-and-soft-tissue infections; BSI-UTI, BSI secondary to urinary tract infections; BSI-Other, BSI secondary to any other primary focus; CA-BSI, catheter-associated primary BSI; NCA-BSI, non-catheter-associated primary BSI. N.B. Between Y4 and Y6, BSIs following invasive procedures were considered primary NCA-BSI if they occurred 2 days after the procedure. Outside this time period, the window of causality was 7 days.

Chapter 4: Manuscript 2

Healthcare-associated bloodstream infection rate trends under a provincial surveillance program

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Abstract

Background: While surveillance has been shown to reduce healthcare-associated infections (HAI), this has not been evaluated specifically for healthcare-associated bloodstream infections (HABSI). Among the few existing HABSI surveillance programs, BACTOT in Quebec (Canada) has been operating since 2007, but its effects have not yet been characterised. In this study, we evaluated the changes in HABSI rates and its most common subtypes under a Bayesian framework over 10 years of surveillance in hospitals with different surveillance entry dates.

Methods: Retrospective, cohort study of eligible hospitals having participated in BACTOT for at least 3 years, regardless of their entry date. Multilevel Poisson regressions were fitted independently for HABSI, catheter-associated bloodstream infections (CA-BSI), non-catheter-associated primary BSIs (NCA-BSI), and BSIs secondary to urinary tract infections (BSI-UTI) cases as the outcome and log of patient-days as the offset. The log of the mean Poisson rate was decomposed as the sum of a surveillance year effect, period effect, and hospital effect. The hospital effect included hospital characteristics, as well as the hospitals' entry years into BACTOT. The main estimate of interest was the cohort-level rate in surveillance years 2 to 10, relative to year 1. A subgroup analysis was performed by fitting the same model to hospitals that participated for less than 10 years, to exclude hospitals that may have been conducting surveillance prior to participation.

Results: Overall, 17,479 cases and 33,029,870 patient-days were recorded for the cohort of 77 hospitals. The pooled 10-year HABSI rate was 5.20 per 10,000 patient-days (95% CI: 5.12-5.28). For HABSI, CA-BSI, and BSI-UTI, there was no difference between the estimated posterior rates of years 2 to 10, compared to year 1. As for NCA-BSI, the posterior means of the rate ratios increased from the 7th year of surveillance until the 10th, when the rate was 29% (95% CI: 1-89%)

higher than the 1st year rate. In the subgroup analysis, no differences in rates were detected between the years for HABSI and all analysed subtypes.

Conclusion: It is concerning that HABSI rates and the most frequent subtypes do not decrease over surveillance time, failing to meet one of BACTOT's objectives. Surveillance on its own has not been sufficient to lead to sustained changes over time. We recommend that more efforts be placed in deploying targeted interventions in addition to surveillance to reduce preventable HABSI.

Surveillance has been cited as a useful tool to reduce healthcare-associated infections (HAI).[1-8] Despite the substantial morbidity and mortality of healthcare-associated bloodstream infections (HABSI), surveillance programs for all HABSIs are rare. Networks more commonly perform targeted surveillance where they favour the monitoring of certain HABSI, such as central-line associated bloodstream infections (CLABSI),[9-11] or limit surveillance to certain wards, such as intensive care units (ICUs).[9,12,13]

However, surveillance limited to CLABSI would miss 70-80% of HABSI cases[14], most of which would be secondary infections that are often more morbid with higher case-fatality than primary infections. The relatively low incidence of CLABSI also limits its power for rate comparisons across time and space.[15] Similarly, surveillance limited to ICUs would miss infections arising in acute care wards, which can represent around 40% to 70% of incident HABSI that may have a better likelihood of prevention as they arise in less vulnerable patients.[16,17] Although it is reasonable that institutions with limited resources focus their attention on the most frequent subtypes or the most vulnerable patients, such methods have impeded a more complete

understanding of HABSI and have hindered a potentially more extensive reduction in preventable cases.

To our knowledge, the handful of existing HABSI surveillance programs have been established in Belgium,[18,19] England,[20,21] Finland,[22] and most recently in Quebec, Canada.[23] In 2007, the *surveillance des bactériémies nosocomiales panhospitalières* (BACTOT) program was initiated in Quebec to monitor all HABSI in the province's acute care hospitals. BACTOT has grown from 40 participating hospitals in 2007-2008 to 89 in 2016-2017.[17] While BACTOT has been operating for more than 10 years, the effect of surveillance on HABSI rates has not yet been characterised. In this retrospective, cohort study, we evaluated the effect of each BACTOT surveillance year on hospitals' HABSI rates, using the first year of surveillance as a baseline. It is hypothesized that rates drop progressively in the first few years of surveillance, then begin to level off.

Methods

Data collection

BACTOT data collection has been described elsewhere.[24] Briefly, beginning on April 1st, 2007, participating hospitals performed active HABSI surveillance in their facility, excluding psychiatric wards, long term care, and nurseries. On April 1st, 2013, participation in BACTOT became mandatory for all hospitals with more than 1,000 admissions per year. For each of the thirteen annual 4-week periods, starting on April 1st, the following data are collected for each facility: total patient-days, patient-days in the ICU, and all relevant information on identified HABSI cases. SPIN collects data on pre-specified variables to meet BACTOT's objectives.

Case definitions

The BSI case definition was described elsewhere,[24] and was based on the National Healthcare Safety Network (NHSN) criteria.[25] To be considered healthcare-associated, a BSI could not be present within 48 hours of admission, except if it resulted from a preceding admission or procedure. Primary BSIs constitute BSIs associated with a venous catheter (CA-BSI), both central or peripheral, and non-catheter-associated primary BSIs (NCA-BSI). Secondary BSIs followed by BACTOT are those arising from a primary surgical site infection (BSI-SSI), urinary tract infection (BSI-UTI), pulmonary infection (BSI-PULM), intra-abdominal (BSI-ABDO), skin-and-soft-tissues (BSI-SST), bone-and-joint (BSI-BONE) or any other primary focus (BSI-Other).

Study design and analysis

We conducted a secondary analysis of BACTOT, a retrospective, cohort study of healthcare-associated bloodstream infection data, pooled by hospital and administrative period, and obtained directly from SPIN. The cohort was open and included hospitals that participated for at least 3 consecutive years from their first entry to BACTOT until 2016-17. This restriction allowed us to compare at least two years of surveillance in comparison to the first year. Participation was defined as contributing at least 11 of the 13 administrative periods in a year. Hospitals with no cases (n=2) were excluded as they would not contribute any information to the fitted models. Ethics approval was obtained from the Institutional Review Board at McGill University.

Numerators. All incident HABSI among admitted patients were considered cases. Cases were pooled by hospital and administrative period and stratified by type of infection.

Denominators. Patient-days were pooled by hospital and administrative period. Every day spent at a participating hospital by a patient was counted as one patient-day. Days of admission and discharge were each counted as half a day.

Descriptive analysis

Hospitals that met the inclusion criteria were described by the number of years they contributed, their teaching status, ICU status (whether the hospital has an ICU or not), and number of beds. The frequency distribution of HABSI cases by infection source over the 10-year period was computed. Raw pooled HABSI incidence rates were calculated, by dividing the number of incident cases from each period by the total number of patient-days of the same period and reported per 10,000 patient-days. Ninety-five percent confidence intervals for these rates were calculated using the normal approximation method. Percentages may not add up to 100 because of rounding.

Statistical analyses

Independent multilevel Poisson regression models were fitted to the data aggregated by hospital and period, with HABSI, CA-BSI, NCA-BSI, or BSI-UTI cases as the outcome and the log of patient-days as the offset. The remaining HABSI subtypes were too rare to achieve a model with satisfactory fit. The log-mean Poisson rate for each observation was decomposed into a surveillance year random effect, a period (seasonal) random effect, and a hospital random effect following a normal distribution with unknown variance. The prior mean of the hospital random effect was modelled as a linear function of the number of beds in the facility and hospital type (Non-teaching without ICU as the reference, Non-teaching with ICU, and Teaching), and a

random effect relating to the year the hospital entered BACTOT. Independent zero mean normal prior distributions, with relatively largevariance (equal to 10) were assigned to the coefficients of the hospital-level variables. As some hospitals participated for less than 13 periods annually, 10 observations were missing. Patient-days for those observations were imputed using multiple regression, with calendar time and number of admissions as covariates. The surveillance effects of years 2 to 10 were exponentiated and compared to that of the first year to get incidence rate ratios. Similarly, the period effects of periods 2 to 13 were exponentiated and compared to that of the first period. The incidence rate ratio of different entry years was estimated by dividing the rate independently associated with the year of interest by that associated with the latest year of entry included in the study, 2014-15. The values from the posterior distributions of the coefficients of number of beds and hospital type were exponentiated to get incidence rate ratios.

The same model was fitted using data from all hospitals, and then separately for 37 hospitals with less than 10 years of participation, for a total of 8 models. The subgroup analysis was done to exclude hospitals that may have been conducting facility-wide HABSI surveillance prior to BACTOT entry, for those that started in 2007-08.

As the analytical form of the posterior distribution of the parameter vector is unknown we used Markov Chain Monte Carlo (MCMC) methods to obtain samples from the resultant posterior distribution.[26] In particular, the models were fitted using the software JAGS within the R package *rjags* version 4-6.[27,28] The model burn-ins were 60,000 followed by 150,000 sampling iterations. Convergence of the chains was visually inspected by running two simultaneous chains starting from different values. All analyses were conducted using R version 3.4.1 with RStudio version 1.0.143 (RStudio Team, Boston, MA).

Results

Cohort description

Seventy-seven hospitals were included in the study, representing 87% of the hospitals eligible to participate in BACTOT. Fifty-one percent (n=40) participated for the full 10 years, contributing 76% of total cases and 71% of total patient-days. Of the included hospitals, 26% (n=20) were teaching hospitals, only one of which did not have an ICU. Among non-teaching hospitals, 60% (n=34) had ICUs. The median number of beds per hospital was 153 (IQR=229). Among hospitals with ICUs, the median number of ICU beds was 10 (IQR=8).

Case and rates

Overall, 17,479 cases and 33,029,870 patient-days were recorded for the cohort. The distribution by infection source of total cases was the following; CA-BSI represented 21% of all HABSI, NCA-BSI 20%, BSI-UTI 22%, BSI-PULM 11%, BSI-SSI 12%, BSI-ABDO 8%, BSI-SST 3%, BSI-BONE 1% and BSI-Other 3%. The raw pooled cohort HABSI rate for the 10-year period was 5.20 per 10,000 patient-days (95% CI: 5.12-5.28). There was no clear trend in the raw pooled annual cohort HABSI rates (Table 1). There was large variability in the overall estimated posterior HABSI rates across hospitals (Figure 1). Teaching hospitals tended to have the highest rates, followed by non-teaching hospitals with ICUs (Table 2). An additional 10 beds in a hospital was associated with slightly higher rates in HABSI and the analyzed subtypes. In most instances, year of entry had no clear influence on the rates (Table 3). HABSI and BSI- UTI rates from hospitals entering in 2008-09, for both the main and subgroup analyses, and in 2009-10, for the subgroup analyses, tended to be lower than those from hospitals that entered in 2014-15.

Surveillance effect

For HABSI, CA-BSI, and BSI-UTI, there was no difference between the estimated posterior rates of years 2 to 10 compared to year 1 (Table 4). This remained the case when only hospitals that participated in BACTOT for less than 10 years were analysed separately. As for NCA-BSI, the posterior means of the rate ratios increased from the 7th year of surveillance until the 10th, when the rate became 29% (95% CI: 1-89%) higher than the 1st year rate. However, in the subgroup analysis, both the means and the credible intervals remained relatively constant. The variance of the posterior mean rates for all the models was consistently very low, highlighting that the year-to-year changes in rates were largely similar across hospitals.

Seasonal effect

The fifth and sixth periods, which overlap with the months of August and September, were associated with higher HABSI rates than the first periods, 8% (95% CI: 1-16%) and 7% (95% CI: 0-14%) higher, respectively. On average, the sixth period of the surveillance year tended to have 15% (95% CI: 1-33%) higher CA-BSI rates than the first periods. There was no difference in NCA-BSI or BSI-UTI rates across periods.

Discussion

Our study is the first to evaluate changes in HABSI rates across surveillance time, independently of calendar time, following participation in BACTOT, Quebec's provincial surveillance program. Despite the dedicated long-term surveillance, we detected no sustained change in rates of HABSI or of its most common subtypes. This remained the case when the 40 hospitals that entered BACTOT since its inception were removed from the analyses. Removing these hospitals generally widened the credible intervals of the posterior rate ratios, as they contributed most of the cases and

patient-days, but the posterior means remained relatively constant except in the case of NCA-BSI. The cohort NCA-BSI rates increased in the 7th year to reach rates only slightly higher than the starting rates in the 10th year of surveillance. The rise was absent in the subgroup analysis. While its absence may have been due to reduced power, it can also suggest that the starting 40 hospitals differed from the rest of the cohort in their response to surveillance, or that changes independent of surveillance have been occurring in them. An increase in NCA-BSI rates in these 40 hospitals between years 2014 and 2017 has also been highlighted when calendar time trends were investigated elsewhere.[24]

The influence of calendar time is difficult to eliminate completely when investigating trends over surveillance time. This is especially true when a large number of hospitals share the same entry year, particularly during the years when only these hospitals remain in the cohort. Adjusting for this by directly including a calendar time variable in the model would create problems due its collinearity with surveillance time. The alternative we opted for in this paper was to adjust for the calendar year of entry as a time-invariant effect captured as a random intercept for the hospital effect. To our knowledge, this method has not been used before in the published surveillance literature. Including calendar year of entry in the model reduces the deviance information criterion (DIC), a hierarchical modeling generalisation of the Akaike information criterion (AIC), indicating it captures enough variation in the data to consider it parsimonious to keep it in the model.[29] Another indication that this component explains some structure in the data is that removing it from the model widens the posteriors of the surveillance years' incidence rate ratios and slightly reduces their means. Using dummy variables instead of a random intercept is unfavourable because of the scarce number of observations available for some entry years (2011-12 and 2012-13), and using a

continuous variable would assume that rates from consecutive years of entry vary linearly at the log scale when there is no indication of that being true.

The large case number and patient-days covered by our study was made possible by using a cohort of hospitals with different lengths of BACTOT participation. Without this novel method, a choice between investigation of long-term trends post-surveillance and representativeness of post-surveillance trends would have been necessary. Limiting the cohort to hospitals with longer participation periods would exclude hospitals that may have not begun participation for reasons related to their surveillance capabilities or HAI incidence. Results from such a cohort would not be considered representative of hospitals eligible to participate in BACTOT. If a representative cohort was instead chosen, analyses would be limited to the first 3 years of surveillance time, preventing a long-term understanding of HABSI post-surveillance. The flexibility of Bayesian model writing allowed the fitting of a multilevel model to the available data for each hospital while borrowing strength across hospitals.

It is important to note that any changes or lack thereof reported here cannot be attributed solely to surveillance. Unavailable HABSI data from hospitals prior to surveillance means an absence of a counterfactual that would allow us to estimate a causal effect. In our study, we used the data from the first year of surveillance as a baseline to which we compared following years to. This has been done before, most notably by the German KISS nosocomial infection surveillance team. Gastmeier et al. evaluated the effect of surveillance on healthcare-associated CA-BSI in ICUs and SSIs in 2006 and Schwab et al. did so for primary HABSI in NICUs.[1,2] Both found that rates in the second and third year were lower than in the first year.

Although the first year of surveillance is not necessarily representative of pre-surveillance rates, we believe that full effects of surveillance require time. After one year of participation within

BACTOT, hospitals receive an annual report with their rates, compared to the rest of the province, stratified by hospital status.[17] This is impactful for two reasons. First, if hospital infection and control professionals were not providing feedback to the hospital staff during the year, this would be the first informative report resulting from the surveillance and if the professionals share it with the responsible parties, it would likely induce changes to try and reduce preventable HABSI. Second, participating hospitals would have access for the first time to other hospitals' rates, which may encourage hospitals to keep their rates in line with hospitals with similar characteristics. To even further isolate the temporal effects of surveillance, we performed subgroup analyses excluding hospitals that had participated for the entire 10-year period in an attempt to focus on hospitals more likely to be beginning their local surveillance of HABSIs. Hence, we believe our results, especially those from the subgroup analyses, are a valuable contribution to the evaluation of HABSI behaviour after beginning participation in BACTOT surveillance.

While our study estimates stable HABSI rates, it remains of concern that these rates showed no reduction with continued surveillance. These results are timely because SPIN-BACTOT is currently re-evaluating its objectives and modalities. The monitoring of all HABSI was initially deemed useful mainly for burden estimation and eventual burden reduction. These objectives can be met with alternative methods. HABSI burden may be estimated through incidence surveys conducted once annually or every other year, instead of mandatory, year-round reporting. Intensive monitoring could be reserved for preventable HABSI types, such as CA-BSI, BSI-UTI, BSI-SSI, and BSI-PULM or specifically target the high burden primary infections, accompanied by interventions to actively reduce their incidence. More targeted surveillance in other SPIN initiatives, such as SPIN-BACC (CLABSI in the ICUs) and BAC-HD (BSI associated with

venous access for dialysis), have been successful at reducing rates. Targeted surveillance alongside interventions of specific infections would also allow for a more precise evaluation of their impact.

Acknowledgements

We are grateful to all the infection control practitioners and infectious disease physicians/medical microbiologists who participate in the SPIN program. SPIN-BACTOT working group members: Élise Fortin, Charles Frenette, Lise-Andrée Galarneau, Sylvie Latreille, Danielle Moisan, Muleka Ngenda-Muadi, Noémie Savard, Marc-André Smith, Claude Tremblay, Mélissa Trudeau, Jasmin Villeneuve.

Financial support. This work was supported by SPIN, a program from the Quebec Institute of Public Health, funded by the Quebec Ministère de la Santé et des services sociaux (Ministry of Health). Dr. Quach is supported through an external salary award (FRQ-S merit, grant # 252775).

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Tables and Figures

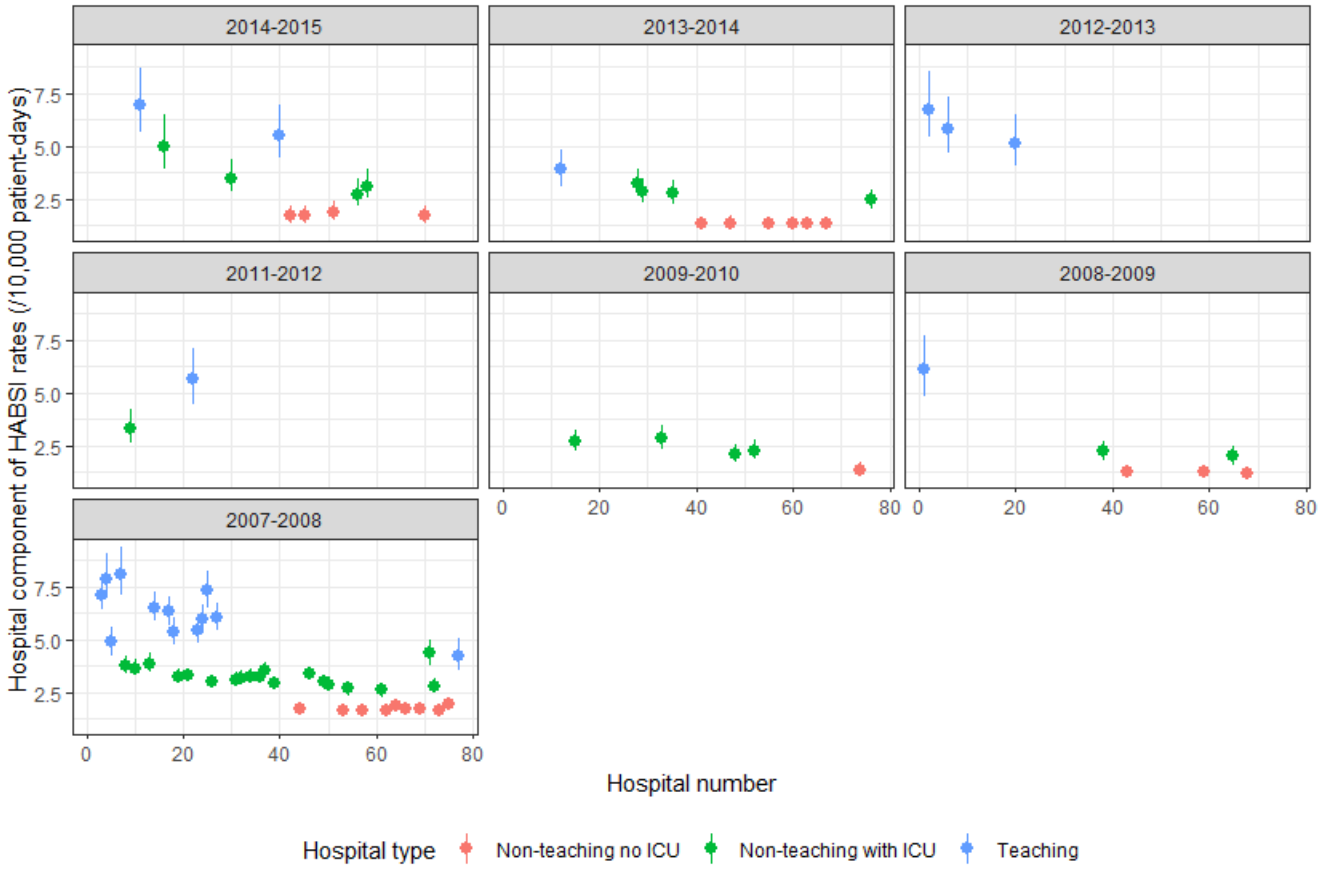

Figure 1. Posterior distribution of the contribution of the hospitals' random effects to the healthcare-associated bloodstream infection rate, stratified by calendar year of entry into BACTOT. Solid circles are the posterior mean and solid lines represent the limits of the 95 % posterior credible intervals.

Table 1. Healthcare-associated Bloodstream Infection Cases, Patient-days and Pooled Incidence Rates for Each BACTOT Surveillance Year.

Surveillance year	1	2	3	4	5	6	7	8	9	10	Overall
Hospitals	77	77	77	67	56	53	51	51	46	40	77
Cases	2169	2248	2038	1942	1788	1563	1479	1356	1323	1275	17181
Patient-days	4176598	4207114	4159564	3618735	3258880	2986131	2762369	2738324	2506465	2278894	33029870
Pooled Incidence Rate (95% CI)	5.19 (4.98-5.41)	5.34 (5.12-5.57)	4.90 (4.69-5.12)	5.37 (5.14-5.61)	5.49 (5.24-5.75)	5.23 (4.98-5.5)	5.35 (5.08-5.63)	4.95 (4.69-5.22)	5.28 (5.00-5.57)	5.59 (5.29-5.91)	5.20 (5.12-5.28)

95% CI; 95% confidence interval

Table 2. Posterior Summary of the Incidence Rate Ratios of Hospital Characteristics for Healthcare-associated Bloodstream Infections and the Most Common Subtypes for the Cohort and Hospitals That Participated in BACTOT for Less Than 10 Years.

	Posterior Mean of the Incidence Rate Ratio (95% Posterior Credible Interval)							
	HABSI		**CA-BSI**		**NCA-BSI**		**BSI-UTI**	
Covariate	**All hospitals**	**<10 years**	**All hospitals**	**<10 years**	**All hospitals**	**<10 years**	**All hospitals**	**<10 years**
Beds*	1.01 (1.01 - 1.02)	1.02 (1.01 - 1.03)	1.01 (1.00 - 1.02)	1.02 (1.01 - 1.03)	1.03 (1.02 - 1.04)	1.03 (1.02 - 1.05)	1.01 (1.00 - 1.01)	1.00 (0.99 - 1.01)
NT with ICU†	1.58 (1.34 - 1.87)	1.78 (1.37 - 2.35)	2.42 (1.71 - 3.56)	1.99 (1.1 - 3.66)	0.89 (0.67 - 1.18)	1.02 (0.63 - 1.69)	1.90 (1.54 - 2.35)	2.14 (1.49 - 3.11)
Teaching†	2.42 (1.95 - 3.01)	2.20 (1.49 - 3.31)	6.12 (4.01 - 9.47)	3.14 (1.54 - 6.66)	1.23 (0.86 - 1.75)	1.42 (0.69 - 2.98)	1.72 (1.32 - 2.23)	1.75 (1.07 - 2.87)

*The effect of 10 beds is estimated by transforming a hospital's number of beds by dividing by 10.

†The incident rate ratio is relative to non-teaching hospitals without ICUs.

HABSI; healthcare-associated bloodstream infection, CA-BSI; catheter-associated bloodstream infection, NCA-BSI; non-catheter-associated primary bloodstream infection, BSI-UTI; bloodstream infection secondary to a urinary tract infection, All hospitals; Models

fitted to data from the entire cohort, <10 years; models fitted separately to data from hospitals that have participated in BACTOT for less than 10 years, NT with ICU; non-teaching hospital with ICU, Teaching; teaching hospital

Table 3. Posterior Summary of the Incidence Rate Ratios of Year of Entry, Relative to Year 2014-15, for Healthcare-Associated Bloodstream Infections and the Most Common Subtypes from Models Fitted for the Cohort and for Hospitals That Participated for Less Than 10 Years.

		Posterior Mean of the Incidence Rate Ratio (95% Posterior Credible Interval)							
Infection		**HABSI**		**CA-BSI**		**NCA-BSI**		**BSI-UTI**	
Hospitals		**All hospitals**	**<10 years**	**All hospitals**	**<10 years**	**All hospitals**	**<10 years**	**All hospitals**	**<10 years**
Calendar year of entry	**2013-14**	0.81 (0.60 - 1.03)	0.78 (0.58 - 0.99)	0.68 (0.35 - 1.04)	0.79 (0.43 - 1.04)	0.99 (0.74 - 1.32)	0.99 (0.73 - 1.36)	0.82 (0.59 - 1.07)	0.76 (0.56 - 1.01)
	2012-13	0.92 (0.69 - 1.19)	0.97 (0.74 - 1.28)	0.78 (0.45 - 1.17)	0.89 (0.57 - 1.14)	1.18 (0.91 - 2.02)	1.20 (0.90 - 2.29)	1.11 (0.85 - 1.54)	1.31 (0.93 - 1.88)
	2010-11	0.84 (0.60 - 1.08)	0.78 (0.56 - 1.01)	0.78 (0.42 - 1.14)	0.83 (0.46 - 1.07)	0.97 (0.68 - 1.29)	0.96 (0.65 - 1.30)	0.88 (0.63 - 1.17)	0.88 (0.64 - 1.19)
	2009-10	0.79 (0.58 - 1.01)	0.74 (0.54 - 0.96)	0.84 (0.51 - 1.20)	0.89 (0.58 - 1.13)	0.95 (0.66 - 1.24)	0.96 (0.66 - 1.28)	0.78 (0.56 - 1.03)	0.70 (0.51 - 0.95)
	2008-09	0.72 (0.53 - 0.94)	0.69 (0.51 - 0.92)	0.82 (0.49 - 1.17)	0.86 (0.53 - 1.08)	0.86 (0.57 - 1.12)	0.87 (0.56 - 1.12)	0.65 (0.45 - 0.92)	0.61 (0.45 - 0.83)
	2007-08	0.98 (0.79 - 1.18)		1.17 (0.83 - 1.61)		0.96 (0.75 - 1.21)		0.93 (0.73 - 1.14)	

HABSI; healthcare-associated bloodstream infection, CA-BSI; catheter-associated bloodstream infection, NCA-BSI; non-catheter-associated primary bloodstream infection, BSI-UTI; bloodstream infection secondary to a urinary tract infection, All hospitals; Models fitted to data from the entire cohort, <10 years; models fitted separately to data from hospitals that have participated in BACTOT for less than 10 years, NT with ICU; non-teaching hospital with ICU, Teaching; teaching hospital

Table 4. Posterior Summary of the Incidence Rate Ratios of Surveillance Years, Relative to the First Year, for Healthcare-Associated Bloodstream Infections and the Most Common Subtypes for the Cohort and for Hospitals That Participated in BACTOT for Less Than 10 Years.

		Posterior Mean of the Incidence Rate Ratio (95% Posterior Credible Interval)							
Infection		**HABSI**		**CA-BSI**		**NCA-BSI**		**BSI-UTI**	
Hospitals		**All hospitals**	**<10 years**	**All hospitals**	**<10 years**	**All hospitals**	**<10 years**	**All hospitals**	**<10 years**
Surveillance year	**2**	1.06 (0.93 - 1.21)	1.04 (0.89 - 1.22)	0.98 (0.81 - 1.19)	0.95 (0.73 - 1.15)	1.05 (0.86 - 1.33)	1.03 (0.86 - 1.29)	1.03 (0.90 - 1.19)	1.00 (0.84 - 1.18)
	3	1.02 (0.9 - 1.17)	1.02 (0.88 - 1.21)	0.97 (0.79 - 1.16)	0.95 (0.73 - 1.16)	1.07 (0.87 - 1.37)	1.03 (0.85 - 1.28)	0.98 (0.86 - 1.12)	0.99 (0.84 - 1.17)
	4	1.04 (0.92 - 1.21)	1.03 (0.87 - 1.23)	0.99 (0.82 - 1.21)	0.95 (0.72 - 1.15)	1.06 (0.86 - 1.37)	1.05 (0.86 - 1.35)	1.00 (0.86 - 1.16)	1.00 (0.84 - 1.19)
	5	1.05 (0.92 - 1.22)	1.03 (0.87 - 1.23)	0.97 (0.78 - 1.16)	0.99 (0.79 - 1.22)	1.07 (0.87 - 1.39)	1.03 (0.86 - 1.33)	1.02 (0.89 - 1.2)	1.00 (0.84 - 1.19)
	6	1.05 (0.92 - 1.22)	1.06 (0.89 - 1.32)	0.93 (0.75 - 1.12)	0.94 (0.7 - 1.15)	1.06 (0.85 - 1.36)	1.05 (0.86 - 1.35)	1.04 (0.91 - 1.22)	1.04 (0.88 - 1.29)
	7	1.06 (0.93 - 1.24)	1.04 (0.88 - 1.27)	0.97 (0.78 - 1.15)	0.94 (0.69 - 1.15)	1.14 (0.92 - 1.53)	1.03 (0.85 - 1.32)	1.03 (0.89 - 1.2)	1.02 (0.86 - 1.24)
	8	1.03 (0.91 - 1.2)	1.04 (0.88 - 1.3)	0.92 (0.71 - 1.09)	0.96 (0.73 - 1.16)	1.25 (0.99 - 1.78)	1.06 (0.87 - 1.4)	0.99 (0.85 - 1.15)	1.01 (0.84 - 1.21)
	9	1.05 (0.92 - 1.23)	1.04 (0.88 - 1.28)	0.94 (0.75 - 1.13)	0.95 (0.70 - 1.16)	1.17 (0.94 - 1.59)	1.02 (0.83 - 1.33)	0.97 (0.82 - 1.12)	1.00 (0.83 - 1.24)
	10	1.06 (0.93 - 1.25)		0.95 (0.76 - 1.13)		1.29 (1.01 - 1.89)		0.96 (0.81 - 1.11)	

HABSI; healthcare-associated bloodstream infection, CA-BSI; catheter-associated bloodstream infection, NCA-BSI; non-catheter-associated primary bloodstream infection, BSI-UTI; bloodstream infection secondary to a urinary tract infection, All hospitals; Models fitted to data from the entire cohort, <10 years; models fitted separately to data from hospitals that have participated in BACTOT for less than 10 years.

Appendix

Model

The number of cases, Y, for each observation, i, for every hospital, h, follows a Poisson distribution with mean lambda[i,h].

$$Y[i,h]\ Poisson(lambda[i,h])$$

The log of the mean Poisson rate, with patient-days as the offset, is modelled as the sum of a random year effect, random period effect, and a hospital random effect. The hierarchical modelling of the year and hospital random effects allow for the year effect to vary by hospital with a variance denoted by sigma.year.

$$log(lambda[i,h]) = log(patient - days[i,h]) + mean[i,h]$$

$$mean[i,h] = year.hospital[s,h] + period.effect[p]$$

$$year.hospital[s,h] \sim Normal(year.effect[s] + hospital.effect[h], sigma.year)$$

The mean of the hospital random effect is modelled as a function of an overall intercept, the type of hospital (A; non-teaching without ICU, B; non-teaching with ICU, and C; teaching with ICU) and the number of beds in the hospital, as well as a random effect relating the calendar year the hospital entered BACTOT.

$$hospital.effect[h] = intercept + beta.typeB * typeB[h] + beta.typeC * typeC[h] + beta.beds * beds[h] + entry[g]$$

Below are the prior distributions for the random effects.

$$entry[g] \sim Normal(0, sigma.entry)$$

$$period.effect[p] \sim Normal(0, sigma.period)$$

$$year.effect[s] \sim Normal(0, sigma2.year)$$

R code

Below is the R code used to fit the model using JAGS. *nhospital* refers to the total number of hospitals. *group.hosp* refers to the year in which a hospital entered BACTOT. *n[h]* refers to the total number of observations available for each hospital. *nyear* refers to the total number of surveillance years for which a hospital has participated in BACTOT. *Togroup* refers to the number of possible years in which new hospitals entered BACTOT. *toperiod* refers to the maximum number of surveillance periods, and *toyear* refers to the maximum number of surveillance years.

```
model{

## Likelihood function
       for(h in 1:nhospital){
              level[h] <-  beta.c + b.beds*beds[h] + phi[group.hosp[h]] + b.typeB*typeB[h] +
       b.typeC*typeC[h]
risk.hosp[h] <- exp(level[h])
        for(i in 1:n[h]){
          y[i,h] ~ dpois(lambda[i,h])
          log(lambda[i,h]) <- offset[i,h] + mean[i,h]
          mean[i,h] <-  gamma[year[i,h],h] + delta.c[period[i,h]]
          y.fitted[i,h] ~ dpois(lambda[i,h])
         } #end of temporal (i) loop
    } #end of hospital loop

  ## Prior specification
      for(h in 1:nhospital){
        for(ii in 1:nyear[h]){
          gamma[ii,h] ~ dnorm(level[h] + gamma.c[ii] , prec.gamma)
          risk.year.hosp[ii,h] <- exp(gamma[ii,h])
        }
      }
      for(i in 1:togroup){
        phi[i] ~ dnorm(0,prec.group)
        risk.group[i] <- exp(phi[i])
    }
      for(p in 1:toperiod){
        delta.c[p] ~ dnorm(0,prec.delta.c)
        risk.period[p] <- exp(delta.c[p])
      }
      for(p in 2:toperiod){
        rr.period[p] <- exp(delta.c[p])/exp(delta.c[1])
    }
    for(i in 1:toyear){
        gamma.c[i] ~ dnorm(0,prec.gamma.c)
        risk.year[i] <- exp(gamma.c[i])
    }
    for(i in 2:toyear){
        rr.year[i] <- exp(gamma.c[i])/exp(gamma.c[1])
    }
    for(i in 2:togroup){
      rr.group[i] <- exp(phi[i])/exp(phi[1])
    }

    beta.c~dnorm(0,0.1)
    prec.gamma.c ~ dgamma(2,0.01)
    sigma.gamma.c <- 1/prec.gamma.c
    prec.gamma ~ dgamma(2,0.01)
```

```
sigma.gamma <- 1/prec.gamma
prec.delta.c ~ dgamma(2,0.01)
sigma.delta.c <- 1/prec.delta.c
prec.group ~ dgamma(2,0.01)
sigma.group<- 1/prec.group

b.beds ~ dnorm(0,0.1)
b.typeB ~ dnorm(0,0.1)
b.typeC ~ dnorm(0,0.1)

rr.beds <- exp(b.beds)
rr.typeB <- exp(b.typeB)
rr.typeC <- exp(b.typeC)
```

Chapter 5: Discussion

5.1 Summary of findings

The most important finding from both studies is that there have been no secular or surveillance-driven changes in HABSI rates in Quebec between 2007 and 2017. While that is the case, the pooled HABSI rate from the first study of 5.59/10,000 patient-days (95% C.I.: 5.54-5.63) is not unusually high, but comparable to those in recent reports in the literature.[101,102] Pooled annual rates from the second study are similar but vary slightly depending on the hospitals included in the particular surveillance year.

The most commonly reported HABSIs were CA-BSI, NCA-BSI, and BSI-UTI. BSI-SSI, BSI-PULM, and BSI-ABDO were less common, and the remaining secondary HABSI were relatively rare. While CA-BSI dropped in 2014, this reduction was not sustained in the secular trend analysis of the first manuscript, despite the reductions commonly described in the literature.[2,43] To our surprise, the analysis showed an increase in NCA-BSI in 2007-08, from 0.69/10,000 patient-days (95% CI: 0.59-0.80) to 1.42/10,000 patient-days (95% CI: 1.27-1.58) in 2016-17. The cause of this rise is unknown, but it is believed to be a real increase. The remaining HABSI subtypes showed no sustained changes in the secular trend between 2007 and 2017.

Both manuscripts showed that HABSI risk differed between hospitals. Teaching hospitals tended to have higher overall HABSI rates, followed by non-teaching hospitals with ICUs, when compared to non-teaching hospitals without ICUs. We reported in the second manuscript that larger hospitals (with higher number of beds) also had an increased risk of HABSI. While this great variability in HABSI risk between hospitals exists, changes in risk from surveillance year to

surveillance year showed little variance, meaning the risks from the different hospitals have been behaving in the same manner over surveillance time. This indicates that the surveillance trend of individual hospitals is very similar to the reported cohort-level trend, and that our conclusions also hold.

5.2 Methodological strengths and limitations

The major methodological strength of both studies is the employment of statistical techniques that adjust for correlation between observations from the same hospitals, which is not done often enough in multicentre studies on HAI. The first manuscript utilises GEE analysis on BACTOT data aggregated by calendar year and hospital, adjusting for correlation by specifying an exchangeable correlation structure for successive observations from the same hospital. The second manuscript adjusts for this correlation by assigning a portion of each observation's HABSI risk to be explained separately by the identity of the hospital, the surveillance year, and the administrative period. Adjusting for correlation between hospitals means we explicitly recognised that hospitals differ from one another in unmeasured ways that would affect HABSI risk, allowing us to estimate the surveillance effect with greater accuracy and precision.

Statistical strength is gained in both manuscripts by including in the analyses a large number of hospitals followed for a lengthy period of time. This is especially favourable in the study of HABSI because cases are relatively rare, and models need sufficient information to produce accurate and precise estimates. In multilevel models especially, hospitals with low case numbers can borrow strength from hospitals with high case numbers to produce these estimates. However, low case number can remain a problem when stratifying the outcome by infection

source. In the second manuscript, models for the rarer HABSI subtypes produced inaccurate estimates, as indicated by fitted values, and were thus excluded from the analyses. We circumvented this problem in the first manuscript by fitting population-average models by year. The only disadvantage of aggregating periodic observations arising in the same year is assuming that those rates do not show trends occurring within that year. While exploratory data analysis did not show any period trends within years, there was substantial irregular variability between the periodic rates. Ignoring this variability may have caused an underestimation of error in our estimates.

The particular strength of the second manuscript comes with dealing with hospitals of different total participation times in surveillance, which to our knowledge, has not been done before in the published literature. The flexibility of building a model in the Bayesian framework allowed us to include the model in a loop that, for each hospital, ran only until its last observation. If examined carefully, the effect of the method is evident in the credible intervals reported in the second manuscript for the surveillance year. They tend to grow wider as hospitals contribute to the estimate.

The main limitation of the second manuscript is the lack of a true counterfactual representing HABSI rates in hospitals prior to BACTOT participation. A classical pre/post analysis is challenging to conduct in the case of surveillance. Data from the pre-surveillance period would have to be collected in the form of systematic monitoring and would hence be classified as a form of surveillance. To escape this dilemma, one could perform retrospective surveillance to extract HABSI cases from hospitals prior to participation, but as mentioned earlier, such a method tends

to be less accurate[62] and may produce seemingly lower estimates by virtue of missing the cases that were misclassified in absence of active, prospective surveillance.

The method we sought to address the second objective of the thesis was assigning the first year of surveillance as a baseline and describing HABSI trend after BACTOT participating by comparing the HABSI risk of the successive years to the first one. Although this does not directly address the causal association between surveillance and HABSI and cannot isolate the effect of surveillance, it is the next best alternative.

A second limitation was the lack of adjustment for factors that may have confounded the effect of surveillance time on HABSI risk, despite our intentions to do so. The relationship between length of stay and HABSI risk is complex. On the one hand, reductions in length of stay can inflate risk if cases tend to occur early during a hospital stay. On the other hand, shorter lengths of stay can result in less exposure to the healthcare environment, and thus lower risk of developing HABSI. Moreover, HABSI itself can be cause for increased length of stay because it requires additional hospitalisation for treatment. Any of these effects may confound HABSI trends over surveillance time. However, when an average length of stay variable was introduced to the models, the associated sampling chains would not converge. The probable explanation for this behaviour is the variable's relationship with the offset. Because the average length of stay was calculated by dividing the offset, patient-days, by the number of admissions for each observation, a form of collinearity may have arisen.

The other potentially confounding variable we attempted to adjust for was the proportion of patient-days contributed by those 65 and older, because an increase in vulnerable patients may obscure a reduction in HABSI. A composite variable was created by multiplying the annual

proportion of the Quebec population over 65 years (retrieved from the Statistical Institute of Quebec website) with the average proportion of patients over 65 years admitted to each hospital. Again, the sampling chains would not converge when the variable was added to the models. It is possible that using a variable that varied with calendar year, as opposed to surveillance year, may have given the simulation chains difficulty to converge. Reduced length of stays and increased proportion of patient-days contributed by the elderly would theoretically increase the risk of HABSI and adjusting for them would have more appropriately isolated the effect of surveillance. This is not fatal to the analysis because by fitting the model using observations ordered by surveillance time and by adjusting for the calendar year of entry, the effect of calendar-time varying covariates on the cohort-level estimates is mitigated.

5.3 Implications

The lack of improvement in overall HABSI rates and its subtypes comes as a break in the HAI surveillance literature. The common trend in multicentre studies is a reduction in rates between 20% and 30%, however most reviewed articles included data from ICUs only.[63,114] While it is possible that a stratification of data from ICUs and outside ICUs would produce a different result, there was no difference in trends between hospitals with and without ICUs, and existing hospital-wide surveillance studies do report reductions. This important result highlights that in hospitals from the province of Quebec, HABSI rates did not decrease after initiation of surveillance. This could mean that the main driver of the surveillance effect, feedback from infection control specialists, was either already present for some time or ineffectual in the methods implemented by SPIN-BACTOT.

It is clear that to achieve reductions in HABSI, additional preventive efforts should be taken. Aside from surveillance, introduction of CLABSI bundles and the implementation of a provincial-wide campaign targeting particular HAI have not appeared to produce sustained change in HABSI rates or its subtypes, as seen in the first manuscript. Given the amount of resources placed by SPIN into the organisation of BACTOT and by participating hospitals in the year-round mandatory reporting, the question also arises if the current type and scope of BACTOT surveillance is justified. Alternative surveillance modalities could be considered.

One such alternative to the current BACTOT surveillance is to limit it to the most prevalent subtypes or to those that have the greatest room for improvement. The main motivation to do so is the recognition that each HABSI type is in fact different from the other. Their different sources and modifiable risk factors result in different clinical treatment and targeted interventions.

However, we continue to believe that monitoring HABSI as a single entity is worthwhile. The arguments for this are numerous. First, the clinical symptoms of bloodstream infection and its manifestations are shared among cases and thus cases warrant to be grouped into a single patient population. Second, it encourages diligent investigation of the HABSI source following blood culture confirmation which promotes more appropriate management of the infection. Additionally, HABSI tend to be rare in lower resource hospitals with smaller patient populations, meaning such facilities are unlikely to be overburdened by the additional monitoring and investigation. Limiting reporting to CA-BSI, NCA-BSI and BSI-UTI, the most prevalent HABSI subtypes, would not reduce the burden of reporting because they already make up around two-thirds of the cases in Quebec. Furthermore, comprehensive HABSI reporting includes secondary HABSI, other than BSI-UTI, which would not be captured in systems that only monitor common HABSI. Information

on these infections is scarce in published literature and as they tend to be the most fatal of HABSI, monitoring them can offer valuable insight to inform future measures for reducing their incidence or severity. They can also provide insight into the burden of severe primary HAI that are developing into secondary BSIs.

Another alternative to facility-wide HABSI monitoring is limiting it to ICUs. The common reason for doing so is targeting the population at highest risk, as ICUs are known to have several-fold higher rates than other wards.[17,29,85] Targeting the most vulnerable patients is a cost-effective method of infection control and prevention, however, it precludes 68% of incident cases occurring outside the ICU.[105] Observations and effects of targeted interventions will differ between the two patient populations, as risk factors differ between ICU and non-ICU patients.[16,115]

BACTOT can also reduce the annual mandatory reporting quota from 11 out of the 13 administrative periods. This would diminish the amount of work required by those doing the reporting, while still maintaining participation. Nonetheless, due to the relative rarity of HABSI, annual case number in hospitals is already too low and reducing reporting frequency would make any statistical analysis even more prone to inaccurate estimates due to little information. Additionally, the knowledge and skills required for proper reporting tend to be forgotten if not implemented frequently.

5.4 Future directions

While it remains disappointing that rates of HABSI have not decreased over such a lengthy period, BACTOT surveillance has allowed the collection of a wealth of data that can be

used to inform further interventions in the hopes of reducing burden, and if it continues to operate, it can be used to evaluate these interventions.

It is worthwhile to compare the trends of ICU and non-ICU HABSI over the course of surveillance in case there is a difference in response. Similarly, risk factors and outcomes of ICU and non-ICU cases can be explored to substantiate any differences between them and cater infection control and prevention measures to match these differences.

Heightened awareness of the infection and attentive follow-up may have reduced the severity and case fatality of HABSI cases, even when the incidence rates remained constant. By comparing HABSI cases of different outcomes, the most morbid and fatal HABSI can be identified, as well as associated risk factors. Targeted preventive or palliative measures can be devised accordingly, and patient-care would undoubtedly improve.

BACTOT's collection of detailed information on HABSI pathogens and their antibiotic resistance profile can inform whether resistance-levels have changed over the course of BACTOT operation. This information, which represents the only provincial data source on hospital-level resistance, can be used by hospitals for a better understanding of their clinical microbiology and for addressing the individual issues their patient-populations face.

Finally, to systematically investigate whether the current form of BACTOT is justifiable a cost-benefit analysis should be conducted. The true value being generated from BACTOT's data collection and reporting should be identified and whether they are in fact worthwhile.

5.5 Conclusion

We have investigated the trends in HABSI over secular and surveillance time under BACTOT. Due to the lack of reduction in rates, more targeted HABSI interventions should be considered. While surveillance forms the foundation of modern infection prevention and control, it is not to be expected that it alone will cause changes in HAI. Reduction in HABSI is only one of the objectives BACTOT set for itself at its inception. The majority of the remaining objectives are related to documentation of HABSI incidence and its causes, which BACTOT continues to do successfully.

Chapter 6: References

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