Impact of Québec MRSA guidelines on incidence rates of MRSA hospital-associated bloodstream infections.

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Abstract (English)

Background: We described the CLABSI incidence rates in Québec and compared them to rates from other jurisdictions to determine trends. We then used CLABSI incidence rates as a comparator to examine impact of MRSA guidelines in Québec adult hospitals from January 1st, 2006 to March 31st, 2015 by looking at incidence rate reduction (IRR) in healthcare-associated MRSA bloodstream infections (HA-MRSA).

Methods: CLABSI incidence rates (IRs) and central venous catheter utilization ratios (CVCURs) by year and ICU type were calculated using 2007-2014 data from the Québec Surveillance Provinciale des Infections Nosocomiales program (SPIN) and benchmarked to American and Canadian surveillance data, using standardized incidence ratios (SIRs). We used a quasi-experimental design and segmented Poisson regression to analyze SPIN surveillance data from 2006 to 2015 for HA-MRSA BSI and CLABSI for successive 4-week surveillance segments, stratified by facility type. Three distinct time intervals with 2 breakpoints were used (April 1st, 2007, and January 3rd, 2010), corresponding to major MRSA guideline and guideline updates.

Results: For SPIN-BACC, 70 intensive care units (ICU) participated in CLABSI surveillance resulting in 1,474 cases, and 1,038,908 catheter-days. CLABSI rates had decreased significantly in ICUs except for pediatric ICUs. Using dynamic American and Canadian CLABSI rates as benchmarks, SPIN adult teaching ICU rates were significantly lower, adult nonteaching ICUs had lower or comparable rates, while NICU and PICU rates were higher. For SPIN-SARM, 56 healthcare facilities participated, resulting in 1,854 HA-MRSA BSI cases and 43,728,219 patient-days. HA-MRSA BSI incidence decreased significantly for adult teaching facilities, but not for adult nonteaching facilities. Before MRSA guideline publication (2006-2007), HA-

MRSA BSI incidence was stable (p=0.89), while CLABSI incidence declined by 4% per 4-week period, (p=0.05). After publication of guidelines (2007 - 2009), HA-MRSA incidence significantly declined at 1% (p=0.04), during which CLABSI incidence was stable (p=0.75). HA-MRSA and CLABSI declines were both significant at 1% in 2010-2015 (p<0.001, p=0.01, respectively). These declines were gradual rather than sudden as breakpoints were not significant. Teaching facilities drove these decreases.

Conclusion: Significant HA-MRSA BSI rate decline in 2007-2009, with stable CLABSI rates, suggests an impact of MRSA-specific guidelines. In 2010-2015, significant and equal IRR for HA-MRSA and CLABSI may be due to continuing impact of MRSA guidelines, an impact of new interventions targeting device-associated infections in general of the 2010-2015 action plan, or of a combination of factors.

Résumé

Contexte: Nous avons décrit les taux d'incidence des bactériémies sur cathéter central (BACC) au Québec et les avons comparé à ceux d'autres juridictions. Nous avons ensuite utilisé les taux de BACC comme comparateur afin de déterminer l'impact des lignes directrices pour le *Staphylococcus aureus* résistant à la méthicilline (SARM) sur les taux de bactériémies nosocomiales à SARM dans les hôpitaux adultes du Québec du 1er janvier 2006 au 31 mars 2015.

Méthodes: Les taux d'incidence et les ratios d'utilisation des cathéters veineux centraux par année et par type d'unité de soins intensifs ont été calculés à partir des données 2007-2014 du programme de Surveillance provinciale des infections nosocomiales (SPIN) et comparés aux données de surveillance américaines et canadiennes à l'aide d'un taux d'incidence normalisé appelé SIR. Nous avons ensuite utilisé un devis quasi-expérimental et un modèle de régression de Poisson segmentée afin d'analyser les données de surveillance SPIN de 2006 à 2015 pour les SARM-AH (acquis à l'hôpital) et BACC, par périodes successives de 4 semaines, stratifiées par type d'installation. Trois intervalles distincts avec 2 points d'arrêt ont été utilisés (1er avril 2007 et 3 janvier 2010), ce qui correspond à la publication des principales lignes directrices et des mises à jour des lignes directrices contre le SARM.

Résultats: Pour SPIN-BACC, 70 unités de soins intensifs (USI) ont participé à la surveillance SPIN-BACC, ce qui a donné lieu à 1,474 cas et à 1,038,908 jours-cathéter. Les taux de BACC ont diminué de façon significative dans les USI, sauf pour les USI pédiatriques. En utilisant les taux dynamiques américains et canadiens de BACC comme comparateur, nous avons démontré que les taux de BACC aux soins intensifs adultes universitaires étaient statistiquement significativement plus bas au Québec, tandis que dans les USI non-universitaires adultes, les taux

étaient inférieurs ou similaires; dans les USI de néonatologie ou pédiatrique, les taux étaient plus élevés. Pour SPIN-SARM, 56 hôpitaux ont participé, pour 1,854 cas de bactériémies à SARM-AH et 43,728,219 jours-présence. L'incidence de bactériémies à SARM-AH a diminué de façon significative pour les hôpitaux universitaires adultes, mais pas pour les hôpitaux adultes non-universitaires. Avant la publication des lignes directrices sur le SARM (2006-2007), la baisse de l'incidence de SARM-AH était non significative ($p = 0,89$), tandis que l'incidence des BACC avait diminué de 4% par période de 4 semaines ($p = 0,05$). Après la publication des lignes directrices (2007-2009), l'incidence de SARM-AH avait diminué de façon significative à 1% ($p = 0,04$). Au cours de la même période, le déclin de l'incidence des BACC était non significatif ($p = 0,75$). Les baisses de SARM-AH et de BACC étaient toutes deux significatives à 1% en 2010-2015 ($p <0,001$, $p = 0,01$, respectivement). Ces baisses ont été progressives plutôt que soudaines car les points d'arrêt n'étaient pas significatifs. Les établissements universitaires ont entraîné ces baisses.

Conclusion: La surveillance de BACC montre une diminution des taux dans les USI adultes au Québec, mais pas pour les USI de néonatologie ou pédiatrique. Une baisse significative du taux de bactériémie à SARM-AH en 2007-2009, avec des taux de BACC stables, suggère un impact des lignes directrices spécifiques au SARM. En 2010-2015, un IRR significatif et égal pour le SARM-AH et les BACC pourrait être dû à l'impact continu des lignes directrices contre le SARM, à l'impact de nouvelles interventions ciblant les infections associées aux dispositifs en général du plan d'action 2010-2015 ou à une combinaison de ces facteurs.

Contributions of Candidate and Co-authors:

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

Dr. Caroline Quach was the supervisor for this thesis work, and co-author on both manuscripts. She guided the work within the manuscripts and the thesis with communicating with the SPIN team to obtain the databases for analyses, methodological advice, and editorial support in the drafting of the manuscripts and this thesis. She was the integral in the statistical analysis, interpretation, preparation and submission of the manuscripts for publication.

Dr. Elise Fortin was the co-supervisor for this thesis work, co-author for manuscripts 1and 2. She provided invaluable statistical and methodological guidance towards both manuscripts, and contributed extensively to editing, revising, and preparation of the manuscripts for publication.

For both manuscripts, SPIN data collection and annual data analysis were done by SPIN-SARM and SPIN-BACC working groups, whose great work has contributed to the promising results seen in both manuscripts. Contributors in both working groups are listed below. Of note, for manuscript 1, Claude Tremblay and Muleka Ngenda-Muadi contributed to the data collection, abstract and manuscript revisions. For manuscript 2, Christophe Garenc, Muleka Ngenda-Muadi, Danielle Moisan and Jasmin Villeneuve were involved in data collection, and editing of abstract and manuscripts. Christophe Garenc provided the database for MRSA analyses.

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Abbreviations

BSI: Bloodstream infection

CA-MRSA: Community-acquired methicillin-resistant *Staphylococcus aureus*

CAUTI: Catheter-associated urinary tract infection

CI: Confidence interval

CLABSI: Central-line associated bloodstream infection

CNISP: Canadian Nosocomial Infection Surveillance Program

CVC: Central venous catheter

CVCUR: Central venous catheter utilization ratio

HAI: Healthcare-associated infection

HA-MRSA: Healthcare-associated methicillin-resistant *Staphylococcus aureus*

ICP: Infection control practitioner

ICU: Intensive care unit

INICC: International Nosocominal Infection Control Consortium

INSPQ: Institut national de santé publique du Québec (INSPQ)

IRR: Incidence rate ratio

LA-MRSA: Livestock-associated methicillin-resistant *Staphylococcus aureus*

LTCF: Long-term care facility

MDRO: Multiple drug-resistant organism

MRSA: Methicillin-resistant *Staphylococcus aureus*

MSSA: Methicillin-sensitive *Staphylococcus aureus*

MSSS: Ministry of Health and Social Services

NHSN/CDC: National Healthcare Safety Network / Center for Disease Control and Prevention

NICU: Neonatal intensive care unit

PBP: Penicillin-binding protein

PICU: Pediatric intensive care unit

PVL: Panton-Valentine leukocidin

SCCmec: Staphylococcal chromosome cassette *mec*

SHEA/IDSA: Society for Healthcare Epidemiology of America/ Infectious Disease Society of America

SIR: Standardized incidence ratio

SPIN: Surveillance Provinciale des Infections Nosocomiales

SPIN-BACC: Surveillance Provinciale des Infections Nosocomiales, Surveillance des bactériémies nosocomiales sur cathéters centraux aux soins intensifs

SPIN-BACTOT: Surveillance Provinciale des Infections Nosocomiales, Surveillance des bactériémies nosocomiales panhospitalières

SSI: Surgical site infection

SSTI: Skin and soft tissue infection

VAP: Ventilator-associated pneumonia

VISA: Vancomycin-intermediate *Staphylococcus aureus*

VRSA: Vancomycin-resistant *Staphylococcus aureus*

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Chapter 1: Introduction

1.1 Overview

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important healthcare-associated infection (HAI), which has increased in incidence since the early 2000s. Several reasons including liberal antibiotic use selecting for resistance, increasing use of invasive interventions, and increased virulence of the organism have all contributed to increasing MRSA rates.[1-3] Initiatives launched in Québec during the last decade in response to rising MRSA incidence include the Institut national de santé publique du Québec (INSPQ) MRSA guidelines, and MRSA surveillance as part of the Surveillance provinciale des infections nosocomiales (SPIN), the Québec's Ministry of Health and Social Services (MSSS) "Prevention and control of nosocomial infections - Action Plan 2006-2009" (subsequently referred to as the Action Plan), then later Action Plans for 2010-2015 and 2015-2020. Decreases in healthcare-associated MRSA bloodstream infection (HA-MRSA BSI) incidence have been observed since, mirroring that of other developed countries.[4-8] However, this ecological observation does not help in understanding if the decrease in incidence rate is a secular trend, paralleling other HAIs or is the result from implemented interventions. To evaluate impact of MRSA-specific prevention efforts in Québec on HA-MRSA BSI incidence, we first describe the incidence of HA-MRSA and CLABSI incidence in Québec, and then examine if significant incidence changes occurred before and after MRSA guidelines publication. If MRSA-specific recommendations had an impact, there should be a significantly greater reduction in incidence when compared to CLABSI after release of guidelines.

Rationale of studying HA-MRSA BSI incidence trends using CLABSI:

The principal objective of this thesis is to quantify changes in HA-MRSA BSI incidence in response to MRSA guidelines and initiatives in Québec over the last decade. However, the declines in HA-MRSA and CLABSI incidence followed a general trend of decreasing HAI incidence also seen in catheter-associated urinary tract infections (CAUTI),[9,10] and *C. difficile*.[11,12] As a result, studying the impact of MRSA-specific interventions on HA-MRSA BSI incidence requires comparing HA-MRSA BSI incidence fluctuations to the overall HAI incidence trend. Using a quasi-experimental study design, we examined HA-MRSA BSI and CLABSI incidence fluctuations around 2 major breakpoints corresponding to 2 important MRSA and HAI prevention initiatives, as a well as a 1-year pre-intervention period to obtain baseline incidence trends before guidelines from January 1st, 2006 to March 31st, 2007. The first breakpoint of April 1st, 2007 coincides with the first surveillance year after INSPQ MRSA guidelines were published in June 2006. Although the publication of INSPQ MRSA guidelines occurred during the pre-intervention period (June 2006), a period of 10 months after publication was given in order to account for distribution of guidelines and implementation of recommendations. The second breakpoint of January 3rd, 2010, marked a post-guidelines time period coinciding with the INSPQ publication of results of MRSA prevention compliance in 2009 and the MSSS Action Plan update for 2010-2015.

Central-line insertion and maintenance practices for CLABSI prevention have greatly improved over the last decade; however, CLABSI epidemiology as these practices evolved has not been well described in Québec intensive care units (ICUs). As such, the first set of objectives of this thesis was to describe and benchmark SPIN CLABSI rates. The obtained CLABSI epidemiological data subsequently provided the required control group data for the second set of thesis objectives – whether MRSA guidelines had impact on HA-MRSA BSI rates in Québec. To

answer this question, quasi-experimental study design with segmented regression was chosen due to its superiority in establishing intervention-outcome causality when randomization is not an option. Having a CLABSI control group and a pre-intervention period strengthened validity by having a comparator to account for secular HAI trends. By understanding incidence trends during the study period, we hoped to understand whether MRSA specific guidelines, and broader governmental policy directives impacted MRSA incidence.

1.2 MRSA Literature Review

1.2.1 Staphylococcus aureus microbiology and pathogenicity:

Staphylococcus aureus is a spherical gram-positive cocci bacteria possessing a thick peptidoglycan cell wall and enzymatic ability to clot blood. It is arguably one of the most clinically significant and virulent species of the *Staphylococcus* species. *S. aureus* can thrive in both aerobic and anaerobic conditions, and has several virulence mechanisms which contribute to its pathogenicity including its protective outer wall, cytotoxins and degradative enzymes, all which lead to a wide spectrum of clinical disease. *S. aureus'* thick polysaccharide inhibits phagocytosis, and the peptidoglycan wall initiates the inflammation via the immune system's complement response by activating pro-inflammatory cytokines.[13] Another *S. aureus* surface protein, Protein A, binds to the constant chain portion of IgG immunoglobulin molecules, which reduces clearance of *S. aureus* from the infection site. Invasion and survival of bacteria are promoted by production of several toxins and enzymes. Among them are alpha, beta, and delta toxins, which work in conjunction respectively to disrupt smooth muscle of blood vessels, catalyze hydrolysis of membrane phospholipid leading to cell lysis, and cause erythrocyte and nonspecific membrane cytotoxicity. Gamma toxin is believed to act together with Panton-

Valentine leucocidin (PVL) toxin, which is highly toxigenic to white blood cells and inhibits immune clearance of the *S. aureus.* PVL enables deeper tissue invasion, resulting in more serious infectious complications such as bacteremia.

In addition to direct invasive infection, *S. aureus* has the ability to cause toxin-mediated disease. A systemic inflammatory response may be induced by potent toxin production, even if the organism remains localized. For example, scalded skin syndrome involves production of a serine protease exfoliative toxin, which unlinks intracellular bridge connections in the epidermis, causing widespread skin sloughing. Toxic shock syndrome toxin is a pyrogenic toxin with systemic effects such as fever, desquamation, and hypotension. Thirty to fifty percent of *S. aureus* strains also produce heat-stable enterotoxins, which are resistant to gastric acid and intestinal enzymes. These enterotoxins can cause food poisoning within 2-6 hours of consumption, and may cause more serious complications such as pseudomembranous enterocolitis or toxic shock syndrome by exacerbating the immune response.[14]

Staphylococci species colonize and live on skin and mucosal surfaces. Asymptomatic carriage of the bacteria in the nares and throat are common. If infection occurs, the clinical disease spectrum caused by *S. aureus* is wide; however, the most frequent by far are skin and soft tissue infection (SSTI). It is the commonest pathogen isolated from purulent cellulitis, skin abscesses, and surgical site infections (SSI).[15] Pulmonary infections can arise from colonization in the nares or throat. Invasive infection usually begins when carried organisms gain entry into sterile sites via breakdown in skin or mucosal surfaces from trauma or abrasion,[14] via haematogenous spread from another infection site, or a combination of these two mechanisms. Iatrogenic infection may result from surgical complications such as colonized prostheses, or use of invasive devices such as urinary catheters, or central lines.

The multiple ways in which *S. aureus* causes direct invasive and toxin-mediated disease makes it one of the most challenging organisms in the clinical setting. That challenge is further compounded by the emergence of multiple drug resistant organisms (MDRO) such as MRSA. Over the last decades, considerable costs and effort have been directed to address MRSA prevention. Explanation of how MRSA resistance works, and why it remains a public health issue is described in the subsequent sections.

1.2.2 MRSA mechanisms of resistance

MRSA is a strain of *S. aureus* bacteria with resistance against the beta-lactam class of antibiotics first described in 1960 in the *British Medical Journal* when physicians noticed extensive methicillin treatment durations for patients with chronic bone infections. [16] Methicillin resistance was later found to be conferred on the gene *mecA* on the genetic element *SCCmec.*[17] It is unknown how the *SCCmec* element first originated- it is dispersed extensively amongst staphylococci species but not in other bacterial species.[17,18] Enright et al. used an international bank of MRSA and MSSA isolates and identified 5 distinct phylogenetic lineages in methicillin resistance.[19] Molecular evolution modeling studies have also shown that early MRSA isolates were both genetically and phenotypically similar to methicillin-sensitive *S. aureus* (MSSA) isolates.

There are three well-characterized mechanisms for methicillin resistance in *S. aureus*: 1) beta-lactamase hyper-production, 2) structural changes in normal penicillin-binding proteins (PBPs), and 3) acquisition of a novel penicillin-binding protein, PBP2a, encoded on the *mecA* gene. Penicillin and other beta-lactam antibiotics inhibit cell wall synthesis by binding to PBPs, which prevents catalysis of the cross-linkage of the cell wall polymers. *S. aureus* first acquired

penicillin resistance from the production of beta-lactamases, an enzyme which hydrolyzes penicillin. In response, methicillin and other similar synthetic penicillins, which are resistant to beta-lactamases, were created. Unfortunately, shortly after development of the synthetic penicillins, further resistance emerged.[20] Currently, most *S. aureus* isolates exhibit the third mechanism of resistance conferred by the *mecA* gene. *S. aureus* contain 4 types of normal PBPs, which are attached to cytoplasmic membrane and functions to cross-link peptidoglycan in the cell wall. PBP2a, separate from the endogenous group of *S. aureus* PBPs, is an acquired and inducible protein encoded by *mecA* that is unique to methicillin resistant staphylococci.[21] PBP2a has low-affinity for beta-lactams, and can replace and substitute function of normal PBPs despite cellular beta-lactam presence. Strains producing PBP2a are resistant to multiple classes of antibiotics including penicillins, cephalosporins, beta-lactam and beta-lactamase inhibitor combinations, monobactams, and carbapenems.

1.2.3 Evolution of multiple drug resistance:

The glycopeptide vancomycin is the first-line of treatment for MRSA infections. Glycopeptides work by also inhibiting cell wall synthesis; these bulky molecules bind polymers along the peptidoglycan wall and inhibit cross-linking by physically preventing enzymatic binding with cell wall polymers. The first report of *S. aureus* with intermediate resistance to vancomycin (VISA) occurred in 1996.[22] The minimum inhibitory concentration (MIC) refers to the lowest dosage of an antimicrobial agent to visibly prevent organism growth after overnight incubation. VISA strains have MICs in the range of 4-8μg/mL, compared to < 2μg/mL for MRSA.[23] Phenotypically, in response to vancomycin, VISA strains develop a substantially thickened cell wall, which causes glycopeptide molecules to become trapped within this thick wall, unable to

bind to cell-wall linking enzymes.[24] Reports of *S. aureus* strains with full resistance to vancomycin (VRSA) arose in 2002.[25] Unlike VISA strains, VRSA resistance is induced, and takes place only after exposure to vancomycin. VRSA strains have MICs of ≥16μg/mL, possessing the *vanA* gene via the Tn1546 plasmid acquired from enterococci species.[26] VISA resistance arises from synthesis of a different terminal cell wall peptide compared with the normal peptide, rendering vancomycin incapable of binding to the polymer terminal.

While rare, reports of resistance to second-line MRSA antimicrobials such as linezolid,[27] and daptomycin, have also been published.[28] Furthermore, steady increase or "creeping" MICs of daptomycin, linezolid, and teicoplanin have been characterized in MRSA BSI isolates in Taiwan.[29] These new patterns of resistance in the context of a limited arsenal of antimicrobial therapies add to the urgency in tackling the issue of MRSA prevention and control.

1.2.4 MRSA epidemiology in bloodstream infections::

Soon after MRSA was first characterized in the 1960s, it became a well-known cause of HAI such as nosocomial pneumonia, CAUTI, SSI and BSI.[30,31] Awareness of MRSA as a serious health problem first arose in the 1980s. The increasing proportion of MRSA isolates in *S. aureus* BSI was then thought to be from an aging population, rising use and reliance on invasive medical interventions, and from overly liberal antibiotic which selected for resistance genes.[32] In the U.S. between 1995-2001, the MRSA proportion from all *S. aureus* BSIs increased from 22% to 57%.[2] Increasing MRSA proportion of all *S. aureus* BSI was seen throughout Europe, and Asia. Although longitudinal data on MRSA BSI over time are limited in Asia due to limited, the most recent surveillance reports of the proportion of MRSA of all *S. aureus* isolates were estimated to be as high as 73% in South Korea, 41% in Japan, and 28% in Hong Kong and China.[33] A regional

surveillance study of 12 nations in Southeast and South Asia found that MRSA of all *S. aureus* isolates ranged from 28% in Indonesia, 45% in India, 59% in the Philippines, to as high as 86.5% in Sri Lanka.[33,34] European MRSA isolate prevalence ranges from <1% in Sweden and Norway,[35] 26% in France,[36] and 40-43% in Belgium, Greece, Ireland and UK, and Israel.[37] Similar proportions are reported in Egypt, Jordan and Cyprus.[38]

In Canada, surveillance of MRSA isolates in tertiary care medical centres showed that MRSA colonization and infection increased 17-fold from 1995 to 2007.[39] Since 2007 however, MRSA percentage of all *S. aureus* isolates decreased significantly from 26% in 2007 to 19% in 2011.[40] The reversal in MRSA secular trends in Canada likely reflects improved MRSA infection control and prevention in order to avert the high burden attributed to infection, which is discussed next.

1.2.5 Costs of MRSA:

MDROs such as MRSA infections have high costs in terms of morbidity, mortality and economy. Several studies demonstrated that the burden of MRSA infections is in addition – not replacing – the already existing burden of methicillin susceptible *S. aureus* (MSSA) infections. In fact, MSSA infection rates may be increasing along with rising MRSA rates.[41] Meta-analysis from Cosgrove et al. summarizing 31 studies showed that MRSA had significantly higher mortality when compared with MSSA bacteremia (OR 1.93, 95%CI: 1.54-2.42).[42] However, not all studies in that analysis controlled for potential confounders such as comorbidities and underlying illness severity. A later study by Yaw et al. adjusted for prognostic factors such as age, comorbidities, long-term care status, acute illness severity and metastatic illness, and found no difference in all-cause mortality (HR 0.98, 95%CI: 0.77- 1.30) or infection-related mortality (HR 1.22, 95%CI:

0.89-1.69) between MRSA and MSSA bacteremia.[43] Nevertheless, both studies found that long-term outcomes were worse for MRSA when compared with MSSA bacteremia. Evidence also reveals consistently higher economic costs and length-of-stay in hospital with MRSA, even after adjusting for confounders.[44] A recent study by Antonanzas et al. showed that when compared with MSSA, MRSA bacteremia had increased length of stay ranging from 2 to 10 days, and 3 times the direct costs ($1,700 –$70,000 CAN).[45]

1.2.6 HA-MRSA and risk factors:

MRSA's ability to form biofilm is thought to contribute to its pervasiveness in healthcare settings and implication in almost every type of HAI. Biofilm on foreign surfaces allows for MRSA survival and reproduction advantage, extending the duration required for antibiotic eradication, which may facilitate transfer of antibiotic resistance genes.[46] Furthermore, acquisition of the *mecA* gene may switch *S. aureus* biofilm from polysaccharide-based to proteinanceous-based, facilitating biofilm formation and colonization of synthetic medical devices such as endotracheal tubes, urinary catheters, and endovascular catheters, which can subsequently lead to HA-MRSA infection.[47,48] As a result, use of these invasive devices is inherently a risk factor for HA-MRSA infection.

Other important risk factors for HA-MRSA include MRSA infection or colonization or contact with individuals who are infected or colonized, selection pressure with increased antibiotic use, prolonged hospitalization, and an ICU stay. [49,50] The selective pressure exerted by excessive or inappropriate antibiotic use is an intuitive and well-described risk factor for MRSA infection. For example, a case-control study with 1981 cases found that increased numbers of antimicrobial therapies were associated with an increased risk of MRSA infection (OR 1.57, 2.46, 6.24 to 1, 2-3,

and ≥ 4 respectively).[51] Another case-control study with 387 patients found patients receiving cephalosporin therapy of ≥ 5 days were three times likelier to acquire MRSA than patients without cephalosporin treatment.[52] Other important risks factors of MRSA infection relate to underlying illness and severity such as human immunodeficiency virus (HIV) infection, hemodialysis and long-term care residency. High viral HIV load, and lack of antiretroviral therapy is correlated with increased MRSA infection.[53,54] Hemodialysis inherently is an invasive and repeated procedure which places higher risk for catheter-related complications such as HAI, resulting in a risk of HA-MRSA infection as much as 100 times greater in hemodialysis patients compared with the general population.[55]

Residents in long-term care facilities have higher MRSA infection rates because they often have frequent transfers between and within healthcare settings. Long-term care facilities (LTCFs) are also becoming more recognized as a MDRO source - a U.S. retrospective cohort study of 133 LTCFs showed increased mean quarterly incidence in MRSA admissions from 23% to 29% from 2009 to 2012,[56] and another Australian study of 4 LTCFs found that 36% of patients screened positive for at least 1 MDRO.[57] Transmission of MRSA in LTCFs may also contribute to the problem of introducing HA-MRSA strains into the community and vice versa.[58] Consequently, a more targeted approach in screening higher-risk groups like LTCF residents may help to decrease the frequency of MRSA infection in community settings.[59]

1.2.7 Community-associated MRSA (CA-MRSA):

Community-associated methicillin-resistant *S. aureus* (CA-MRSA) infection occurs in absence of exposure to healthcare settings, and is classically associated with SSTI, younger age, and healthier individuals when compared to patients with HA-MRSA infection.[46] Beyond SSTI,

CA-MRSA can also cause invasive disease like necrotizing pneumonia, osteomyelitis, infective endocarditis, and BSI. Strains frequently have *SCCmec* types IV or V, and encode for the PVL cytotoxin.[60-62] Outbreaks in various communities have been reported such as indigenous communities, childcare facilities, sports teams, military, and prison inmates and guards.[63-69] Importantly, patients with CA-MRSA often have no identifiable risk factors.[70]

Epidemiologically, since the 1990s, CA-MRSA rates and burden have risen.[71] In Canada, from 2007 to 2011, the proportion of MRSA of *S. aureus* isolates sampled from inpatients and outpatients across tertiary hospitals decreased; however, proportion of MRSA represented by CA-MRSA genotypes increased from 20% to 36%.[72] These results are in keeping with ever blurring lines of distinction between traditional HA-MRSA and CA-MRSA classifications.

Patients with traditional "CA-MRSA" strains are increasingly identified among hospitalized patients, and patients with "HA-MRSA" strains are also growing in frequency in community settings. In one prospective cohort study, among 209 inpatients colonized with MRSA 18 months after discharge, 29% developed recurrent MRSA infections of which 49% had an onset outside hospital settings.[73] In a later series of 102 patients with clinically defined CA-MRSA infection, 29% had HA-MRSA strain types.[74] Likewise, patients admitted to hospital with CA-MRSA strains can cause transmission leading to HAI via colonization of healthcare workers or patients. A retrospective study of 352 patients with clinical HA-MRSA infection found that the *SCCmec* type IV CA-MRSA phenotype increased from 17% in 1999 to 56% in 2003.[75] Furthermore, there is some evidence that CA-MRSA could be supplanting traditional HA-MRSA strains. Molecular typing of 208 isolates from one study saw an increasing proportion of MRSA BSI attributed to community-acquired strains from 24% to 49% from 2000 to 2006.[76] One concern about CA-MRSA is that it can infect healthier populations without previous known risk factors,

which presents a greater at-risk group than the traditionally at-risk population for HA-MRSA infection. Importantly, CA-MRSA BSI mortality and clinical outcomes are no different when compared with HA-MRSA strains.[77,78,79] The aging population and resulting increased transfer between community and healthcare settings in this group will continue to blur traditional molecular and geographic distinctions between CA-MRSA and HA-MRSA, further adding imperativeness for good MRSA infection control and prevention.

1.2.8 Livestock-associated MRSA (LA-MRSA):

Recently, newly described animal reservoirs of MRSA particularly in pigs, reveal a new source of MRSA transmission. Whole genome sequencing has shown that LA-MRSAs are a genetically diverse group, and that transmission amongst veterinary household members is widespread.[80] To date, the main LA-MRSA strain characterized is the multi-locus sequence type 398 (ST398); this strain has been implicated in every type of clinical infection, similar to non-livestock MRSA.[81]

Mathematical modeling calculates that LA-MRSA transmissibility is 4.4 times lower than non-livestock MRSA. However, persistent colonization of LA-MRSA amongst livestock workers creates opportunity for increased transmissibility to the wider community.[82] European epidemiological studies have shown MRSA nasal colonization to be as high as 98% among pig farmers. Among Belgian pig farmers, 87% were persistent carriers.[83,84] Household members who were persistent carriers ranged from 4% to 11%, and 30% of livestock veterinarians and household members had carriage periods spanning between 4 to 14 months.[80,83,84] In the Netherlands, LA-MRSA prevalence of all MRSA isolates is as high as 20%,[85] and an outbreak in one hospital with 5 cases was reported, which was eventually traced to a healthcare worker who resided on a pig

farm.[86] By contrast, in Canada, the proportion of LA-MRSA type ST398 of all MRSA isolates remains low at 0.14%.[87] In terms of potential resistance patterns, a small study in rural U.S. found that swine workers had 6 times greater likelihood of being resistant to ≥ 3 classes of antibiotics.[88]

Many questions still persist about what leads to maintenance of LA-MRSA colonization. Paradoxically, usual infection control efforts such as disinfection did not change colonization rates, and donning gloves, apron and hand disinfection actually increased risk of LA-MRSA colonization in one study.[89,90] While studies with a better design and replication of these results are still pending, these early results highlight that there is still much to learn about the transmission of and maintenance of LA-MRSA.

1.2.9 MRSA colonization and transmission:

MRSA colonizers become reservoirs for transmission/infection and predispose individuals to infection after skin and mucosal breakdown. In one prospective study, 19% to 25% of MRSA colonizers developed MRSA infection within 1 year.[49] In the U.S., a point prevalence study from 2010 showed that 7% of hospitalized patients are colonized with MRSA.[91] Individuals become carriers in several ways - contact with contaminated wounds or dressings, direct person-to-person contact, contact with contaminated objects, and inhalation or aerosolised droplets.[92] Median duration of carriage is 88 weeks,[93] although prolonged carriage for up to 4 years was seen in 21% of 1,564 MRSA-positive patients screened in one cohort of hospitals.[94]

Transmission of HA-MRSA occurs typically through the contaminated hands of healthcare workers. Amongst healthcare workers, colonization ranges from 4% to 15% in the U.S., with similar rates in France (10%),[95] and Brazil (5-7%).[96,97] Nurses and emergency department workers had the highest prevalence of MRSA amongst positively-screened healthcare workers with

prevalence from 5% to 10% amongst nurses, 9.6% in emergency departments workers, 5% in ICU workers, and 2% in emergency service responders.[98,99] Inpatients may become colonized from contaminated surfaces and foreign objects and transmission may also result from sharing medical instruments such as stethoscopes.[100,101]

1.3 MSSS Action Plan:

The Committee on Nosocomial Infection in Québec (CINQ) estimated that 10% of patients receiving healthcare would acquire a nosocomial infection, which would cost the province $180 million per year based on rates in the early 2000s.[102] The 2006 publication of the "Action Plan on the Prevention and Control of Nosocomial Infections 2006-2009" by the MSSS incorporated objectives from both CINQ and the Vigilance Group, a patient safety advisory group created in 2001 initially in response to the *C. difficile* epidemic in Québec. Given that MRSA transmission involves both environmental and human components, infection prevention and control strategies required a multifactorial approach, one of which included surveillance and screening, stopping transmission and antibiotic stewardship. These elements are focal points in the INSPQ MRSA guidelines, published in response to the urgency and directives from the MSSS Action Plan. The next sections describe elements of both the Action Plan and the MRSA guidelines.

The 6 elements of the MSSS Action Plan 2006-2009:

1) Establishing a reference framework:

This action step calls for clarification and reinforcement of the role of infection control practitioners (ICP), and to highlight their role in the interdisciplinary setting. In addition to the main ICP objectives of protecting personnel, patients and visitors from infection, six other specific

components must also be addressed which are: 1) HAI surveillance, 2) development of policies, guidelines and supportive measures, 3) education, 4) evaluation of monitoring progress, 5) communication of information, and 6) management of outbreaks. The above components would form the reference framework required to inform and to instruct institutions, patients and clinicians in how to approach HAI prevention. To fulfill these tasks, the 2006 INSPQ MRSA guidelines call for at least one full-time position for every 100 to 133 acute care beds – depending on the type of institution (teaching vs. non-teaching), or one for every 250 residential or LTCF beds. Consequently, the recommendation has seen doubling of the number of full-time ICP nurses from 88 to 177 between 2004 and 2009.[103]

2) *Surveillance*

Active surveillance as part of the Action Plan involves collection, processing, analysis, interpretation and dissemination of HAI data to stakeholders to allow for feedback, prevention planning, implementation and benchmarking. A strong surveillance framework would also help promote appropriate antibiotic therapy by monitoring resistance patterns. HAI and MDRO to be monitored as specified in the Action Plan included *C. difficile*, MRSA, VRSA, VRE, and CLABSI. Other HAI that may warrant surveillance include SSI, pneumonia and gastroenteritis, depending on location and hospital type.

3) Support for Actors:

Support for actors refers to measures and conditions that would enable ICPs, clinical decision makers, environment service workers, and research personnel to support infection prevention and control. For clinicians, support takes form in making infection control resources

more readily available, such as uploading updated MDRO recommendations online at the institution website, or having easy access to hand hygiene materials in healthcare facilities. For environment services workers, the action plan calls for standardization and updates of best practices for cleaning and disinfection. Upgrading of equipment, and switching to single-use equipment when suitable should also be considered. In terms of research, strengthening and promoting exchange of HAI research to access expertise between Québec and other regions in Canada would facilitate shared knowledge and problem-solving.

4) Structure:

Structure here refers to defining the roles of key players and ensuring each player is accountable. The legal framework in Québec allows the government to make important public health decisions when the health of the general population is threatened. This legal mandate is what led to the development of the Action Plan and its implementation. The focus at the regional and departmental level is on monitoring, infection control of HAI based on local needs and to ask for ministerial help if needed. At the facility level, the infection control team and committee enact the mandates and communicate results to the ministry, board of directors and members in in the Vigilance Committee, Quality Control and Risk Management Committee, and other pertinent governing boards.

5) Monitoring and Evaluation:

Regular monitoring and evaluation should be conducted by comparing Québec rates with those of other jurisdictions for eventual decision-making in terms of cost-benefit analysis

associated with MRSA infection control and prevention. Other areas of evaluation include benchmarking regional rates and analysis of institutional infrastructure support.

6) Communication:

The final element in the 2006-2009 Action Plan involves regular communication with stakeholders and with the public on results of progress in order to inform, update, share and implement knowledge. Ideally, the communication plan takes into account the target audience and communication occurs at regular intervals.

1.4 Infection control and prevention of MRSA:

Reversal of rising MRSA incidence in the 2000s is largely attributed to effective infection prevention and control strategies by stopping transmission, identifying MRSA carriers, reducing inappropriate antibiotic use, and by the elimination of reservoirs.[104] Evidence-based practices within each of these targeted prevention methods are discussed below. Unless otherwise specified, each of the listed practices is recommended in the INSPQ MRSA guidelines published in 2006.

Stopping Transmission:

Hand hygiene and contact precautions are cornerstones of interrupting MRSA transmission from patients with known MRSA carriage. Hand hygiene involves cleaning hands thoroughly with either soap and water, or alcohol-based hand gel at five moments before and after patient contact: 1) prior to touching a patient, 2) prior to cleaning or conducting aseptic procedures, 3) after exposure to body fluid, 4) after touching a patient, and 5) after touching patient surroundings. A pilot trial saw that even suboptimal hand hygiene compliance of 48% to 66% resulted in reducing

MRSA transmission rate from 2.16 to 0.93 cases/10,000 patient-days.[105] In addition to hand hygiene, contact precautions create a physical barrier between the potential transmitter and receiver by using single-use gown and gloves (and masks in MRSA respiratory infection) in clinical encounters with patients who have MRSA infection or colonization. Use of isolation rooms or cohorting patients requiring contact precautions also limits further transmission.

Because MRSA colonization can persist for months, optimal documentation of clearance and discontinuation of precautions is still up for debate. The CDC recommends discontinuing contact precautions when three or more surveillance cultures become negative. Placement of patients onto contact precautions and subsequent discontinuation of precautions relies on having a good MRSA screening surveillance program. The essential role of active surveillance plays a crucial part in directing MRSA infection control, and represents another pillar of MRSA prevention.

Active Surveillance

Active MRSA surveillance identifies colonized patients who are asymptomatic in order to minimize transmission by proper implementation of contact and isolation precautions. This is because patients with MRSA colonization are likelier to develop infection.[106] Sampling is done from the anterior nares, oropharynx or perineum, with the anterior nares as the commonest site of colonization.[107] Active surveillance cultures are particularly useful during outbreaks, or for patients at high risk for MRSA infection like patients with previous MRSA infection, current MRSA colonizers, or patients in ICU, hemodialysis, or LTCFs. In Québec, MRSA screening protocol includes patients who have been admitted for at least 24 hours, transferred from other hospitals, LTCFs, rehabilitation centers, or who have previous history of MRSA colonization or

infection. Nasal screening is the preferred screening site. Increased screening is also warranted during outbreaks, and in units where there is a higher risk for medical complications of infection such as ICU, dialysis and burns. A report of acute care hospitals in Québec looking at implementation of MRSA infection control practices found that hospitals with MRSA admission screening protocol increased from 75% to 99% from 2004 to 2009, and that the percentage of hospitals conducting inpatient MRSA screening rose from 53% to 94%.[103] The improved consistency of MRSA screening within Québec is a noteworthy accomplishment, and likely contributed to declining HA-MRSA rates in the last decade.

Decolonization:

The practice of decolonization remains varied due to inconclusive evidence due to significant heterogeneity in study methodology and populations. Furthermore, MRSA decolonization often occurs in conjunction with other MRSA infection control practices, making it hard to quantify the impact of decolonization alone.[108] Methodologically, decolonization most commonly involves the use of chlorhexidine gluconate solution daily washes and application of mupirocin ointment to the anterior nares for 5-10 days. Most chlorhexidine bathing studies have been conducted in ICUs, and evidence of daily bathing in this population has shown to be effective, especially considering ease of use, low cost and low risk of adverse effects. Universal chlorhexidine bathing in the ICU reduced rates of HA-BSI compared with bathing with soap and water and targeted decolonization based on MRSA screening.[109] A large subsequent study with 43 hospitals also concluded that universal decolonization with both chlorhexidine bathing and intranasal mupirocin together was more effective than targeted screening and decolonization.[110] That said, rising mupirocin resistance is a growing issue, especially without current standardized

laboratory testing for mupirocin resistance.[111] Resistance to both chlorhexidine and mupirocin may also be one reason for persistent MRSA colonization.[112]As a result, its use for universal decolonization in ICUs is not recommended due to heightening selective pressure with increasing use.[113]

The limited endurance of decolonization and high rates of resistance to decolonization agents also present strong arguments against the practice. Recolonization, at 12 months after treatment in healthcare workers and dialysis patients, was detected in 50% to 75% of cases. In the shorter term, 56% became recolonized in 4 months.[114,115] Despite the above challenges, proponents of decolonization favor its use given its success in low MRSA-endemic countries such as the Netherlands and Scandinavia.[31] However, the generalizability of aggressive decolonization effectiveness remains uncertain due to different MRSA endemicity levels, mupirocin resistance and overall cost-effectiveness. As a result, in the 2006 INSPQ MRSA guidelines, no explicit recommendation for decolonization was made given the inconclusive evidence and high reported rates of mupirocin resistance. Decolonization practices were left at the institution's discretion with inclusion of mupirocin antibiogram if used. Similarly, new HAI prevention guidelines from SHEA/IDSA recommend universal MRSA decolonization in ICU patients under "Special Approaches," in its 2014 guidelines, "A Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals."[116]

Environmental cleaning

MRSA survives on inanimate surfaces for days to months depending on the temperature, surface material, humidity, and organism load on the surface. As such, routine and thorough cleaning of patient equipment and surfaces, and limited sharing of patient medical equipment

plays an important role in reducing transmission. Fortunately, MRSA is sensitive to hospital disinfectants, and checklists for cleaning of frequently touched items have been useful for maintaining consistency.[117] Integration of environmental services with the infection control team is increasingly encouraged in order to ensure proper cleaning and disinfection.

Antibiotic Stewardship

Excessive and inappropriate antimicrobial use has inevitably selected for resistance since antibiotics were first produced. MRSA colonization has been associated with increased frequency and duration of antibiotic therapy, especially with fluoroquionolone use.[118,119] Nevertheless, delaying and decreasing appropriate antibiotic therapy leads to increased mortality.[120] Furthermore, changing antibiotic formularies could alter selective pressure, leading to emergence of other resistant organisms.[121] SHEA/IDSA guidelines on antimicrobial stewardship program development makes several key recommendations: development of institution-specific antibiotic evaluation committees, protocols to promote appropriate use, hospital formulary restrictions, preferential use of narrow-spectrum agents, and mandatory consultation with infectious disease specialists for appropriateness of therapy.[121] To date, evidence shows that antimicrobial stewardship programs have been particularly useful in improving susceptibilities of gram-negative organisms.[122] Evidence of antibiotic stewardship effectiveness is scarcer for MRSA. Nevertheless, increasing establishment of stewardship programs inevitably will play a progressively important and crucial role in infection control and prevention of further MDRO emergence.

1.5 SPIN Program

Surveillance is an essential component in HAI infection control and prevention, and plays a crucial role in MRSA prevention and the MSSS Action Plans. In Québec, , the Surveillance Provinciale des infections nosocomiales (SPIN) had already been put in place since 2003 to monitor CLABSI incidence. Since then, using SPIN's existing platform for CLABSI, surveillance for other HAI was added – *C. difficile* in 2004, *S. aureus* BSI, MRSA and VRE in 2006, hemodialysis-associated BSI and all other HA-BSIs in 2007, and most recently, carbapenemase-resistent Enterobacteriaceae in 2014. For MRSA BSI surveillance, in addition to establishing and monitoring incidence trends geographically, additional objectives were to capture the number of MRSA of all *S. aureus* (SA) BSI, determine the origin for each case (i.e. community or healthcare-associated) in order to decipher its origin and type strains.

Procedures and yearly results for SPIN's MRSA BSI program, and SPIN's ICU CLABSI surveillance, Surveillance des bactériémies nosocomiales sur cathéters centraux aux soins intensifs (SPIN-BACC) are publicly available on the INSPQ website.[123]The National Healthcare Safety Network (NHSN) definitions for BSI and CLABSI are used and all identified cases need to be lab-confirmed with microorganism identification and antibiogram testing, in the local microbiology laboratory. All confirmed cases are reviewed by an infectious disease or medical microbiologist epidemiologist, to ensure quality control and avoid misclassification. Protocol manuals for quality assurance, definitions, reporting, and timelines are periodically updated, released to participating institutions and published online, with training modules.[123,124] Detailed description of SPIN-BACC implementation and validation have also been published.[125,126] Definitions and surveillance timeframes are further discussed in subsequent article chapters.

1.6 CLABSI Literature Review:

1.6.1 Pathogenesis and microbiology:

CLABSIs develop from 4 mechanisms: colonization of the skin, intraluminal or hub port contamination of the IV tubing system, contamination of the IV infusate, or secondary seeding from an existing infection. The two most common routes of infection are contamination from skin colonization of microorganisms, and intraluminal or hub contamination. A strong association between heavy skin and catheter colonization and CLABSI have been demonstrated.[127] Skin microorganisms gain direct access to the CVC insertion site and travel subcutaneously along the catheter's fibrin sheath that lines the lumen and eventually enters the bloodstream.[127,128] *S. aureus'* ability to produce biofilm also promotes bacterial catheter colonization, which is aided by host production of fibrinogen and fibrin, and pathogen biofilm components like glycocalyx for deposition. Risk of CLABSI increases when CVC remains in place for more than 2 weeks, which may predispose the hub to contamination.[129,130] The use of iodinated alcohol impregnated hubs reduced both bacterial colonization load and subsequent CLABSI, and are becoming more frequently used.[131] It may also happen that central-line infections are due to an IV infusate contamination or secondary infections from haematogenous seeding at another site, in which case they would not be considered a CLABSI by SPIN/NHSN definitions. Contaminated infusate infusions from heparin flush, IV medications, and chlorhexidine disinfectant have all occurred.[132-134] The same microorganism cultured from both blood and infusate confirms this mechanism. CLABSI via contaminated infusate often occurs in lower-risk patient with unusual microorganisms cultured, factors that can help point towards the diagnosis.

Unsurprisingly, the commonest CLABSI etiologies involve skin commensals, with coagulase-negative staphylococci being by far the most frequent organism (31%), followed by

Staphylococcus aureus (20%), Enterocci species (9%), and *Candida* species (9%) in the U.S. from 1995 to 2002; these are also the top four CLABSI microorganisms in Québec in the last 8 years.[2,135] Increased reporting from recognizing coagulase-negative staphylococci as a true CLABSI cause likely contributed to the higher incidence of CLABSI from these skin flora organisms, which were previously considered to be from contaminated samples. Although the majority of CLABSIs are caused by gram-positive bacteria, gram-negative bacteria and the fungal *Candida* species account for 20% and 25% of CLABSIs, respectively.[2,135] Patients with hematologic malignancy and burns are most susceptible to gram-negative CLABSIs, like *Pseudomonas*.[136,137]

Use of antimicrobial impregnated catheters has been shown to reduce CLABSI incidence and has become more commonly used. Use of chlorhexidine-silver-sulfadiazine impregnated catheters had significantly reduced risk of CLABSI.[138] Minocycline/rifampin impregnated catheters have also be shown effective and potentially superior to chlorhexidine-silver-sulfadiazine-impregnated catheters.[139] Antibiotic lock solutions, which fill the catheter lumen with highly concentrated antibiotic solution for several hours have also been tested for CLABSI prevention. The idea is to prevent colonization at the intraluminal catheter surface, thereby, reducing infection risk. In a recent meta-analysis, antimicrobial lock solution reduced CLABSI risk by 69% compared with traditional heparin-lock solution.[140] Nevertheless, there is still lack of data on how wider use of antimicrobial lock solutions affects resistance patterns. While evidence for using antimicrobial-impregnated catheters and lock solution is strong, pitfalls include anaphylactic reactions and enabling evolution of MDROs. Suggestions to reserve their use to centers with higher CLABI incidence compared to the national average have been voiced,[141] however, many centers still use them regularly.

1.6.2 Risk Factors

Host risk factors are usually unmodifiable at time of CVC insertion and generally are linked to the deterioration in immune function such as: immune deficiency, chronic illness, bone marrow transplant, malnutrition, loss of skin integrity and extremes of age.[142] Burn patients have a particularly high risk for CLABSI due to multiple factors such as loss of skin integrity and augmentation of the inflammatory response. Neutropenic patients have immune compromise, and patients with hematologic malignancies harbour greater CLABSI risk than patients with solid tumours.[143]

Catheter-related risk factors can be somewhat modifiable at time of CVC insertion, and include catheterization duration, material, insertion technique, and maintenance care. The top three major catheter-related risks are catheter type, site of insertion and duration of placement. Intravascular catheterization in and of itself increases HAI risk; different catheter types confer different risks. A meta-analysis by Maki et al. found that peripherally inserted central catheters (PICC) generally have the lowest infection risk, followed by (in ascending order) cuffed and tunneled CVCs, arterial catheters, non-cuffed tunneled CVCs, and non-cuffed non-tunneled CVCs, however, case-mix was not adjusted for in the study. Location of insertion also determines CLABSI risk - femoral vein, and to a lesser extent, jugular vein placement confers higher risk (OR 2.7 95%CI 1.0-7.5; HR 4.83 95%CI 1.96-11.93, respectively) when compared to subclavian placement in adults.[144-146] Risk can be mitigated with experience, good sterile technique and maintenance care.[147] Surgical placement of CVCs is associated with lower BSI risk than percutaneously inserted catheters.[148] However, this option requires access to a skilled team, which may not be available in resource-limited centres.

Lastly, CVC placement duration is also a key determinant of infection risk. CVC placement for more than 3 to 4 days for PICCs and 6 days for CVCs has been associated with increased CLABSI risk.[149,150] Although duration of placement is correlated with increased infection risk, ideal timeframes for routine catheter change are not established. Current CDC recommendations call for regular and diligent clinical evaluation and assessment of the catheter site, which should be ideally performed at least every other day and catheter need. Purulence at insertion site and onset of hemodynamic stability should immediately raise suspicion of CLABSI.[151]

1.6.3 Epidemiology:

A recent meta-analysis of CLABSI attributable mortality found significant increased risk of death.[152] The CDC estimates that CLABSI mortality ranges from 12-25%, and that the cost per episode ranges from $30,900 - $65,000.[153,154] Fortunately, secular trends in developing countries show decreasing CLABSI incidence in ICUs – from 3.65 to 1.65 cases/ 1000 CVC-days in the U.S. between 2001 and 2009, 1.78 to 0.94 cases/ 1000 CVC-days in adult ICUs in Canada (CNISP) between 2006 and 2009, and 2.94 to 1.01 cases/ 1000 CVC-days in Québec adult ICUs from 2007 to 2015.[124,153,155] Although results from 36 developing countries participating in INICC showed higher incidence overall (6.8 cases/ 1000 CVC-days), the general decreasing trend was also seen from 2002 to 2010.[10] Incidence reduction is attributed to development of CLABSI insertion and maintenance checklist bundles – a set of steps in a checklist format combined with readily available "bundles" of materials and equipment used for safe CLABSI insertion and maintenance practices. The contents of the checklist and bundles are discussed in the following section.

1.6.4 CLABSI Prevention and checklist bundles:

Both Canadian and American CLABSI surveillance programs experienced an overall decline in CLABSI rates since 2006.[155-159] In the province of Québec, the clinical and public health importance of CLABSI has led to regular CLABSI surveillance in ICUs via SPIN since 2003.[125] Regionally, Québec CLABSI rates have also fell from 2003 to 2009.[160] During this time, a standardized collection of evidence-based CLABSI prevention interventions called checklist bundles, were increasingly used. In the pilot study by Provonost et al., follow-up at 18 months after checklist bundle introduction resulted in sustained reduced incidence by 66%.[161] Items in the checklist bundle for catheter insertion include: hand hygiene, aseptic technique, maximal sterile barrier precautions, chlorhexidine skin antisepsis, and avoidance of femoral access. In the updated CDC CLABSI prevention guidelines in 2011, a second checklist for CVC maintenance was added, which include: hand hygiene adherence, antiseptic scrub of access hub, use of only sterile devices for access, replacement of soiled, dislodged or wet dressings, and dressing changes with aseptic techniques using clean and/or sterile gloves.[151] In Canada, the Canadian Patient Safety Institute's program, *Safer Healthcare Now!* was created in 2009 for implementation of checklist bundles.[162,163] Individual items within the checklist bundles as per CDC in detail are listed and described below.[164,165]

<u>CVC Insertion Checklist bundle:</u>

- ❖ Performance of hand hygiene prior to insertion.
    - Removal of jewelry or watches and avoidance of clothing contact with sinks.

- Vigorous and thorough hand scrubbing with soap and water for at least 40 seconds as per WHO protocol.[166]

❖ Aseptic technique adherence:

- Barrier creation between sterile site and microorganisms by using masks, caps, sterile gloves, gowns and drapes.[167]

❖ Insertion site preparation:

- Apply disinfectant to clean skin at insertion site with chlorhexidine 0.5% solution in alcohol.
- In patients with chlorhexidine contraindications, iodine tincture or 70% alcohol can be used. Allow skin to dry completely prior to insertion.

❖ Choice of best insertion site to minimize infection:

- Avoidance of femoral site whenever possible in adult patients.
- Consider ultrasound-guided insertion which has shown to have better first-attempt success.[168]

❖ Dressing care: Cover dressing with sterile gauze (preferred), or transparent semipermeable dressings.

<u>Checklist bundle for maintenance of central line catheters:</u>

❖ Hand hygiene compliance before manipulation of catheter site.

❖ Scrubbing the access port or hub with antiseptic (chlorhexidine and alcohol, or povidone-iodine solution)

❖ Use of aseptic technique when handling catheter access.

❖ Replace dressings regularly or when wet/soiled/dislodged

- Every 2 days for gauze dressings, and every 7 days for transparent dressings.

❖ Dressing changes using aseptic technique with clean or sterile gloves.

*Facility duties include:

❖ Assembling all supplies into a "bundle" kit to make readily available for use.

❖ Providing above checklists to clinicians

❖ Supply and ensure easy access to hand hygiene

❖ Surveillance of compliance to hand hygiene and feedback to members

❖ Ensure education and training for central line insertion and maintenance techniques.

(*Additional measures include consideration of using antimicrobial locks, chlorhexidine impregnated dressings, and 2% chlorhexidine bathing.)

In 2013, a survey of ICUs in Québec revealed that most ICUs had already implemented bundled practices as of 2012. Experience within one teaching hospital ICU in Québec saw introduction of insertion bundles in 2009, followed by maintenance bundles in 2010. The rollout of the program then expanded to the emergency department and interventional radiology. A media campaign was also launched in hospitals.[169] Despite continuous introduction of these practices, performing regular audits were sub-optimal in most facilities.[170] A recent study of American pediatric ICUs (PICUs) showed similar bundle use and compliance practices.[171] CLABSI rates were already decreasing in Québec prior to formal introduction of CLABSI checklist bundles; incidence had decreased by 11% in adult ICUs, and 50% and 18% in PICU and NICUs from 2003 to 2009, respectively.[160] However, SPIN CLABSI epidemiology and comparison with other regions after 2009 in response to new interventions had been less explored.

This research question also brings to light how to best benchmark SPIN CLABSI rates with those of other surveillance programs. Using a combination of fixed and dynamic benchmarks from SPIN, Canada, and the U.S., SPIN CLABSI rates were thoroughly compared to rates of those jurisdictions. Results would hopefully illuminate how effective CLABSI prevention efforts have been and ascertain areas for future improvements.

1.7 Objectives:

To quantify impact of the INSPQ MRSA guidelines on SPIN HA-MRSA BSI rate, SPIN CLABSI rates were used as a comparator to proxy general HAI incidence trends. The next chapter describes methodological rationale of choosing segmented Poisson regression for these analyses. Subsequent article chapters first characterize CLABSI epidemiology in Québec during the last decade and then SPIN HA-MRSA BSI incidence trends are compared to the described CLABSI trends. The step-wise objectives of this thesis include:

1) To describe the epidemiology of CLABSI in Québec ICUs using incidence rates by year and ICU type from the outset of mandatory CLABSI reporting from 2007 in Québec.
2) To benchmark SPIN CLABSI rates over time and to compare with other jurisdictions.
3) To describe the epidemiology of HA-MRSA BSI incidence in Québec since 2006.
4) To evaluate the impact of MRSA guidelines in Québec by studying incidence change of HA-MRSA BSI with CLABSI incidence change as the control comparator, using segmented Poisson regression. Time segments include: before, immediately post-guideline publication, and later post-guideline time duration.

Chapter 2: Methods and Materials

2.1. CLABSI benchmarking:

Benchmarking is the method of evaluating processes and outcomes and comparing it to a standard, which allows for performance assessment and identification of strengths and weaknesses. Benchmarking is further classified into internal and external comparisons. In terms of HAI surveillance, internal benchmarking compares processes or outcomes to a baseline within the surveyed population. External benchmarking compares processes and outcomes in one healthcare population with another jurisdiction's healthcare population, which typically has similar surveillance practices and definitions. In addition to describing SPIN CLABSI epidemiology, the second objective of this thesis is to compare SPIN CLABSI rates with other jurisdictions, which involves finding a standard to compare to and benchmark against. Both internal and external CLABSI benchmarking were done because of the availability of CLABSI surveillance data from CNISP and NHSN. However, the question of how best to benchmark SPIN CLABSI rates from 2007 to 2014, and how to compare SPIN CLABSI rates to other jurisdictions put forth an interesting challenge. Several methods were explored including Poisson regression, comparison of incidence rate alone, or indirect standardization. Although each method had benefits and drawbacks, the most commonly used methods in literature are reporting of incidences directly or indirect standardization using the standardized incidence ratio (SIR) in the U.S.[172] Consequently, this indicator was used for CLABSI rate comparisons.

SIR was first used by the CDC after implementation of nationally mandated HAI reporting. Information on the number of cases and CVC-days are reported and compared to a national benchmark. Risk-adjustment is done based on ICU type and size. SIRs are obtained by

dividing the observed number of CLABSI cases by the expected number of cases. Expected rates are taken from a reference population and multiplied by the observed amount of CVC-days to generate the expected numbers of CLABSI cases. SIR of 1 denotes no difference between the observed and expected number of CLABSIs; SIR <1 means the rate was less than expected, and a SIR > 1 denotes a rate higher than expected.

In the U.S., SIRs at the national, state, and hospital-level are publicly available via the CDC, state departments, and the consumer purchasing website, "Hospital Compare".[173] The advantages of SIR include ease of interpretation and derivation. That said, the choice of benchmark is often difficult. Arguments for both more and less risk-adjustment, incorporating patient risk factors, and creating dynamic benchmarks have all been made.[173-175] Meanwhile, the current practice of using NHSN CLABSI incidence benchmarks from 2006-2008 remain, despite compelling arguments that this benchmark is outdated and misrepresenting because CLABSI rates then were higher than current averages.[173] Furthermore, the interpretation of SIR is limited between the two groups compared within the ratio; current consumer reports lists SIRs from different hospitals and regions, which promotes erroneous inter-facility interpretation.[176,177] We wanted to compare Québec SPIN CLABSI rates over time intra-regionally and inter-regionally to NHSN and CNISP rates, but to avoid using dated benchmarks, we used both fixed and dynamic benchmarks. We used fixed SIRs with pooled 2007-2010 SPIN CLABSI rates and 2006-2008 NHSN CLABSI rates to be consistent with current comparison methods in the literature. In addition, dynamic benchmarks using pooled mean of SPIN, NHSN and CNISP rates in the preceding 3 years would provide a more up-to-date comparison. Using a combination of these benchmarking methods would allow for broad and quantifiable rate comparisons to shed light on how SPIN CLABSI fared over time when compared with other jurisdictions.

2.2 Segmented Poisson regression study design and methods:

Quasi-experimental study designs allow the analysis of non randomized interventions to examine pre- and post- intervention outcomes when use of randomized control trials is limited due to ethics, location restriction and the need for expeditious intervention.[178] Requirements for the design include a time series (regular and evenly-spaced time periods) with continuous or count measures in each time series period.[179] The most advantageous feature of quasi-experimental design is the ability to establish causality between an intervention and outcome. The method can also inform on the timing of intervention effect: did the effect occur instantly, immediately, or gradually?

Several types of quasi-experimental study designs have been characterized; the main variations are in the use of a control group, and/or a pre-test (pre-intervention) period. Use of both pre-test periods and control groups result in greater validity by taking into account effects that undermine internal validity such as time-varying confounders, and regression to the mean.[178,180] When breakpoints occur during the study interval separating the time series into segments, individual regression of time segments is performed – this method is called segmented regression. Analysis of the impact of MRSA guidelines on MRSA rates, in this thesis, included both a control group (CLABSI rates) and a pre-test period to strengthen study validity. Two distinct breakpoints in time divide the study period into 3 segments – a pre-intervention period and 2 post-intervention periods. Using segmented Poisson regression, both CLABSI and HA-MRSA incidence changes were analyzed by looking at secular incidence trends within each time segment, and by looking for intercept changes between time segments corresponding to abrupt incidence fluctuations. By accounting for time-varying effects and by having a comparator in using CLABSI, the true impact

of MRSA guidelines on HA-MRSA BSI incidence could be more carefully and accurately assessed.

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Central Line Association Bloodstream Infections in Québec Intensive Care Units: Results from the Provincial Healthcare-Associated Infections Surveillance Program (SPIN)

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Abstract: (247 words)

Background: Following implementation of bundled practices in 2009 in Québec and Canadian intensive care units (ICUs), we describe CLABSI epidemiology during the last 8 years in the province of Québec (Canada) and compare rates with Canadian and American benchmarks.

Methods: CLABSI incidence rates (IRs) and central venous catheter utilization ratios (CVCURs) by year and ICU type were calculated using 2007-2014 data from the Surveillance Provinciale des Infections Nosocomiales program (SPIN). Using American and Canadian surveillance data, we compared SPIN IRs to rates in other jurisdictions using standardized incidence ratios (SIRs).

Results: A total of 1355 lab-confirmed CLABSIs over 911,205 central venous catheter days (CVC-days) were recorded. The overall pooled IR was 1.49 cases/1000 CVC-days and rates for adult teaching and nonteaching ICUs, neonatal ICUs (NICUs) and pediatric ICUs (PICUs) were 1.04, 0.91, 4.20, and 2.15 cases/1000 CVC-days, respectively. Using fixed SPIN 2007-2009 benchmarks, by 2014, CLABSI rates had decreased significantly in all ICUs except for PICUs. Rates declined by 55% in adult teaching ICUs, 52% in adult nonteaching ICUs, and 38% in NICUs. Using dynamic American and Canadian CLABSI rates as benchmarks, SPIN adult teaching ICU rates were significantly lower, adult nonteaching ICUs had lower or comparable rates, while NICU and PICU rates were higher.

Conclusion:

Québec ICU CLABSI surveillance shows declining adult ICUs rates. Lack of CLABSI rate decrease in NICUs and PICUs highlight need for continued surveillance and analysis of factors contributing to higher rates in these populations.

Introduction:

Central line-associated bloodstream infection (CLABSI) is associated with serious morbidity and mortality in intensive care units (ICUs), and is one of the costliest hospital-acquired infections (HAI).[154,181] In the province of Québec, the perceived clinical and public health importance of HAI due to the high incidence of CLABSI at the time led to the development of a provincial surveillance program in 2003: Surveillance Provinciale des Infections Nosocomiale (SPIN) under the Institut National de Santé Publique du Québec (INSPQ).[125] Currently, all ICUs in Québec with ≥ 10 beds are required to report CLABSIs year-round to SPIN, giving the program the advantage of having representative population surveillance.[182] SPIN objectives include acquiring data to track epidemiology, incidence and causative pathogens, and providing benchmark incidence rates. Importantly, the program's continuous surveillance throughout the year enables both intra- and inter-facility benchmarking of CLABSI rates and central line use. Canadian and American surveillance have shown an overall decline in CLABSI since 2006.[156,183] Québec CLABSI rates have also reflected this downward trend from 2003 to 2009.[160] These declines coincide with the implementation of several important programs and guideline updates such as the Centre of Disease Control (CDC) revised intravascular catheter related infection prevention guidelines,[184] and the Canadian Patient Safety Institute's program, *Safer Healthcare Now!*, which was created in 2009 for implementation of evidence-based bundles of central line insertion and maintenance, which has shown to be effective in decreasing CLABSI rates.[185] On a regional level, a survey of ICUs in Québec revealed that most ICUs implemented bundled practices; however, practices such as performing regular audits were less optimal in most adult ICUs.[170] A recent study of American pediatric ICUs (PICUs) showed similar bundle use and compliance practices.[171] Due to changing practices and overall decreasing CLABSI rates within

the last decade seen in several national and regional surveillance programs including Québec, our study's overall objective was to determine the effect of changing practices and culture of CLABSI prevention efforts in Québec during the last 8 years, as well as to ascertain how SPIN rates compared with other populations to guide future prevention efforts. To do so, our specific aims were 1) to describe CLABSI rates in Québec during the surveillance period, 2) to examine if any significant rate trends existed, especially after newer guideline publications, and 3) to benchmark Québec rates dynamically with annual SPIN, Canadian and American surveillance CLABSI rates.

Methods:

SPIN Surveillance Network:

SPIN is a year-round active and prospective CLABSI surveillance program, mandatory for all ICUs with ≥ 10 beds in the province of Québec since 2007. ICUs with < 10 beds voluntarily submit data. Retrospective analysis of the program's reporting validity within the study period showed excellent results when compared with other regional surveillance networks, having a sensitivity and specificity of 88% and 92%, respectively.[126] By 2014, 70 ICUs from 51 different hospitals participated in the program (969 beds). This comprised of 33 nonteaching adult ICUs, 24 adult teaching ICUs, 8 NICUs, and 5 PICUs. Of these, 57 ICUs (851 beds) participated in all 8 years of surveillance (Table 1) and were used in describing rates. All ICUs were included in benchmarking for SIR analyses, regardless of full or partial participation, as subgroup analyses demonstrated similar incidence. A previously published surveillance report of SPIN CLABSI rates included 2 years that overlap the present study (2007-2008, and 2008-2009);[160] nevertheless, because mandatory SPIN CLABSI surveillance began in 2007, we included data from 2007 onwards for optimal validity.

Definitions and CLABSI Identification:

Central venous catheters (CVCs) were defined as intravenous catheters that end in a vessel in proximity to the heart, such as the subclavian, internal jugular or femoral vein. In accordance with NHSN and CNISP practices, peripherally inserted catheters, total implanted catheters and umbilical catheters were also considered CVCs. SPIN has been following the National Healthcare Safety Network (NHSN) definition of CLABSI as of April 1, 2010.[186] SPIN CLABSI cases from 2007 to 2010 were retrospectively recomputed to reflect the new definition. NHSN 2006-2008 data reports already reflected this new definition, while CNISP CLABSI reports adopted the change as of April 1, 2010.[159,183]

Data Collection and Surveillance

Patients with CVC in the ICU were followed 48h after CVC removal or discharge from the ICU. Infection control practitioners (ICP) prospectively identified positive blood cultures in ICU patients, confirmed CVC placement and timing, and chart reviewed for criteria fulfillment. Data on CLABSIs that occurred between April 1st, 2007 and March 31st, 2015 were extracted in June, 2015. The present study is a retrospective longitudinal cohort analysis that was approved by the INSPQ and did not require institutional board review because it was a secondary analysis of collected data.

Statistical Analysis

Pooled CLABSI incidence rates (IRs; per 1000 CVC-days), CVC utilization ratios (CVCURs, an indicator of units' CVC use), and standardized incidence ratios (SIR) were calculated by ICU type (adult teaching or nonteaching, pediatric or neonatal) and by surveillance year. Incidence rate by each reporting period (one calendar year comprises thirteen 4-week intervals) was

examined for seasonal trends. The surveillance year begins April 1st, which acts as day 1 of reporting period 1. Henceforth, calendar years written singly such as "2007" refers to the start of surveillance year, which spans from April 1st, 2007 to March 31st, 2008. ICUs were defined as "teaching" if associated with medical training and research programs, and "nonteaching" if otherwise. NICUs and PICUs are all associated with teaching hospitals. Poisson confidence intervals for rates and SIRs were used to compare CLABSI rates. Statistical calculations were performed using Stata version 14 (StataCorp 2015; College Station, Texas).

SIRs use indirect standardization to compare rates between two different populations.[172] SIRs were obtained by dividing the observed number of CLABSI cases by the expected number of cases. Expected rates were taken from a reference population, were multiplied by the observed amount of CVC-days to generate expected numbers of cases. SIR of 1 denotes no difference between the observed and expected number of CLABSIs; SIR <1 denotes a rate less than expected, and SIR > 1 denotes a rate higher than expected. The 95% SIR confidence intervals (CIs) were derived using upper and lower 95% CI limits of CLABSI IRs to calculate corresponding number of expected cases.

To examine intra-regional CLABSI rate trends over time, we used pooled SPIN rates from April 2007 to March 2010 as the benchmark because several important prevention guidelines and initiatives were published in 2009 (e.g., *Safer Healthcare Now!* program in Canada; World Health Organization's launch of the Save Lives: Clean Your Hands initiative for hand hygiene).[187] Using these pooled rates as the benchmark allowed us to measure impact of these initiatives over time. To determine if sustained rate trends existed, dynamic SPIN benchmarks were also used: SIRs for a particular year were calculated using pooled SPIN rates from preceding 3 years for a given ICU type (e.g., the 2010 adult teaching ICU SIR used pooled

CLABSI rates of 2007 to 2009 in adult teaching ICUs as the benchmark to calculate expected rates).[173]

To compare SPIN rates with American and Canadian ICU CLABSI rates, we obtained published CLABSI rates from available CNISP and NHSN reports during 2007-2014. CNISP surveillance data were extracted from published reports for 2006, 2009, 2010 and 2011,[183] and NHSN data extracted for years 2006-2008 (pooled rates),[159] and subsequent yearly reports from 2009 to 2013.[156-158,188,189] CDC/NHSN and consumer groups release ongoing reports publishing SIRs using NHSN 2006-2008 CLABSI benchmarks; therefore, we included this benchmark to be consistent with ongoing publications. However, to better explore if SPIN rates matched similarly to NHSN rate over this period in the context of practice changes affecting both healthcare populations, dynamic SIRs using NHSN rates from the preceding 3 years were also used as benchmarks for the examined year. CLABSI rates for NHSN medical and/or surgical ICUs described as "major teaching" were used in obtaining expected rates for SPIN adult teaching ICU SIR derivations; ICUs classified as "all other" were considered nonteaching adult ICUs. NICUs were not compared due to differential reporting of NHSN NICU rates, which uses birth weights, information not collected in SPIN.

Due to gaps in published reports between CNISP and SPIN during this period, the most recently available CNISP rates were used as benchmarks for any corresponding SPIN year. CNISP 2006 rates served as benchmark for SPIN surveillance years 2007 to 2009 inclusive, pooled CNISP 2009-2010 rates were used to benchmark SPIN years 2010 and 2011, and CNISP 2011 rates were used for benchmarking SPIN surveillance years 2012 to 2014, inclusive. Since the vast majority of CNISP hospitals are tertiary hospitals with academic affiliations, adult nonteaching ICUs were excluded from CNISP SIR derivations.

RESULTS:

CVCURs and Pooled IRs:

Total participating ICUs, CLABSI cases, CVC-days, CVCUR and pooled IR by year and ICU type are shown in Table 1. Over the surveillance period, ICU participation increased from 56 to 67 facilities, 11 of which were nonteaching adult ICUs. A total of 1428 laboratory-confirmed CLABSIs and 970,498 CVC-days were recorded, for an overall pooled mean rate of 1.47 (95% CI: 1.40, 1.55) cases/ 1000 CVC-days. Restricting analysis to ICUs that participated to the entire surveillance period, the overall incidence remained at 1.49 (95%CI: 1.41, 1.57). Incidence by ICU type and year are shown in Table 1. Figure 2 shows rates by reporting period - there was no significant evidence of seasonality observed in rates for each ICU type. Incidence and CVCURs for all years and ICU types are graphically shown in Figure 1. CVCURs for adult teaching and nonteaching, pediatric and neonatal ICUs, which participated for the entire 8 years were 0.62, 0.37, 0.57 and 0.20, respectively (Table 1).

SIRs against SPIN 2007-2009 and NHSN 2006-2008 benchmarks:

SIRs with fixed SPIN 2007-2009 and NHSN 2006-2008 benchmarks were calculated to study rate changes over time before and after important guideline and program launches in 2009-2010. Table 2 presents SIRs for each ICU type and by year: adult teaching ICUs showed a significant rate decline over the period, with 2014 SIRs of 0.45 (95%CI: 0.33, 60) and 0.26 (95%CI: 0.19, 0.36) using SPIN and NHSN benchmarks, respectively. Adult nonteaching ICUs also decreased, with SPIN SIR of 0.48 (95%CI: 0.30, 0.73), and NHSN SIR of 0.39 (95%CI: 0.24, 0.59) in 2014. PICUs did not show a significant rate change with either benchmark. Neonatal ICUs rates varied

with a significant rate increase seen in SIRs for years 2011 and 2012, followed by a significant rate decrease in 2014, with an SIR of 0.62, (95%CI: 0.44, 0.84).

SIRs using dynamic benchmarks:

Dynamic SIRs using SPIN, CNISP and NHSN benchmarks by ICU type are shown in Table 3. For adult teaching ICUs using SPIN benchmarks, rates for most years were similar to preceding years' rates, except for 2014, which showed a statistically significant decline with an SIR of 0.71 (95%CI: 0.52, 0.96). With CNISP benchmarks, SPIN adult teaching ICUs had lower rates compared to most recent CNISP rates published in 2007, 2009-11 and 2014. Dynamic NHSN benchmarks yielded significantly lower SIRs for adult teaching ICUs for all years. In adult nonteaching ICUs, SIRs in 2013 and 2014 using SPIN benchmarks showed significantly lower rates compared with preceding years, and SIRs using NHSN benchmarks were significantly lower in 2010 and 2014.

NICU SIRs showed significantly higher rates with SPIN benchmarks in 2010 and 2011, having SIRs of 1.39 (95%CI: 1.09, 1.74), and 1.44 (95%CI: 1.17, 1.75), respectively. Likewise, using CNISP benchmarks, NICUs SIRs for 2012 (1.82; 95%CI: 1.42, 2.24) and 2013 (1.40; 95%CI: 1.09, 1.76) were also significantly higher. PICUs demonstrated no significant differences in dynamic SIRs using SPIN data, but did yield significantly higher SIRs when using NHSN benchmarks in 2011 (SIR 1.92; 95%CI: 1.16, 3.00), and CNISP data in 2012 (SIR 2.12; 95%CI: 1.28, 3.31).

DISCUSSION:

From 2007 to 2014, the overall rate of 1.49 cases/1000 CVC-days for all ICU types was comparable to CLABSI rates in other developed countries after bundle intervention, such as Germany (1.64 cases/ 1000 CVC-days in 2008-2010),[190] and Victoria, Australia (1.26 cases/ 1000 CVC-days between 2009-2013).[191] No seasonality, nor "July effect" on rates due to influx of new residents in hospitals was identified.[192]

Importantly, Québec adult teaching and nonteaching ICUs showed lower and decreasing CLABSI rates over the surveillance period. Later adult teaching and nonteaching ICU rates demonstrated statistically significant declines when using SPIN 2007-2009 benchmarks, decreasing by 55% (95% CI: 40%, 67%) for adult teaching ICUs, and by 52% (95% CI: 27%, 70%) for adult nonteaching ICUs in 2014. Using dynamic benchmarks to examine significant year-to-year changes, SPIN adult ICUs also had lower rates compared with NHSN and CNISP benchmarks for most years. There was no statistically significant SIR when using dynamic SPIN benchmarks. This may be due to a lack of power, as SPIN is a smaller network. Post-hoc power calculation showed that power was less than 80%, ranging from 5-51% for most ICU types and most years. Dynamic adult nonteaching ICU SIRs with NHSN referents were more comparable to SPIN rates overall, with significantly lower SIRs in 2008 and 2010.

Adult ICU rate reduction may be attributed to several factors. In 2009, a national campaign from the Canadian Patient Safety Institute implemented guidelines on use of evidence-based bundles in hospitals. Furthermore, greater HAI awareness from updated CDC intravascular catheter guidelines in 2011, and WHO hand hygiene recommendations in 2009 may have contributed to decreasing rates,[184,187] which was seen in a multi-center time series study in Germany.[190] SPIN rates for adult teaching ICUs were comparable to CNISP benchmarks, suggesting Québec CLABSI interventions paralleled that of national efforts. Recent results from one Québec

academic centre with 7 ICUs demonstrated continual decreases in its ICUs during the last 8 years of step-wise prevention.[193] Moreover, surveillance in itself has been shown to decrease rates of device-associated infections, which may in part explain decreasing rates prior to guideline changes.[194]

Unlike adult ICUs, Québec NICU and PICU rates did not show the same downward trend. In PICUs, no significant rate changes were seen using either fixed or dynamic SPIN-derived SIRs, although smaller sample size should be noted. PICU rates at outset of SPIN surveillance were comparable with NHSN rates, and lower than CNISP rates. SPIN PICU rates remained constant over time with no decrease in rates during the period, while NHSN and CNISP PICU rates decreased more than SPIN PICU rates.

When compared with SPIN 2007-2009 benchmarks, SPIN NICUs had statistically significant rate increases from 2007 to 2011, peaking at 5.96 (95%CI: 4.86, 7.25) cases/1000 CVC-days in 2011, corresponding to an SIR of 1.65 (1.35, 2.01). Subsequently, rates and SIR declined, resulting in a statistically significant SIR decreases of 48% (95%CI: 16%, 56%). Prior to 2012, NICU SPIN SIRs for most years were significantly lower using CNISP benchmarks; however, CNISP-derived SIRs became significantly higher in 2012-2013. Similarly, dynamic SPIN-derived SIRs were also significantly higher in 2010-2012.

Several reasons may explain higher NICU and PICU rates: Firstly, evidence for insertion and maintenance bundles in these populations are less robust than in adults. Several studies show children have longer central catheter dwell times, emphasizing greater importance on maintenance bundle adhenerence.[195,196] Consequently, there is greater heterogeneity in bundle element types in children compared to adults.[197,198] Successful strategies described include incorporating elements based on facility-specific challenges, involving parents in prevention

efforts, and holding regular meetings with stakeholders to discuss outcomes and directions.[199-201] The rising NICU and PICU rates during in Québec around 2012 may also be due to outbreaks leading to persisting local CLABSI endemics. For example, between 2010-2013, 46% of all CLABSI NICU cases and 52% of all PICU CLABSIs came from one facility, compared to 30% and 37%, respectively, in that facility for all other years. HAI rates also greatly differ across NICUs in Canada, and may be explained by regional strains, difference in case-mix and clinical practices.[202] Québec has four large academic centres, a distinguishing feature offering unique challenges. Following a combination of molecular and epidemiological characterization of what led to rate increase and subsequent decline in PICUs and NICUs, sharing of knowledge and strategies regularly amongst the four centres will be important for future prevention efforts.

Strengths and Limitations:

A major strength of the study is the complete population-level surveillance of SPIN ICUs, which includes a mix of different hospitals (both teaching and non-teaching) and ICU types in Québec, leading to accurate CLABSI benchmarking. This surveillance program has been validated in the past and shown to be accurate,[7] resulting in greater accuracy in intra-regional rate comparisons. That said, as always when comparing rates and generalizability between different networks, differences in surveillance methods and infection control practice should be kept in mind. Nevertheless, here, both incidence rates and SIRs illustrate that CLABSI rates are declining in Québec adult ICUs during 2007 to 2014.

Our study demonstrates that CLABSI rates in adult teaching ICUs in Québec were significantly lower compared with CNISP and NHSN rates, and that rates continued to decline throughout the surveillance period. SPIN adult nonteaching ICUs rates also decreased, at a pace more

comparable to NHSN nonteaching adult ICUs. On the contrary, SPIN NICUs and PICUs experienced an increase in rates from 2011 to 2013, unlike other American and Canadian facilities, which saw a continual decline in rates. Future efforts should be directed at delineating and understanding causes of persistently higher rates in the NICU and PICU and identify strategies to further decrease these rates.

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Figures and Tables for Manuscript 1:

Table 1: Total ICU units, CLABSI cases, CVC-days, pooled means (95% confidence interval), and CVCUR by year and ICU type.

Surveillance Year:	2007-2008	2008-2009	2009-2010	2010-201	2011-2012	2012-2013	2013-2014	2014-2015
Adult Teaching ICUs								
Number of units (number all participators)	24 (383)	24 (383)	24 (399)	23 (399)	23 (399)	23 (399)	23 (399)	23 (399)
Number of fully participating ICUs (number of ICU beds)	18 (383)							
Total cases full participators, (total cases all participators)	90	107	85 (81)	78	59 (57)	63 (62)	64 (62)	44 (43)
Total CVC-days (CVC-days full participators)	67,992 (67992)	67,402 (67,402)	69,835 (68,483)	72,491 (70,928)	71,397 (69,805)	72,250 (70,431)	71,867 (70,038)	71,698 (70,132)
IR full participators	1.32 (1.06, 1.63)	1.59 (1.30, 1.92)	1.18 (0.94, 1.47)	1.10 (0.87, 1.37)	0.82 (0.62, 1.06)	0.88 (0.67, 1.13)	0.89 (0.68, 1.13)	0.61 (0.44, 0.83)
CVCUR for full participators	0.65	0.64	0.62	0.64	0.61	0.61	0.59	0.59
Pooled IR all years	1.04 (0.96, 1.13)							
Adult Nonteaching ICUs								
Number of units (number of beds)	22 (248)	22 (250)	24 (270)	26 (286)	27 (292)	29 (308)	31 (319)	32 (332)
Number of fully participating ICUs (number of ICU beds)	21 (242)							
Total Cases (cases full participators)	30 (29)	20 (20)	40 (23)	29 (20)	32 (23)	38 (28)	24 (16)	21 (12)

Total CVC-days (CVC-days full participators)	21,272 (20,758)	21,743 (21,553)	27,051 (23,072)	30,095 (23,208)	32,426 (24,862)	34,140 (24,912)	35,549 (23,808)	34,377 (24,912)
IR for all participators	1.40 (0.94, 2.01)	0.93 (0.57, 1.43)	1.00 (0.63, 1.50)	0.86 (0.53, 1.33)	0.93 (0.59, 1.39)	1.12 (0.75, 1.62)	0.67 (0.38, 1.09)	0.48 (0.25, 0.84)
CVCUR for complete participators only	0.33	0.35	0.37	0.36	0.39	0.39	0.38	0.38
Pooled IR all years	0.91 (0.78, 1.06)							
NICUs								
Number of Units (number of beds)	7 (172)	7 (172)	7 (172)	7 (172)	7 (172)	7 (172)	8 (184)	8 (184)
Number of fully participating ICUs (number of ICU beds)	7 (172)							
Total Cases (cases for full participators)	40	35	53	74	101	80	71	40
CVC-days (total CVC-days full participators) †	11,129	11,585	12,762	14,793	16,939	15,100	17,454 (17,452)	17,898 (17,895)
IR overall (95% CI)	3.59 (2.49, 4.79)	3.02 (2.10, 4.20)	4.15 (3.11, 5.43)	5.00 (3.93, 6.28)	5.96 (4.86, 7.25)	5.30 (4.14, 6.52)	4.07 (3.18, 5.13)	2.23 (1.60, 3.04)
CVCUR †	0.15	0.15	0.17	0.19	0.22	0.19	0.23	0.24
Pooled IR all years	4.20 (3.84, 4.59)							
PICUs								
Number of units (number of beds)	5 (54)	5 (54)	5 (54)	5 (54)	5 (54)	5 (54)	5 (54)	5 (54)
CLABSI Cases	12	10	12	15	12	19	15	15
Total CVC-days	5,375	5,629	6,194	6,531	6,643	6,730	6,855	7,283

IR	2.23 (1.15, 3.89)	1.78 (0.85, 3.27)	1.94 (1.00, 3.38)	2.30 (1.29, 3.79)	1.81 (0.93, 3.20)	2.82 (1.70, 4.41)	2.19 (1.22, 3.61)	2.06(1.15, 3.40)
CVCUR	0.54	0.55	0.59	0.60	0.56	0.51	0.60	0.59
Pooled IR all years	2.15 (1.76, 2.59)							

Abbreviations: CLABSI – central-line associated bloodstream infection, CVC – central venous catheter, CVCUR - central venous catheter ratios (CVCUR)

Table 2: SIR by ICU type using baseline NHSN 2006-2008 and SPIN 2007-2009 rates as benchmarks for all SPIN surveillance years from 2007 to 2014.

Adult Teaching	**Benchmark used**		**Neonatal**	**Benchmark used**	
Year	**SPIN 2007-2009**	**NHSN 2006-2008**	**Year**	**SPIN 2007-2009**	**NHSN 2006-2008**
2007-2008	0.97 (0.78, 1.19)	0.57 (0.46, 0.70)	**2007-2008**	1.00 (0.69, 1.33)	N/A
2008-2009	1.16 (0.95, 1.40)	0.68 (0.56, 0.83)	**2008-2009**	0.84 (0.58, 1.16)	N/A
2009-2010	0.89 (0.71, 1.10)	0.52 (0.42, 0.65)	**2009-2010**	1.15 (0.86, 1.50)	N/A
2010-2011	0.79 (0.62, 0.98)	0.46 (0.37, 0.58)	**2010-2011**	1.39 (1.09, 1.74)	N/A
2011-2012	0.60 (0.46, 0.78)	0.36 (0.27, 0.58)	**2011-2012**	1.65 (1.35, 2.01)	N/A
2012-2013	0.64 (0.49, 0.81)	0.38 (0.29, 0.48)	**2012-2013**	1.47 (1.15, 1.81)	N/A
2013-2014	0.65 (0.50, 0.83)	0.38 (0.30, 0.49)	**2013-2014**	1.13 (0.88, 1.42)	N/A
2014-2015	0.45 (0.33, 0.60)	0.26 (0.19, 0.36)	**2014-2015**	0.62 (0.44, 0.84)	N/A
Adult Nonteaching	**Benchmark used**		**Pediatric**	**Benchmark used**	
Year	**SPIN 2007-2009**	**NHSN 2006-2008**	**Year**	**SPIN 2007-2009**	**NHSN 2006-2008**

2007-2008	1.10 (0.74, 1.57)	0.90 (0.61, 1.28)	**2007-2008**	1.12 (0.58, 1.96)	0.95 (0.49, 1.66)
2008-2009	0.72 (0.44, 1.11)	0.59 (0.36, 0.90)	**2008-2009**	0.90 (0.43, 1.65)	0.76 (0.36, 1.39)
2009-2010	1.16 (0.83, 1.57)	0.94 (0.67, 1.28)	**2009-2010**	0.98 (0.51, 1.71)	0.82 (0.43, 1.44)
2010-2011	0.75 (0.50, 1.08)	0.61 (0.41, 0.88)	**2010-2011**	1.16 (0.65, 1.91)	0.98 (0.55, 1.61)
2011-2012	0.77 (0.53, 1.09)	0.63 (0.43, 0.89)	**2011-2012**	0.91 (0.47, 1.59)	0.77 (0.40, 1.34)
2012-2013	0.87 (0.58, 1.15)	0.71 (0.47, 0.94)	**2012-2013**	1.43 (0.86, 2.23)	1.20 (0.72, 1.88)
2013-2014	0.53 (0.34, 0.78)	0.43 (0.28, 0.64)	**2013-2014**	1.11 (0.62, 1.82)	0.93 (0.52, 1.54)
2014-2015	0.48 (0.30, 0.73)	0.39 (0.24, 0.59)	**2014-2015**	1.04 (0.58, 1.72)	0.88 (0.49, 1.45)

Figure 1: Incidence Rate (IR) expressed as CLABSI cases / 1000 CVC-days, with 95% Poisson confidence interval bars, and central venous catheter utilization Ratios (CVCURs) by year for a) Adult nonteaching ICUs, b) Adult teaching ICUs, c) PICUs and d) NICUs.

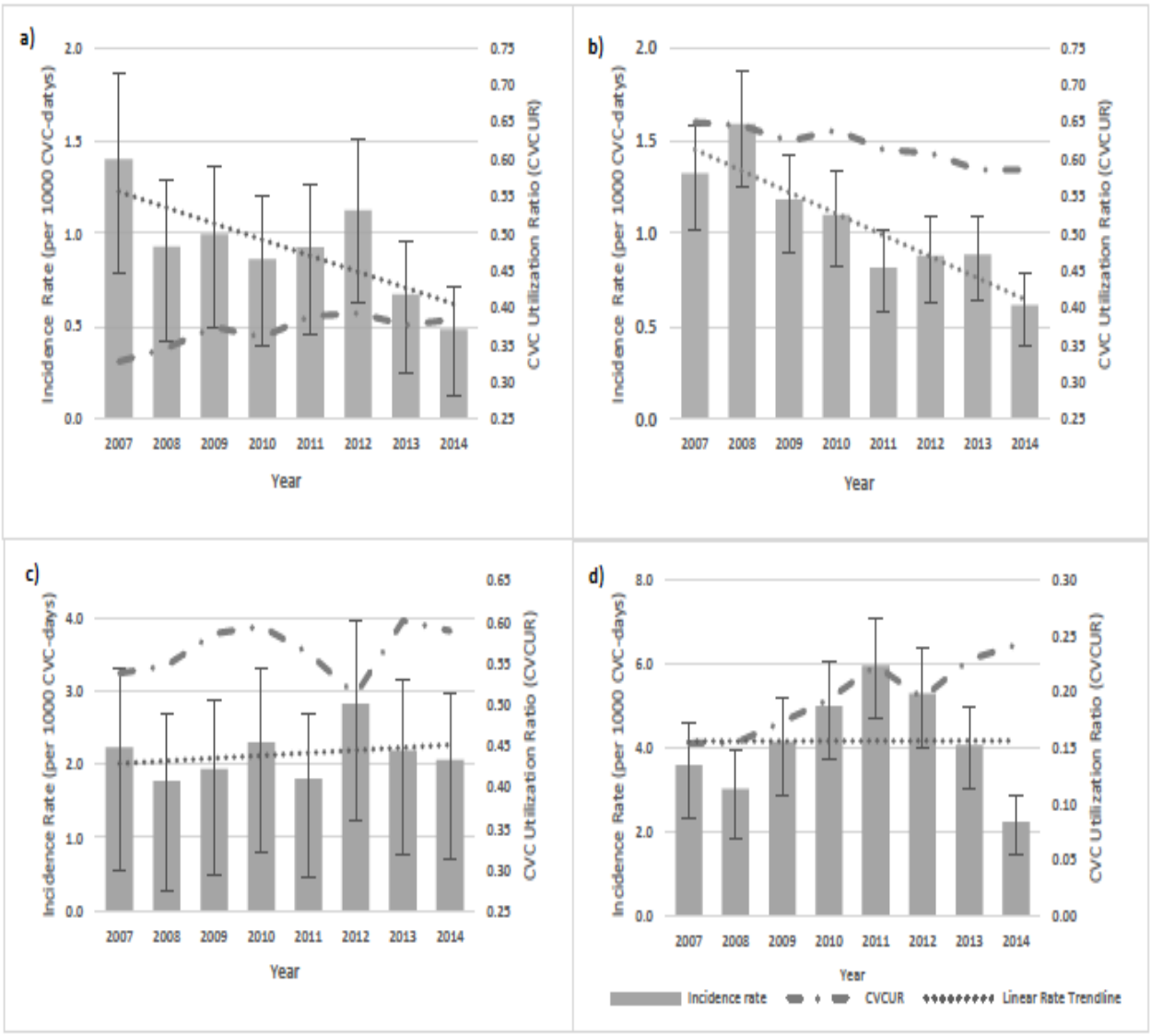

Figure 2: Incidence by each calendar period for each ICU type by year for a) Adult nonteaching ICUs, b) Adult teaching ICUs, c) PICUs and d) NICUs. Periods are calendrical, with April 1st (start of yearly reporting period) corresponding to period 4 in graphs. Shading represents 95% CI.

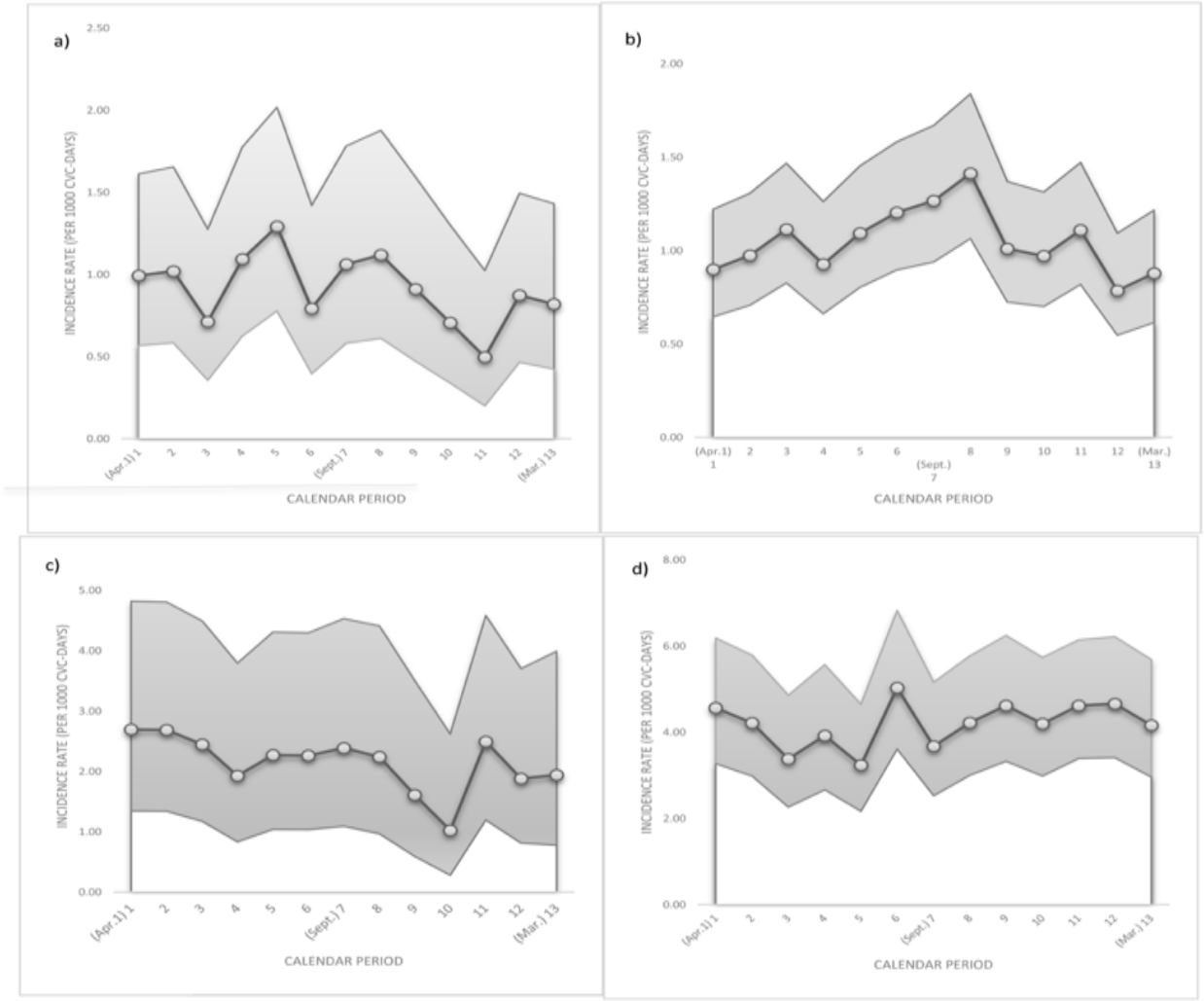

Table 3: SIR using dynamic SPIN, NHSN or CNISP benchmarks of either preceding 3 years or most recent preceding CLABSI rates, by ICU type:

ICU Type and Year	**SIR SPIN**			**ICU Type and Year**			
Benchmark	**SPIN *****	**CNISPł**	**NHSN ††**		**SPIN *****	**CNISPł**	**NHSN ††**
Adult Teaching				**Neonatal**			
2007-2008	N/A	0.74 (0.60, 0.91)	N/A	**2007-2008**	N/A	0.69 (0.48, 0.91)	N/A
2008-2009	N/A	0.89 (0.73, 1.08)	N/A	**2008-2009**	N/A	0.58 (0.40, 0.80)	N/A
2009-2010	N/A	0.68 (0.55, 0.85)	0.52 (0.42, 0.65)	**2009-2010**	N/A	0.79 (0.59, 1.04)	N/A
2010-2011	0.79 (0.62, 0.98)	0.60 (0.48, 0.75)	0.46 (0.37, 0.58)	**2010-2011**	1.39 (1.09, 1.74)	0.72 (0.54, 0.95)	N/A
2011-2012	0.64 (0.49, 0.83)	0.62 (0.47, 0.80)	0.64 (0.49, 0.82)	**2011-2012**	1.44 (1.17, 1.75)	0.62 (0.47, 0.80)	N/A
2012-2013	0.84 (0.62, 1.07)	0.93 (0.71, 1.19)	0.58 (0.45, 0.74)	**2012-2013**	1.03 (0.81, 1.27)	1.82 (1.42, 2.24)	N/A
2013-2014	0.96 (0.74, 1.22)	0.95 (0.73, 1.21)	0.67 (0.52, 0.86)	**2013-2014**	1.04 (0.81, 1.31)	1.40 (1.09, 1.76)	N/A
2014-2015	0.71 (0.52, 0.96)	0.65 (0.47, 0.88)	0.59 (0.36, 0.66)	**2014-2015**	0.44 (0.31, 0.60)	0.77 (0.55, 1.05)	N/A
Nonteaching Adult				**Pediatric**			
2007-2008	N/A	N/A	N/A	**2007-2008**	N/A	0.74 (0.60, 0.91)	N/A
2008-2009	N/A	N/A	N/A	**2008-2009**	N/A	0.89 (0.73, 1.08)	N/A
2009-2010	N/A	N/A	0.94 (0.67, 1.28)	**2009-2010**	N/A	0.68 (0.55, 0.85)	0.82 (0.43, 1.44)
2010-2011	0.75 (0.50, 1.08)	N/A	0.61 (0.41, 0.88)	**2010-2011**	1.16 (0.65, 1.91)	0.60 (0.48, 0.75)	0.98 (0.55, 1.61)
2011-2012	0.87 (0.60, 1.23)	N/A	1.15 (0.76, 1.52)	**2011-2012**	0.89 (0.46, 1.56)	0.93 (0.48, 1.62)	1.92 (1.16, 3.00)

2012-2013	0.99 (0.65, 1.30)	N/A	0.99 (0.65, 1.30)	**2012-2013**	1.40 (0.84, 2.18)	2.12 (1.28, 3.31)	1.47 (0.89, 2.30)
2013-2014	0.66 (0.42, 0.98)	N/A	0.68 (0.43, 1.00)	**2013-2014**	0.95 (0.53, 1.56)	1.65 (0.92, 2.71)	1.33 (0.75, 2.20)
2014-2015	0.66 (0.41, 1.02)	N/A	0.64 (0.40, 0.98)	**2014-2015**	0.91 (0.51, 1.50)	1.55 (0.87, 2.55)	1.43 (0.80, 2.36)

Abbreviations: SIR – standardized incidence ratio; NHSN – National Healthcare Safety Network; SPIN – Surveillance Provinciale des Infections Nosocomiale; CNISP – Canadian Nosocomial Infection Surveillance Program.

*** SPIN dynamic benchmarks for each year calculated using the incidence rates for preceding 3years of surveillance; dynamic SIRs for SPIN surveillance years 2007-2009 were thus not calculated due to being the benchmark.

ǂ Dynamic SIR calculations for SPIN years 2007-2009 used CNISP 2006 rates; SPIN years 2010 and 2011 used CNISP 2009-10 pooled rates; SPIN years 2012 to 2014 used CNISP 2011 rates. SIRs for nonteaching adult ICUs were not calculated due to majority of CNISP surveillance occuring in teaching hospitals.

††NHSN dynamic benchmarks for each year calculated using the incidence rates from preceding 3 years of surveillance for SPIN surveillance years 2009 onwards. Dyanmic SIRs for SPIN years 2007 to 2008 were not calculated due to time overlap with NHSN 2006-2008 benchmark. SPIN year 2011 used aggregated NHSN 2009-10 rates. Neonatal intensive care units (NICUs) were excluded from analysis due to differential classifications for NICUs between SPIN and NHSN.

Chapter 4: Preface to manuscript 2

Design and study rationale:

This thesis aims to determine the impact of MRSA guidelines and policy initiatives on HA-MRSA incidence trends in Québec from 2006-2015. In terms of quantifying the impact of a healthcare intervention, like physics, one requires knowing the momentum of change before and after intervention introduction. The strength of quasi-experimental study designs resides in that they allow for assessing the pre- and post-intervention trends of outcomes before quantifying the impact of an intervention. Validity can be further strengthened by the inclusion of a sufficiently long pre-intervention period and a control comparator.

For MRSA, numerous studies have established a temporal association in MRSA rate declines with improvements in infection control and prevention and active surveillance. Temporal associations of decreased MRSA incidence has been shown with increased use of alcohol hand rub, alcohol wipes, the number of patients screened for MRSA, and increased use of antibiotics with increased HA-MRSA incidence [203,204]. However, these studies purely examined rates before and after interventions. Quantifying the impact of these factors requires accounting for already existing secular trends, which may be also impacting MRSA rates. Furthermore, specificity of the intervention also requires analysis – was there a trend specific to MRSA which cannot be detected in other HAIs, suggesting an impact of MRSA guidelines? Accounting for these baseline trends and analysis of intervention specificity can both be addressed by quantifying the rate fluctuations of a control group, which would be reflective of these secular changes.

Well-documented secular trends in declines of several HAIs have been seen worldwide.[205] In the U.S. from 2008-2012, CLABSI rates decreased by 14.1%, SSI by 5.8% per year, and HA-

MRSA fell by 8.7%. In ICUs in developing countries, part of the INICC, a trend of consistently decreasing incidence has been seen in CLABSI, CAUTI and VAP.[30]

To date, quasi-experimental or time series studies examining impact of MRSA interventions on incidence with a pre-intervention period are scarce, and those with a control group are even scarcer. For MRSA BSI, segmented regression by Rodriguez-Bano et al., showed a decline in MRSA bacteremia infections after 3 successive breakpoints from 1995 to 2008 which were: 1) implementation of contact precautions, 2) targeted active surveillance of patients and workers in specific hospital wards, and 3) targeted active surveillance in patients from other centres.[206] The study had a good pre-intervention period of 1 year, but did not have a control group. Two quasi-experimental studies looked at HA-MRSA outcomes. Mestre et al. demonstrated a small but significant qualitative difference in HA-MRSA incidence after a hand hygiene audit program was implemented.[207] Again, there was a pre-intervention phase, but no control comparator. Conversely, Kaier et al. conducted 2 multivariate time-series analyses for nosocomial MRSA and *C. difficile* infection from 2003 to 2007, which showed an association between decreased nosocomial MRSA incidence and increased alcohol handrub use but no association between handrub use and rates of *C. difficile* infection.[208]

While the above results show evidence of an association of alcohol handrub use and lower MRSA incidence, no defined intervention breakpoints were used. To date, no studies have incorporated both a control group and a pre-intervention period in a quasi-experimental design in studying HA-MRSA bacteremia. In this thesis, CLABSI incidence in Québec was used as a control comparator during the study period to better isolate HA-MRSA trends, strengthening the study methodology. CLABSI served as the comparator because it is a good proxy for other HAI for several reasons. CLABSI is non-specific for any one organism and captures all potential

HAI-causing microorganisms, including a very small proportion of MRSA. Secondly, SPIN provides population-level surveillance in Québec for CLABSI, and quality of CLABSI surveillance data makes it an excellent comparator.[129] Finally, patient-specific risk factors overlap such as increasing age, ICU transfer and failure of proper antimicrobial therapy within 24 hours,[209,210] which decreases heterogeneity between the populations at-risk. By including a pre-intervention study period and secular trends, we hope to accurately assess the impact of MRSA guidelines on HA-MRSA BSI incidence.

Chapter 5: Manuscript 2 (Submitted to Infection Control and Hospital Epidemiology January 2017).

Changing rates of hospital-acquired methicillin-resistant *Staphylococcus aureus* bloodstream and central-line associated bloodstream infections in Québec from 2007 to 2015.

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WORD COUNT: 2985

Abstract: (word count: 250)

Background: We examined the impact of MRSA guidelines in Québec adult hospitals from January 1st, 2006 to March 31st, 2015 by examining the incidence rate reduction (IRR) in healthcare-associated MRSA bloodstream infections (HA-MRSA), using central-line associated bloodstream infections (CLABSI) as a comparator.

Methods: Quasi-experimental design, using Poisson segmented regression to model HA-MRSA and CLABSI incidence for successive 4-week surveillance segments, stratified by teaching status. Three distinct time intervals with 2 breakpoints were used (April 1st, 2007, and January 3rd, 2010), corresponding to major MRSA guidelines and updates.

Results: Over the study period, HA-MRSA incidence decreased significantly in adult teaching facilities, but not in non-teaching facilities. Prior to MRSA guideline publication (2006-2007), HA-MRSA incidence decline was non-significant ($p=0.89$), while CLABSI incidence declined by 4% per 4-week period, ($p=0.05$). After the publication of guidelines (2007-2009), HA-MRSA incidence decreased significantly by 1% ($p=0.04$), while there was no significant decrease in CLABSI incidence ($p=0.75$). HA-MRSA and CLABSI declines were both significant at 1% in 2010-2015 ($p<0.001$, $p=0.01$, respectively); these declines were gradual rather than sudden as breakpoints were not significant. Teaching facilities drove these decreases.

Conclusion: During the study period, HA-MRSA and CLABSI rates decreased significantly. The significant decrease in HA-MRSA rates in 2007-2009, with stable CLABSI rates, suggests an impact of MRSA-specific guidelines. In 2010-2015, significant and equal IRR for HA-MRSA and CLABSI may be due to continuing impact of MRSA guidelines, an impact of new interventions targeting device-associated infections in general of the 2010-2015 action plan, or of a combination of factors.

Background:

Healthcare-associated methicillin resistant *Staphylococcus aureus* bloodstream infections (HA-MRSA) result in significant morbidity, mortality, and healthcare costs.[42] Over the last two decades, well-documented decreases in HA-MRSA incidence occurred in the U.S.,[4,5] Germany,[7] Europe,[6] and Australia.[8] Concomitantly, decrease in central line associated bloodstream infections (CLABSI) incidence also occurred,[155,156,160,211] largely attributed to evidence-based interventions in infection prevention and control, such as hand hygiene and checklist bundles. Many of these interventions are also cornerstones in MRSA prevention. In the Canadian province of Québec, the Institut national de santé publique du Québec (INSPQ) through its healthcare-associated infections (HAI) surveillance program (Surveillance Provinciale des Infections Nosocomiales – SPIN), reporting on *S. aureus* bloodstream infections also demonstrated decreasing HA-MRSA incidence rates from 2006 to 2015.[135]

Given the rising MRSA incidence and associated costs and sense of urgency in the early 2000s, the Québec Ministry of Health and Social Services (MHSS) included in its strategic goals for the prevention of HAI, the prevention of HA-MRSA. A first Action Plan was published for 2006-2009, later updated and reaffirmed for 2010-2015, which included progress and milestones, while also reinforcing the fundamental goals in HAI prevention: 1) creating a strong and easily accessible surveillance program, 2) facilitating laboratory and disinfection processes, 3) antibiotic stewardship, and 4) use of evidence-based practices for preventing HAIs that included CLABSI and prevention of multidrug resistant organisms. [102,212] Provincial MRSA prevention guidelines were developed in 2006 and their implementation evaluated in 2009.[213] We aimed to quantify the incidence rate change in HA-MRSA following the implementation of MRSA prevention guidelines and policy directives, by comparing changes in HA-MRSA incidence with

incidence variations for another HAI: intensive care units (ICU) associated CLABSI. Although CLABSI incidence decreased during the study period,[160,214] we expect that the timing of CLABSI decline should be, for the most part, independent from that of HA-MRSA, as ICU CLABSIs are not organism-specific and only a few cases (MRSA CLABSI in ICU) are common to both surveillances. In this study, we looked at incidence rate fluctuations for the following time segments: 1) prior to the release of INSPQ MRSA guidelines: January 1st, 2006 to March 31st, 2007, 2) immediately after MRSA guideline release: April 1st, 2007 to January 2nd, 2010, and 3) post-guidelines segments: January 3rd, 2010 to March 31st, 2015, a timeframe within the updated second MHSS Action Plan for 2010-2015 (Table 1). By examining incidence fluctuation trends for HA-MRSA and CLABSI during these time intervals, we intended to investigate whether combined guideline directives and policy had impact on reducing incidence of HA-MRSA in Québec.

Methods:

SPIN Surveillance Network:

SPIN is a year-round prospective provincial-wide surveillance program, which monitors both HA-MRSA (SPIN-SARM),[215] and CLABSI (SPIN-BACC).[216] HA-MRSA reporting has been mandatory for all healthcare facilities with more than 1000 admissions since January 7th, 2007. CLABSI reporting has been mandatory for all intensive care units (ICUs) with ≥ 10 beds in the province of Québec since 2007.[214] Retrospective analysis of SPIN-BACC's reporting validity showed excellent results when compared with other regional surveillance networks, having a sensitivity and specificity of 88% and 92%, respectively.[126] Thirty-seven of 56 adult facilities (66%), including 21 non-teaching and 16 adult teaching ICUs, participated in the ICU CLABSI

surveillance program for all years, while 79 of 86 (92%) acute care hospitals, including 57 non-teaching and 22 teaching facilities, participated in the HA-MRSA surveillance during all study years.

Definitions and data collection:

CLABSI meeting SPIN definitions require that a bloodstream infection occur in patients in the ICU or within 2 days after ICU discharge, with a central venous catheter (CVC) in place and inserted prior to infection onset. Since April 1st, 2010, SPIN has used the most recent National Healthcare Safety Network (NHSN) CLABSI definition.[217] Cases from 2007 to 2010 were retrospectively reclassified to reflect the new definition. SPIN surveillance measures and definitions have been described previously and are publicly available.[125,214,218]

Starting in April 2013, MRSA bloodstream infections were classified as HA if the infection occurred ≥ 2 days after admission, or within 2 days following discharge (within 7 days for procedure-related bloodstream infections and within longer delays for surgical site infections).[218] Prior to that date, a period of 4 weeks following discharge was used to classify MRSA BSI as HA. Data were extracted in June (CLABSI) and July 2015 (HA-MRSA). The present study is a retrospective longitudinal cohort analysis, which was approved by the INSPQ and did not require institutional board review because it was a secondary analysis of previously collected data.

Statistical Analyses:

Incidence rates:

Pooled HA-MRSA and CLABSI incidence rates for adult facilities were computed by facility type (teaching vs. non-teaching), surveillance year, and 4-week period. Poisson confidence

intervals were used. Facilities were defined as "teaching" if associated with medical training and research programs, and "non-teaching" otherwise.

Segmented Poisson Regression Analysis:

To evaluate effectiveness of Québec MRSA guidelines on HA-MRSA incidence rates, we performed segmented Poisson regression to examine incidence rate change for CLABSI and HA-MRSA for three distinct time segments (Table 1). Models were built using data from facilities that participated in each surveillance program from 2006 to 2015. SPIN-SARM surveillance began in 2006 and thus, the model's first time interval coincides with the pre-MRSA guideline period (January 1st, 2006 to March 31st, 2007), with March 31st, 2007 as the first breakpoint. The next time segment, interval 2, spanned from April 1st, 2007 to January 2nd, 2010, and represents the duration immediately after INSPQ MRSA guideline publication. Although INSPQ guidelines were published in June of 2006, an 11-month window was left within the pre-guidelines interval to account for distribution, training and implementation times. Interval 2 also encompasses the MHSS "Action Plan on the prevention and control of Nosocomial Infections" for 2006-2009, as well as the evaluation of guidelines implementation.[213] The second breakpoint of January 3rd, 2010 marked the start of interval 3, which encompasses the time period post-MRSA guidelines from January 3rd, 2010 to March 31st, 2015, and corresponded to the timeframe outlined in the MHSS "Action Plan on the prevention and control of Nosocomial Infections 2010-2015".[102] Equations used in segmented regression for HA-MRSA and CLABSI incidence variations are shown in Table 1. Incidences for each successive 4-week surveillance periods were calculated from January 1st, 2006 to March 31st, 2015. Choice of time intervals was based on data availability and publication date of MRSA guidelines; corresponding calendar timing of each

interval and period are also shown in Table 1. Due to well-established secular trends of decreasing rates of HAIs,[156-160,188,189,214] we wanted a control comparator that would not be impacted by the change in MRSA guidelines: CLABSI rates.

The coefficients of segmented regression include: $ß_o$, the baseline rate at the start of surveillance; $ß_1$, $ß_2$ and $ß_3$ – the coefficients for incidence change by 4-week periods during the respective time intervals as indicated in Table 1. The change in baseline incidence from interval 1 to interval 2, as denoted by int2 with the coefficient $ß_4$; similarly, the change in baseline incidence from intervals 2 to 3, is denoted by int3 and the coefficient $ß_5$. All coefficients presented have been adjusted for autocorrelation for counts by incorporating an error term for short-term (4 months) effects of guidelines on incidence change, as specified by Schwartz J. et al., and Katsouyanni K., et al.[219,220] The duration of 4 months was empirically estimated by examining residual function plots. The outcomes of interest from segmented regression models were the incidence rate ratio (IRR), defined as the ratio of rates for any one time segment compared to the previous one. IRR was modeled for 1) the ratio of any one 4-week period compared to the previous period, and, 2) the ratio of baseline rates from one interval to the next. The covariate of interest was time, as measured by periods (4-week surveillance intervals). Models were run for all facilities, and also separately for teaching and non-teaching facilities. Subgroup analyses were also performed between full and partial participators in surveillance. All statistical calculations were performed using Stata version 14 (StataCorp 2015; College Station, Texas).

Results:

Incidence rates of HA-MRSA and CLABSI:

Table 2 summarizes the annual incidence rates of HA-MRSA and CLABSI. Adult teaching facilities had higher incidence compared to non-teaching facilities. HA-MRSA incidence dropped in teaching facilities from 9.56 in 2006 (95% CI: 8.34, 10.9) to 1.86 cases /100,000 patient-days in 2015 (95%CI: 0.85, 3.53). For non-teaching facilities, incidence remained stable during the study period: 3.42 (95% CI: 2.70, 4.37) in 2006, and 2.79 cases /100,000 patient-days (95%CI: 1.56, 4.60) in 2015 (Table 2). CLABSI incidence was also higher in teaching facilities compared to non-teaching facilities. Incidence rates decreased in both facility types: adult teaching CLABSI incidence dropped from 2.24 (95% CI: 1.86, 2.67) to 0.68 cases/1,000 CVC-days (95% CI: 0.35, 1.20) while adult non-teaching incidence dropped from 1.71 (95% CI: 1.19, 2.38) to 0.46 cases /1,000 CVC-days (95% CI: 0.13, 1.19). There was no significant change in incidence for CLABSI incidence between the subgroups of full and partial participators. For HA-MRSA, significant differences were seen in 2007 and 2011 for non-teaching, and 2007 for teaching facilities. The addition of new facilities to the small number of partial participators (8% of total facilities) may account for these differences. The results shown in Table 2 include both partial and full participators. Figure 1 graphically shows the incidence of HA-MRSA and of CLABSI by 4-week periods with breakpoints, for teaching and non-teaching facilities.

Segmented regression for HA-MRSA and CLABSI:

Table 3 details coefficients and IRRs for all facilities for each interval, separated by the two breakpoints (April 1st, 2007 and January 3rd, 2010). In terms of quantification of the incidence trends, when looking at all adult facilities, IRR per 4-week period for HA-MRSA was not different from 1 during interval 1, but was significant at 0.991 during interval 2 (95%CI: 0.982, 1.00), and interval 3 at 0.990 (95%CI: 0.986, 0.995), corresponding to decreases of 0.9% and

1.0% per 4-week period, respectively. Cumulatively, this amounted to an estimated 25% and 22% relative rate reduction during intervals 2 and 3, respectively. By facility type, the significant reductions were seen only in teaching facilities, which had IRR of 0.989 for interval 2 (95%CI: 0.979, 0.998) and interval 3 at 0.987 (95%CI: 0.982, 0.992), corresponding to incidence decreases of 1.1% and 1.3% per 4-week period or, cumulatively, of 30% and 49%. Teaching facilities also had a significant decrease in baseline incidence between intervals 1 and 2, with an IRR of 0.706 (95%CI: 0.522, 0.955), a decrease of 29.4%. Non-teaching facilities did not have significant incidence rate reductions for any time interval.

The IRR for CLABSI, including all facilities, showed a significant decreasing incidence rate, pre-guidelines at 0.957 (95% CI: 0.917, 1.00), corresponding to a 4% decrease per 4-week period. However, when analyzed by teaching vs. non-teaching status, CLABSI IRR pre-guidelines became non-significant (Table 3). CLABSI IRR did not show any decrease in rates immediately post-MRSA guideline publication (IRR 1.00, 95%CI: 0.990, 1.01), but became significant again during interval 3 (IRR 0.993, 95%CI: 0.987, 0.998), which corresponded to a decrease of 1% per 4-week period. When stratifying by facility type, teaching facilities had a significant 1% incidence rate reduction per 4-week period from 2010 to 2015; non-teaching facilities had no significant reduction for any interval. Figure 1 illustrates CLABSI and MRSA rates during each time interval.

Discussion:

Our study's overarching findings revealed that in Québec, HA-MRSA incidence significantly decreased after MRSA guidelines implementation, while CLABSI rates remained stable. Later, rates for both infections followed similar decreasing trends over time, with teaching facilities

driving these decreases. To examine pre-guidelines incidence fluctuations, we analyzed incidence changes for thirteen 4-week periods from 2006 to 2007 for HA-MRSA and CLABSI. Our analysis showed non-significant rate fluctuations in HA-MRSA incidence, but significant declines in CLABSI incidence at 4% per 4-week period when including all facilities. Because of small sample size, CLABSI IRR became non-significant once stratified by facility type. During that time period, as provincial guidelines were not yet released, we did not expect any significant decreases in HA-MRSA incidence.

The first breakpoint of January 1st, 2007 represents the immediate period after the publication of INSPQ MRSA guidelines, which shows a statistically significant sudden decrease in teaching facilities' HA-MRSA incidence rates, followed by a decrease of 1% per 4-week period from 2007 to 2009. In comparison, CLABSI incidence rates did not change significantly. This strongly suggests that the MRSA guidelines had a direct impact on lowering HA-MRSA incidence. A survey of preventive measures' implantation showed that in 2004, only 53% of Québec hospitals had implemented MRSA screening upon hospital admission and during hospitalization, while in 2009, 94% of facilities had implemented these protocols.[213] Undoubtedly, MRSA screening was and continues to be an important measure in infection prevention and control.

Interval 3, spanning from 2010 to 2015, marked a post-guidelines period when many of the evidence-based MRSA prevention measures continued to be implemented. During this time, concurrent significant incidence reductions in both CLABSI and HA-MRSA occurred at 1% per 4-week period, corresponding to an overall decrease of 51% for both infections, with both infections incidence rates declining at the same rate. Interestingly, the resumption of significant decrease in CLABSI rates during interval 3 may suggest an increased effort to target device-related HAIs such as CLABSI. For instance, new NHSN guidelines on CLABSI practices were

published in 2010 [151] and guidelines for catheter-associated urinary tract infections, in 2009.[221] These newer recommendations may have prompted CLABSI incidence trend declines. A new web portal for surveillance data entry (April 1st, 2013) and related training sessions might have improved the quality of data, decreasing the number of skin contaminants reported as CLABSIs. For HA-MRSA, the continuing and steady significant incidence reductions from interval 2 likely stemmed from ongoing infection prevention and control efforts introduced during interval 2. As mentioned earlier, the MHSS published the "Action Plan on the Prevention and Control of Nosocomial Infections" for 2006-2009, which included specific steps towards prevention and control of HAI; the plan was later updated for the 2010-2015 period. Meanwhile, during this interval, both HAI and MRSA-specific prevention measures continued. Internationally, 2009 marked the year of the World Health Organization Hand Hygiene Campaign launch.[187] and the Association of Professionals in Infection Control (APIC) guidelines on elimination of MRSA in hospital settings published in 2010.[222] These continued and new initiatives could have contributed to a decrease in all HAIs, including HA-MRSA and CLABSI. However, the 2nd breakpoint of January 3rd, 2010 was not significant for HA-MRSA incidence declines: the rate of decline was the same in intervals 2 and 3. This may suggest either that effectiveness of the MRSA guidelines diminished over time and were replaced by an effect from new transversal HAI interventions, that guidelines continued to have an effect over time, as the rate of decrease remained constant between intervals 2 and 3, or that a combination of both occurred. However, given that this study was ecological in nature, it is impossible to infer causality between interventions and decline in rates. Assuming independence between HA-MRSA rates and CLABSI rates, the abrupt decline in HA-MRSA rates and not in CLABSI rates after the first

breakpoint may allude to a temporal association with compliance to provincial MRSA guidelines.

Another interesting finding was that the incidence declines in HA-MRSA and CLABSI were seen only in teaching facilities. These results suggest that a swifter response and implementation of MRSA guideline recommendations may have occurred in these facilities. Non-teaching facilities did not demonstrate the same significant decreases. One reason may be that teaching facilities have greater lengths of stay and perform more invasive procedures than non-teaching hospitals, [223,224] thereby having higher infection rates and thus a greater potential for improvement. While all facilities surveyed have acute care, non-teaching facilities may have lower acuity and a lower risk case-mix compared to teaching facilities. Consequently, the incidence of any HAI may be lower in non-teaching facilities.

Limitations:

Limitations of the study include its ecologic design, potential selection bias from the ongoing enrolment of facilities into the surveillance programs, and instruction and detection bias for facilities at the start of surveillance participation. While transversal interventions such as hand hygiene promotion might explain observed time trends for both HA-MRSA and CLABSIs, the effect of MRSA-specific guidelines should be mostly observed in HA-MRSA as the only cases common to both surveillances are MRSA CLABSIs occurring in the ICU. This study's ecological design also limits our ability to infer causality between guidelines implementation and incidence rates, as previously explained. Nevertheless, using the quasi-experimental study design with a comparator group, we showed an immediate significant incidence decline after breakpoint 1, with MRSA guidelines introduction, and prolonged incidence declines afterwards. This

suggests that these recommendations were associated with the lowering of HA-MRSA incidence. It should be noted that MRSA surveillance became mandatory for all acute care facilities in January 2007, and that CLABSI surveillance became mandatory for ICUs with 10 beds or more in April of the same year. SPIN monitors both HA-MRSA and CLABSI, and having a centralized surveillance system may minimize systematic errors due to data entry. Finally, although there was a change in definition in HA-MRSA bloodstream infection, whereby to be considered HA, the MRSA bloodstream infection had to occur within 2 days rather than 4 weeks after discharge, this occurred in April 2013 during a time interval (interval 3) for which the breakpoint was not significant.

In summary, this study has shown that province-wide efforts in Québec following the release of MRSA guidelines, has resulted in a significant and abrupt decrease in HA-MRSA incidence rates with no temporal change in CLABSI rates. The sustained significant reduction in HA-MRSA incidence in the post-guidelines period suggests a continued impact of the MRSA-specific guidelines years after its publication, along with improved control of both MRSA and other HAIs. The results demonstrated are encouraging, and future analysis to follow the continuing trend of incidence decline for CLABSI and HA-MRSA would be helpful to determine if continuing and new interventions, have been helpful to sustain this incidence decline.

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Figures and Tables for Manuscript 2:

Table 1: Description of Poisson segmented regression models variables, time intervals, and breakpoints with corresponding guidelines publication dates:

The full equation is denoted by the following (the successive 4-week periods are in subscripts): $$Y(t) = ß_o + ß_1(t_{1\text{-}16}) + ß_2(t_{17\text{-}52}) + ß_3(t_{53\text{-}120}) + ß_4(t_{int1}) + ß_5(t_{int2})$$		
Time Intervals	**Temporal Association**	**Major guideline/ policy correspondence**
Interval 1	Time between January 1st, 2006 to March 31st, 2007 Periods 1 to 16	Pre-MRSA guidelines and MHSS Action Plan 2006-2009 in effect
Interval 2	Time between April 1st, 2007 to January 2nd, 2010 Periods 17 - 52	MRSA Guidelines published and MHSS Action Plan 2006-2009 in effect
Interval 3	Time between January 3rd, 2010 to March 31st, 2015 Periods 53 - 120	MRSA Guidelines Update Published and MHSS Action Plan 2010-2015 in effect

Variables:	
$ß_o$	Baseline rate at outset of interval 1.
$ß_1$	Rate change per period during interval 1.
$ß_2$	Projected rate per period increase for interval 2.
$ß_3$	Projected rate per period increase for interval 3.
$ß_4$	Change in baseline incidence from interval 1 to 2.
$ß_5$	Change in baseline incidence from interval 2 to 3.

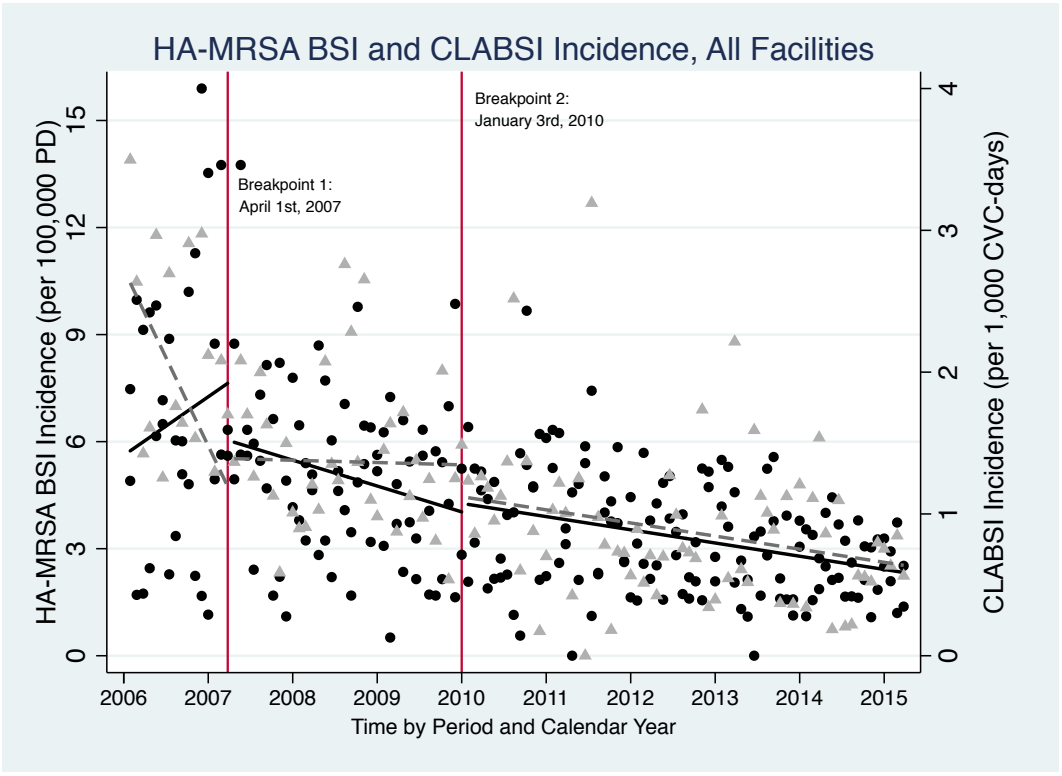
Table 2: Number of facilities (full and partial participator), and incidence of HA-MRSA and CLABSI by year and facility type, with 95% CI.

All Facilities:	**Facilities in SPIN-SARM**	**Facilities in SPIN-BACC**	**HA-MRSA Incidence (cases/100,000 PD; 95%CI)**	**CLABSI Incidence (cases/1,000 CVC-days; 95%CI)**
2006-2015*	86	56	4.24 (4.04, 4.44)	1.13 (1.06, 1.20)
Teaching				
2006	22	16	9.56 (8.34, 10.9)	2.24 (1.86, 2.67)
2007	24	18	8.11 (6.99, 9.36)	1.49 (1.21, 1.81)
2008	24	18	6.30 (5.32, 7.40)	1.51 (1.30. 1.83)
2009	24	20	5.73 (4.81, 6.78)	1.27 (1.01, 1.56)
2010	24	20	5.01 (4.16, 5.99)	1.09 (0.86, 1.36)
2011	24	20	4.76 (3.92, 5.71)	0.92 (0.71, 1.18)
2012	24	20	3.73 (3.01, 4.57)	0.77 (0.59, 1.00)
2013	24	20	3.33 (2.63, 4.16)	0.93 (0.72, 1.19)
2014	24	20	2.91 (2.24, 3.72)	0.68 (0.50, 0.90)
2015	24	20	1.86 (0.85, 3.53)	0.68 (0.35, 1.20)
All years**	22	16	5.44 (5.14, 5.76)	1.16 (1.08, 1.25)
Non-teaching				
2006	58	22	3.42 (2.70, 4.37)	1.71 (1.19, 2.38)
2007	58	22	4.26 (3.46, 5.20)	1.32 (0.88, 1.91)
2008	60	22	3.88 (3.13, 4.76)	1.04 (0.65, 1.58)
2009	61	24	2.94 (2.30, 3.71)	1.57 (1.13, 2.13)
2010	61	26	3.04 (2.38, 3.82)	0.87 (0.57, 1.29)
2011	62	27	3.06 (2.40, 3.84)	1.12 (0.78, 1.55)

2012	62	29	2.71 (2.11, 3.43)	1.05 (0.74, 1.45)
2013	62	31	2.58 (1.98, 3.30)	0.74 (0.48, 1.09)
2014	62	33	2.34 (1.77, 3.03)	0.66 (0.42, 1.00)
2015	62	33	2.79 (1.56, 4.60)	0.46 (0.13, 1.19)
All years**	57	21	3.06 (2.84, 3.30)	1.05 (0.93, 1.18)

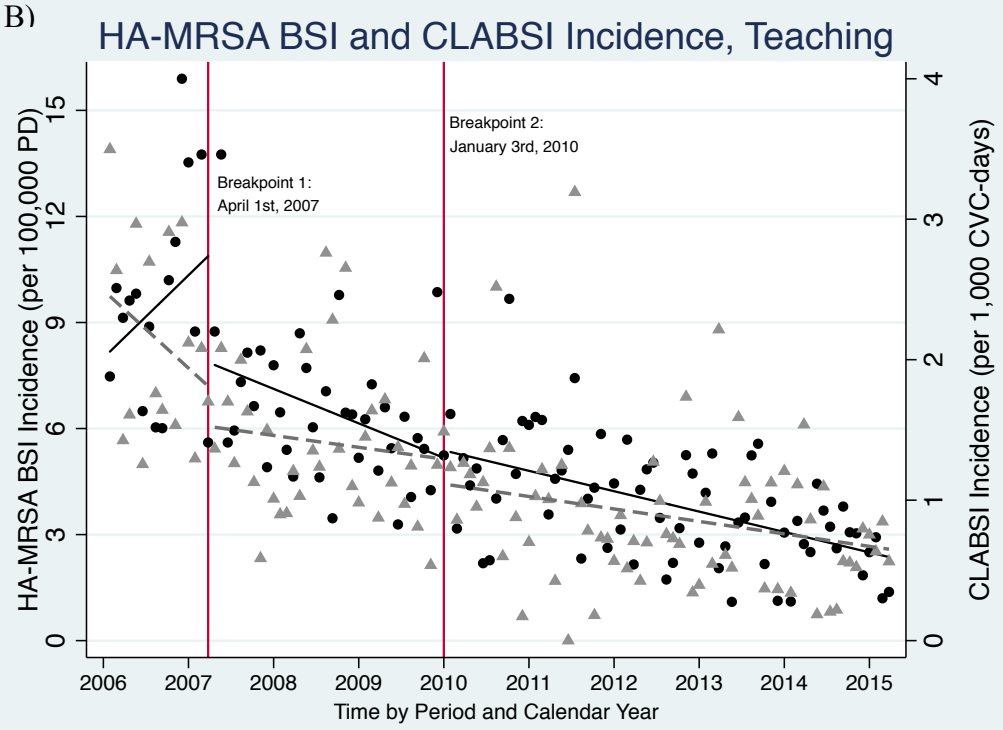
*Participation at any time throughout the study period.
**Continuous participation throughout the study period.

Figure 1: HA-MRSA (circle) and CLABSI (triangle) incidence trends from January 1st, 2006 to March 31st, 2015 for a) all facilities, b) teaching facilities and c) nonteaching facilities. Red vertical line denotes break point of April 1st, 2007 and January 3rd, 2010.



A)

B)


HA-MRSA BSI and CLABSI Incidence, Teaching
Breakpoint 1:
April 1st, 2007
Breakpoint 2:
January 3rd, 2010
HA-MRSA BSI Incidence (per 100,000 PD)
CLABSI Incidence (per 1,000 CVC-days)
0
3
6
9
12
15
0
1
2
3
4
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Time by Period and Calendar Year

C)

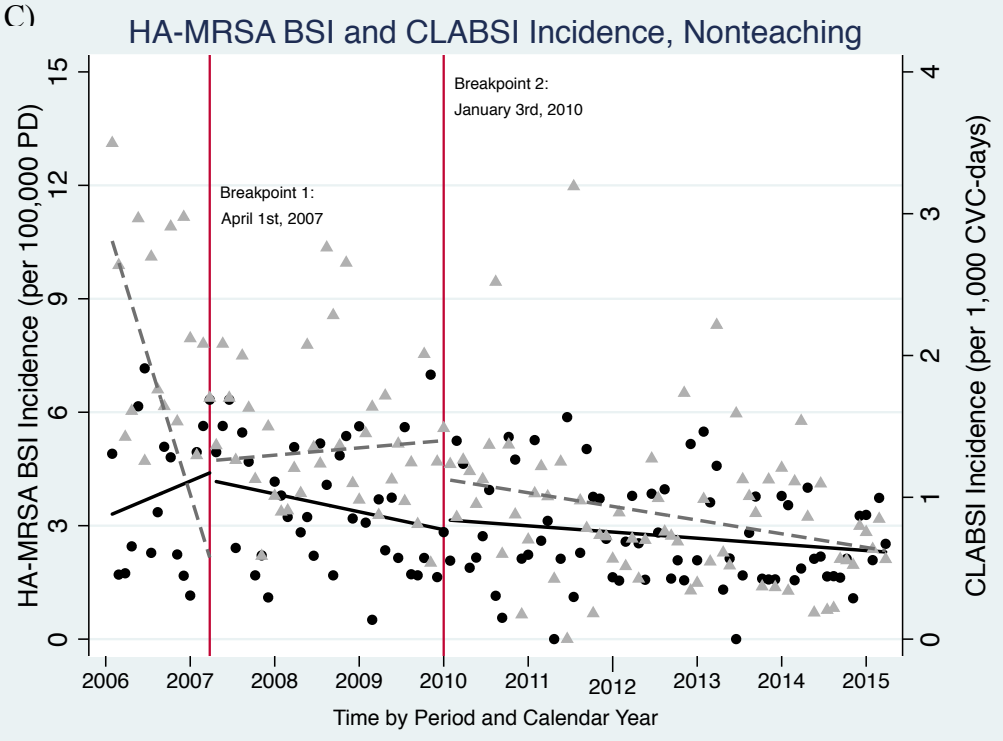

HA-MRSA BSI and CLABSI Incidence, Nonteaching
Breakpoint 1:
April 1st, 2007
Breakpoint 2:
January 3rd, 2010
HA-MRSA BSI Incidence (per 100,000 PD)
CLABSI Incidence (per 1,000 CVC-days)
0
3
6
9
12
15
0
1
2
3
4
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Time by Period and Calendar Year

Table 3: Incidence rate ratio (IRR) for HA-MRSA and CLABSI incidence for A) all facilities, B) teaching facilities, and C) non-teaching facilities. Interval 1 spans from January 1st, 2006 to March 31st, 2007 (periods 1-16). Interval 2 spans from April 1st 2007 to January 2nd, 2009 (periods 17-52). Interval 3 is from January 3rd 2010, to March 31st, 2015 (periods 53-120). Int 2 represents the change in baseline rate going from interval 1 to 2, and Int 3 represents change in baseline rate going from interval 2 to 3.

3A:

All facilities	***HA-MRSA***		***CLABSI***	
	IRR	**p**	**IRR**	**p**
$\beta_o^{\ddagger}$ *(Intercept)*	-	<0.001	-	<0.001
Interval 1 (β_1, pre-guidelines)	1.00 (0.972, 1.033)	0.89	0.957 (0.917, 1.00)	0.05
Interval 2 (β_2, post-guidelines)	0.991 (0.982, 1.00)	0.04	1.00 (0.990, 1.014)	0.75
Interval 3 (β_3, post-guidelines update)	0.990 (0.986, 0.995)	<0.001	0.993 (0.987, 0.998)	0.01
Int 2 (β_4, level change post-guidelines)	0.841 (0.628, 1.128)	0.25	0.965 (0.620, 1.503)	0.88
Int 3 (β_5, level change post guidelines update)	0.910 (0.595, 1.393)	0.66	0.861 (0.469, 1.582)	0.63

3B

Teaching facilities	***HA-MRSA***		***CLABSI***	
	IRR	**p**	**IRR**	**p**
$\beta_o^{\ddagger}$ *(Intercept)*	-	<0.001	-	<0.001
Interval 1 (β_1, pre-guidelines)	1.022 (0.995, 1.050)	0.11	1.004 (0.964, 1.047)	0.84
Interval 2 (β_2, post-guidelines)	0.989 (0.979, 0.998)	0.02	0.996 (0.983, 1.009)	0.55
Interval 3 (β_3, post-guidelines update)	0.987 (0.982, 0.992)	<0.001	0.992 (0.986, 0.998)	0.01
Int 2 (β_4, level change post-guidelines)	0.706 (0.522, 0.955)	0.02	0.827 (0.532, 1.286)	0.40
Int 3 (β_5, level change post guidelines update)	0.804 (0.512, 1.263)	0.34	0.768 (0.410, 1.439)	0.41

3C

Non-teaching facilities	***HA-MRSA***		***CLABSI***	
	IRR	**p**	**IRR**	**p**
$\beta_o^{\ddagger}$ *(Intercept)*	-	<0.001	-	0.27
Interval 1 (β_1, pre-guidelines)	0.980 (0.909, 1.056)	0.60	0.997 (0.877, 1.134)	0.97
Interval 2 (β_2, post-guidelines)	0.990 (0.976, 1.005)	0.20	1.013 (0.990, 1.037)	0.26
Interval 3 (β_3, post-guidelines update)	0.995 (0.989, 1.001)	0.11	0.994 (0.985, 1.003)	0.21
Int 2 (β_4, level change post-guidelines)	1.196 (0.678, 2.110)	0.53	0.905 (0.308, 2.661)	0.86
Int 3 (β_5, level change post guidelines update)	1.350 (0.630, 2.893)	0.44	0.835 (0.225, 3.099)	0.79

Table 4: Summary of MRSA Guidelines and Publication by Year and Organization:

Organization	**Year published**	**MRSA Guidelines**
Institut national de santé publique du Québec (INSPQ)	2006	Publication 2nd ed. Of INSPQ MRSA prevention measures [225]
Ministry of Health and Social Services, Government of Québec	2006	Action Plan on the Prevention and Control of Nosocomial Infection (2006-2009)[102]
Center of Disease Control and Prevention (CDC)	2006	CDC Contact Precautions [226]
Center of Disease Control and Prevention (CDC)	2007	CDC Standard Precautions [227]
The Society for Healthcare Epidemiology of America/ Infectious Diseases Society of America (SHEA / IDSA)	2008	Strategies to prevent transmission of methicillin-resistant *Staphylococcus aureus* in acute care hospitals [116]
Institut national de santé publique du Québec (INSPQ)	2009	Study on prevention and control measures (MRSA) applied in hospitals acute care Québec [213]
World Health Organization (WHO)	2009	Hand Hygiene Campaign [187]
Ministry of Health and Social Services, Government of Québec	2011	Prevention and Control of Nosocomial Infections- Action Plan 2010-2015; Progress of Work - Summary and Highlights [212]

Chapter 6: Discussion of results:

6.1 Summary of findings and implications of research:

The overarching result of this thesis strongly suggests a significant impact corresponding to INSPQ MRSA guidelines introduction on HA-MRSA BSI incidence rate fluctuations. The temporal correlation of significant reduction in HA-MRSA BSI, but not CLABSI incidence, convincingly supports the finding that HA-MRSA BSI rates were decreasing faster compared with other HAIs at the time. More specifically, declines were driven by teaching hospitals. One reason may be that smaller, nonteaching hospitals generally see less HA-MRSA BSI.[228] Among SPIN facilities, nonteaching HA-MRSA BSI cases accounted for 36% of all cases, whereas teaching facilities accounted for 64% of cases. As a result, MRSA-specific prevention methods may not have as big of an impact in lower incidence hospitals. However, smaller nonteaching hospitals may still be a problem for HA-MRSA infection. A Californian study with 30 hospitals found that CA-MRSA strains were more predominant in smaller hospitals, representing 46% (1,033) of a total of 2,246 MRSA isolates identified over 18 months, and affected healthier but a more socially disadvantaged population.[229] Consequently, smaller hospitals may see more cases of new CA-MRSA infection, which stresses importance of good hand hygiene to prevent transmissions of infection or colonization, especially during the emergency department stay and hospital admission when screening results are not yet available and contacts with multiple healthcare workers tend to happen.

Transmission of MRSA via hands of healthcare workers is well established, and current infection control efforts emphasize stopping person-to-person transmission, as well as horizontal transfer of MRSA from inanimate surfaces by environmental cleaning. Promising results were

shown in the 2009 INSPQ study surveying Québec facilities on MRSA guidelines implementation, which found a substantial increase in ongoing inpatient MRSA screening, jumping from 53% to 94% between 2004 and 2009. However, hand hygiene auditing practices were only done in 44% of surveyed centres. In terms of hand hygiene compliance by profession, one prospective study found nurses to have the highest adherence rates at 64%, followed by physicians at 22%, and other healthcare workers at 13%.[230] Similar compliance was seen in a Québec study with a 31% increase in global hand hygiene compliance. Despite suboptimal compliance however, there was 51% reduction in MRSA incidence.[231]

Increasing hand hygiene compliance among healthcare workers certainly can be improved; however, encouraging hand hygiene practices for hospital visitors may be the next critical prevention method in limiting spread of MDROs like MRSA. Transmission dynamics studies support and emphasize a broader prevention strategy, especially for hand hygiene among hospital visitors. Macal et al. showed that newly MRSA-colonized individuals tend to acquire it from existing colonized individuals and not from those with active MRSA infections. The majority of MRSA transmission occurred within households, and only 7.8% of new MRSA colonizations occurred in hospitals.[232] There may be a large population of at-risk MRSA colonizers in the community for whom current infection control and prevention measures may be lacking. In addition to increasing hand hygiene compliance for hospital visitors, future areas of infection control may require targeting high transmission areas within communities like schools, community centers, daycares and households in order to limit new and re-colonizations.[233]

This thesis has showcased the decreasing CLABSI rate since 2006. However, the declines were only seen in adult ICUs, and not in NICU or PICUs. Reasons for the lack of decrease in CLABSI rates in NICUs and PICUs may be due to outbreaks, longer duration of central line

placement and different host risk factors.[197] Fagan et al. similarly found lack of decrease in PICU CLABI burden when compared to adult ICUs over a 20-year period from 1990 to 2010. Furthermore, no PICU has had near elimination of CLABSI as adult ICUs had after implementation of insertion bundles.[195] Because of longer central line placement times, the importance of maintenance bundles in NICU and PICUs may reduce CLABSI more effectively.[234,235] As maintenance bundles become more widely used, it would be interesting and important to follow how NICU and PICU CLABSI rates may be affected.

As CLABSI practices improve, the etiology of CLABSI may be shifting. From 1990 to 2010, the incidence density of CLABSI caused by gram-negative organisms, *Enterococcus*, and *Candida* species has increased, while that of *S. aureus* declined since 2002.[236,237] Future CLABSI prevention measures may require accounting for this etiological change such as answering what factors are favoring this shift. Clinical prescribing practices would also need to be adjusted for appropriate antimicrobial coverage when CLABSI is suspected. Finally, it would be interesting to see how new infrastructure changes in Québec healthcare facilities may affect HAI rates. Newer facilities may relieve crowding but also face other challenges. With having NICU, PICU and adult ICUs within the same facility such as the new McGill University Health Centre's Glen Hospital, new challenges include infection control and prevention among healthcare workers and visitors who move between these wards. NICUs and adult ICUs also differ in flora causing infection with NICUs having a higher prevalence of *Enterobacteriacae* than adult ICUs and lower prevalence of typical adult ICU HAI organisms such as *Klebsiella pneumoniae, Acinetobacter baumannii* and vancomycin-resistant Enterococci.[238,239] Going forward, it will be interesting to see whether CLABSI microbiology becomes more homogenous.

The broader MSSS-directed Action Plans for infection prevention and control directives leading to development of HAI-specific guidelines is an effective strategy for future HAI prevention, as shown by the impact of INSPQ MRSA guidelines on lowering HA-MRSA BSI. These results are encouraging because with the increasing detection and spread of other MDROs like extended-spectrum beta-lactamases (ESBL) and carbapenem-resistant organisms (CRO), the screening, detection and isolation practices from MRSA prevention and control could also be adapted for use.

6.2 Methodological strengths and limitations:

The SPIN program in Québec has several advantages including population-level surveillance in ICUs for CLABSI, and acute care facilities for MRSA BSI. This provides a centralized platform for surveillance data entry and analysis, which reduces administrative data entry error. Because SPIN comprises a mixture of large, medium and smaller facilities, case-mix representation also varies. As a result, when comparing SPIN rates to those of other jurisdictions, it is important to account for different surveillance program methodologies when possible and, at minimum, be mindful of any varying methods or populations.

For CLABSI, comparing inter-jurisdictional benchmarks was a challenge precisely because surveillance methods and case-mix differ between regions. The widespread comparisons of state, regional and hospital SIRs to one another on consumer reports websites also added to the confusion – it was unclear initially if these websites were presenting SIRs adjusted for case mix; however, it was soon discovered that this was not the case. The SIRs were derived using one common benchmark as the denominator (NHSN 2006 to 2008 pooled CLABSI rates). Furthermore, not all participation between states was equal. Some states mandate NHSN

participation while others leave it to the discretion of individual hospitals or health networks. In manuscript 1, similar difficulties arose when comparing SPIN and CNISP CLABSI rates. CNISP facilities comprise of mainly tertiary centres across Canada – the majority of which are teaching facilities and represent 10% of Canadian hospitals. Therefore, by hospital type, case-mix in CNISP CLABSI measures most similarly resembles SPIN teaching facilities, which would be important to note when comparing rates or SIRs.

From this work, the lessons learned are that SIR is a useful measurement for comparing two rates, however, problems of confounding arise when two or more SIRs are compared with one another. Comparing two or more SIRs involve at least 3 different rates. If both numerator population rates were collected from very dissimilar health populations, one cannot infer that one population has "better" rates, as risk profile may be vastly different. In Consumer Report websites, this practice is common. Furthermore, confidence intervals are often not provided and margin of error is unknown to readers. Unfortunately, the attempt to inform consumers may actually be misinforming them. In the NHSN, CLABSI rates are stratified and benchmarked by ICU type– which at least serves as broad indicator of case-mix and population. Worldwide outside the U.S., CLABSI SIRs are not often used, probably in part because of the aforementioned limitations.

Strengths of the quasi-experimental study design have been outlined in the methods chapter; namely, it is the study design of choice for examining pre- and post- intervention outcomes when randomization is not an option. In this thesis, incorporation of a pre-intervention period and a control group were used to further enhance validity of the study design. Two limitations, which arose in the analysis, were the inability to specifically time the intervention and the inability to account for MRSA interventions affecting CLABSI rate fluctuations.

Guidelines were not uniformly implemented at the same time across Québec. For example, from 2004 to 2009, hospital admission screening programs for MRSA increased from 53% to 94%, with ongoing rollout during this interval.[135] Secondly, prevention methods in the MRSA guidelines may have affected CLABSI incidence fluctuations. Some of these transversal methods include hand hygiene, surveillance, and environmental cleaning. Several CLABSI prevention guidelines were published after breakpoint 2 from 2010 to 2011, and hand hygiene inevitably was a crucial element in these guidelines. Consequently, confounding was possible after breakpoints 1 (April 1st, 2007) as MRSA guidelines may have also impacted CLABSI rates to decline; however, eliminating this bias would have led to an even greater impact effect size and consequently, does not invalidate the obtained results. Distinguishing if MRSA guidelines impacted CLABSI rates would have required a second control group.

Despite strengths of quasi-experimental study design and the SPIN program, the study's ecologic design limits causal inference. Conclusions can only be made that HA-MRSA BSI incidence trends significantly declined after breakpoint 1, which corresponded to the release of guidelines. Although unmeasured interventions or factors at the time contributing to falling rates cannot be ruled out, this was less likely given the use of a control group where this change in incidence was not observed, suggesting an effect possibly specific to MRSA. Finally, HAI rates at individual facilities and on specific wards may vary widely and caution must be heeded towards the ecologic fallacy as time variations in HA-MRSA and CLABSI rates cannot be extrapolated to individual facilities in the study.

6.3 Conclusion:

This research demonstrates that rates for CLABSI and HA-MRSA BSI adult teaching facilities in Québec significantly fell from 2006 to 2015. On the contrary, SPIN NICUs and PICUs experienced an increase in rates from 2011 to 2013, unlike American and Canadian facilities, which saw a continual decline in rates. Future efforts should be directed at delineating and understanding causes of persistently higher rates in the NICU and PICU and identifying strategies to further decrease these rates. The impact of INSPQ MRSA guidelines immediately after publication later led to continuous reduction in HA-MRSA incidence in the post-guidelines period. The results are encouraging, and future analysis to follow the continuing trend of incidence decline for CLABSI and HA-MRSA BSI would be helpful to determine if continuing and new interventions, especially from 2010-2015, have been helpful to sustain this incidence decline.

Chapter 7: References

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