EMBEDDED RESEARCHER-LED LEARNING HEALTH CENTRE DEVELOPMENT

BLUEPRINT FOR AN EMBEDDED RESEARCHER-LED TRANSFORMATION OF A LARGE COMMUNITY HOSPITAL INTO A LEARNING HEALTH CENTRE

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Lay Abstract

Over 30% of the health services provided by our healthcare systems does not benefit and may actually harm patients. Health services research is therefore a necessary activity required to reduce this waste. In Ontario, over 65% of patients receive their acute care in large community-based hospitals, and yet, these hospitals have minimal research activity and capacity despite repeated attempts by the academic research community to engage these institutions through a variety of *collaborative* models such as integrated knowledge translation. This thesis provides a blueprint for the transformation of a large community hospital into a learning health centre through the use of a locally created, locally relevant, embedded researcher model. Starting with a proof of concept through the systematic evaluation of an antimicrobial stewardship program, the thesis ends with a 'how to' guide for the implementation of the foundational elements needed to support health services research in similar organizations.

Abstract

There is a pandemic of low-value clinical care that threatens the sustainability of our publicly funded healthcare systems. Over 30% of the health services provided to patients provide no benefit or may actually result in harm. Health services research is needed to critically evaluate our clinical practices and programs to ensure we create systems that consistently deliver high-value care. Unlike drug trials, health services research is complicated by enormous heterogeneity across cultures, environments, behaviours and systems. Ideally, local research communities should devise and conduct health services research to ensure that both the research questions and outcomes are relevant to community members, and thus more likely to result in sustainable healthcare systems.

Embedded researcher models are emerging as a viable approach to supporting local research activities. Embedded researchers are part of the community they serve, provide research expertise to local investigators and community members, and help develop local research systems that facilitate health services research activities. While they may still collaborate with academic partners, this is not necessary for their research success.

This thesis documents the transformation of a large community hospital in Ontario into a learning health centre through the use of an embedded researcher model. The first part of the thesis is focused on the results of incorporating an embedded research plan into the hospital's new antimicrobial stewardship program. The research that emerges from this work contributes new knowledge about the value of antimicrobial stewardship to important patient outcomes such as reduced lengths of hospital stay and rates of *Clostridium difficile* infections. The thesis concludes with a discussion of the implementation of all the necessary components needed to support a learning health centre and how an embedded researcher model facilitated this transformation and could be used by any similar organization to achieve the same result.

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Undertaking a PhD thesis in mid-life is never an easy decision because it can never be made without causing major disruption and inconvenience to others and there is really very little to be gained by all those involved including the author.

My beautiful wife, Kirsten Alice DiDiodato (née Ertel), has been unwavering in her support and in her resolve to accommodate this disruption to our family. There are two authors that should be listed on this thesis and they should be listed in this order, first my wife and then myself.

Our kids, Jacob Isaac (chachi), John Alexander (squeegie) and Carina Frances (boonie), who have been and will always be both my greatest joy and my greatest consternation. While I would never recommend your reading this thesis for pleasure or for any other reason, quite frankly, I do hope that when I am gone it may occasionally serve to remind you of

something I may have said in the way that I was accustomed to saying it in the sentences contained herein.

Ai miei meravigliosi genitori, Enzo and Maria Teresa (née Leone) DiDiodato, voglio ringraziarti per il vostro supporto nel consentirmi la libertà di diventare chiunque voglia essere.

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And lastly, to the passage of Time that has provided me the academic freedom to challenge all the structural conventions and conventional wisdom that obstruct the democratization of research across our healthcare system to the ultimate detriment of everyone. After all, "Research by all … for all" is the rallying cry of this thesis.

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List of Figures and Tables

List of all Abbreviations

MOHLTC	Ministry of Health and Long-Term Care
FTE	Full-time equivalent
LCHs	Large community hospitals
CAHO	Council of Academic Hospitals of Ontario
sd	standard deviation
CIHR	Canadian Institute of Health Research
RCTs	Randomized clinical trials
RR	Relative risk
CI	Confidence interval
OR	Odds ratio
HR	Hazard ratio
LHS	Learning health system
KT	Knowledge translation
KTA	Knowledge to Action
iKT	Integrated knowledge translation
PIs	Principal investigators
UK	United Kingdom
CLAHRCs	Collaborations for Leadership in Applied Health Research and Care
IQR	Interquartile range

MOHLTC	Ministry of Health and Long-Term Care
CINAHL	Cumulative Index to Nursing and Allied Health Literature
ASP	Antimicrobial stewardship program
ASP-i	Antimicrobial stewardship program interventions
AS	Antimicrobial stewardship
LOS	Length of stay
CAP	Community-acquired pneumonia
FRI	Febrile respiratory illness
ICU	Intensive care unit
REB	Research ethics board
PCT	Pragmatic clinical trial
DOT	Days of therapy
DuT	Duration of therapy
CURB-65	Confusion, Urea, Respiratory rate, Blood pressure-65 score
AIC	Akaike information criterion
BIC	Bayesian information criterion
SHR	Subdistribution hazard ratio
ID	Infectious diseases
IDSA	Infectious Diseases Society of America
CDI	*Clostridium difficile* infection
HA-CDI	Hospital-associated CDI
CA-CDI	Community-associated CDI

IPAC	Infection prevention and control
LTCF	Long-term care facility
ASHP	American Society of Health-System Pharmacists
SIDP	Society of Infectious Disease Pharmacists
PS	Propensity score
IPWs	Inverse probability of treatment weights
VRE	Vancomycin-resistant Enterococcus
MRSA	Methicillin-resistant *Staphylococcus aureus*
ESBL	Extended-spectrum *beta*-lactamase
CRE	Carbapenem-resistent Enterobacteriaceae
LR	Likelihood ratio
PPI	Proton pump inhibitor
PHL	Public health laboratory
BCFHT	Barrie and Community Family Health Team
SCCS	Self-controlled case series
RVRHC	Royal Victoria Regional Health Centre
IRR	Incidence rate ratio
REDCap®	Research Electronic Data Capture
DA	Delegated agent
RA	Research assistant
VforCE^{2}S	Volunteers for the Conduct of Experimental and Effectiveness Studies

Declaration of Academic Achievement

Giulio DiDiodato is the principal investigator, primary author and corresponding author in every published study included in this thesis. Giulio DiDiodato had primary involvement in the design, data collection, analysis, interpretation, and writing of every published study included in this thesis.

Chapter 1: Introduction

Acute Hospital Care System

In Canada, acute hospital care is 100% publicly funded and access is universally guaranteed for all citizens and landed immigrants. In Ontario, Canada's most populous province with over 13 million residents, the Ministry of Health and Long-Term Care (MOHLTC) is the provincial agency responsible for the funding and oversight of Ontario's acute care hospital system. For fiscal year 2015/2016, the MOHLTC budget for health and long-term care was approximately $51 billion dollars, accounting for over 38% of the entire provincial budget (1). The acute care hospital system received over $23 billion dollars, accounting for the largest component of the 2015/2016 health care budget.

Ontario's acute hospital care system is composed of 7 facility types (Table 1) (2). Small and large community hospitals and teaching hospitals consistently account for over 90% of the acute hospital care system budget (3). According to the MOHLTC, there are currently 12 teaching hospital corporations, 45 large community hospital corporations and 78 small community hospital corporations that serve adults (≥ 18 years) needing inpatient care (2). According to the Public Hospitals Act, teaching hospitals are defined as "general hospitals providing facilities for giving instruction to medical students of any university, as evidenced by a written agreement between the hospital and the university with which it is

Table 1: Hospital types and associated budgets, employees, beds in operation and various health care-related activities, fiscal 2015/2016.

Hospital type	Budget ($)	Employees (FTE)	Beds	Inpatients	Acute inpatient days	Inpatient cost per day ($)	Total surgical cases
Small Community	665,598,354	4,645	3,239	117,215	247,823	354	42,222
Large Community	11,916,314,280	78,613	14,873	778, 507	3,765,363	518	1,070,803
Teaching	8,613,199,701	55,206	8,617	361,652	1,954,270	645	412,864
Children	744,580,860	5,180	415	22,720	110,408	1,119	20,231
Chronic/ Rehabilitation	714,587,407	6,280	2,419	14,670	6,181	301	Not applicable
Mental Health	739,991,902	5,440	1,669	11,216	3,486	427	Not applicable
Other	148,824,190	707	98	6,308	26,536	208	17,808

Source: Ministry of Health and Long Term Care. *Health Data Branch Web Portal*. https://hsim.health.gov.on.ca. Accessed March 21, 2017.

affiliated, and hospitals approved in writing by the Royal College of Physicians and Surgeons for providing post-graduate education leading to certification or a fellowship in one or more of the specialties recognized by the Royal College of Physicians and Surgeons". Large and small community hospitals have no mandate to educate medical students or residents, but are simply classified according to their size, with large hospitals defined as those facilities with ≥ 100 beds.

Large community hospitals (LCHs) represent the largest and most diverse component of the acute hospital care system. LCHs range in size from an average of 102 beds to 1234 beds in daily operation, with a mean of 338 beds (standard deviation (sd) 227 beds). During fiscal 2015/2016, LCHs admitted from as low as 1,511 patients to as high as 62,754 patients, with a mean of 17,693 patients (sd 12,836 patients). The patients admitted to LCHs are complex and ill, as exemplified by their near comparable inpatient costs per day to teaching hospitals (Table 1). Many LCHs have become referral centres themselves for specialized care, with many LCHs hosting cancer centres, specialized surgical services such as cardiac catheterization and cardiovascular surgery, neurosurgical services and advanced critical care services. In 2015/2016, there were only 22,284 inter-hospital transfers from LCHs to teaching hospitals for advanced care, representing less than 3% of the total patients cared for by LCHs (4). This exemplifies the ever-increasing medical and surgical capacity and

competency of these LCHs that has resulted from the dissemination of specialized services and personnel from their traditional perches in teaching hospitals over the last several decades. As a result, LCHs now provide care for approximately 62% and 70% of the province's hospitalized medical and surgical patients, respectively (3).

Health Care-related Research System

Along with providing medical and surgical care, some hospitals participate in research. In Ontario, these acute care hospitals have organized themselves into the Council of Academic Hospitals of Ontario (CAHO) (5). Of the 24 members, 12 are teaching hospital corporations, 1 is a large community hospital corporation, and with the remainder being mental health, chronic/rehabilitation, or children hospital types. The research being conducted varies both within and between member hospitals, and includes basic science, experimental and observational clinical studies. The primary mission of CAHO is to advance patient care and build a high-quality health care system.

Most health care-related research funding opportunities are provided through Canada's network of public and privately managed research-funding agencies such as the Canadian Institute of Health Research (CIHR). The distribution of these research-funding opportunities for fiscal 2015/2016 is displayed in Table 2. The attribution of research awards and grants to specific institutions using the Canadian Research

Table 2: Research awards and grants distributed to Ontario's acute care hospital corporations, fiscal 2015/2016.

Corporation	Awards/Grants ($)	Awards/ Grants (Number)	Percentage of Total (Number/$)
CAHO			
University Health Network	28,892,870	230	8.03/8.63
London Health Sciences Centre	3,604,112	35	1.22/1.08
The Ottawa Hospital	21,499,657	161	5.62/6.42
Hamilton Health Sciences Corporation	294,149	3	0.11/0.09
Kingston General Hospital	60,000	1	0.04/0.02
Mount Sinai Hospital	9,224,949	59	2.06/2.76
Sunnybrook Health Sciences Centre	11,250,334	96	3.35/3.36
St. Michael's Hospital	10,137,226	99	3.46/3.03
Thunder Bay Regional Health Sciences Centre	11,000	2	0.07/0.003
Health Sciences North	103,535	1	0.035/0.03
North York General Hospital (LCH)	90,496	1	0.035/0.03
Non-CAHO			
Trillium Health Partners (LCH)	750	1	0.035/0.0002

Source: Canadian Research Information System. http://webapps.cihr-irsc.gc.ca/cris/search. Search strategy: Region "Ontario" + Funding From "2015-2016" To "2015-2016" (All other fields left at default). Accessed March 21, 2017.

Information System is limited by the principal investigator's self-identified affiliation status. For example, if a principal investigator is a physician who practices and conducts their research from St. Joseph's Healthcare Hamilton, a CAHO member, but applies for research awards and grants as a faculty member of McMaster University, then any successful bids will be attributed to McMaster University. A search for research awards and grants for McMaster University for fiscal 2015/2016 reveals 307 successful bids totalling $37,057,356. Without doubt, many of these are due to successful bids from researchers affiliated with St. Joseph's Healthcare Hamilton. The same is true for other CAHO members whose researchers may be affiliated with the University of Toronto (575 awards/$65,785,165), University of Western Ontario (228 awards/$24,373,475), Queen's University (127 awards/$16,577,932), University of Ottawa (168 awards/$17,654,847), Laurentian University of Sudbury (5 awards/$310,085), or Lakehead University of Thunder Bay (5 awards/$365,754). Unlike the way that the Canadian Research Information System underestimates the research awards and grants distributed to CAHO members in close geographic proximity to Ontario's university centres, it is highly unlikely that this reporting system underestimates research awards and grants distributed to both CAHO and non-CAHO LCHs (Table 2).

It should be obvious from the previous section that Ontario's health

care-related research activity is concentrated in CAHO member hospitals, most of which are teaching hospitals. While there is a strong north to south disparity in funding even among CAHO member hospitals, there is an even greater disparity in funding and research activity between CAHO member hospitals and non-CAHO LCHs. The only reason this would be of any significance is if this inequality in access to funding resulted in inequities in important patient and health care system outcomes. Before reviewing the evidence describing the association between research activity and patient outcomes, it is important to describe the association between access to quality health care and patient outcomes as the value of health care-related research is solely conditional on the influence that health care has on overall morbidity and mortality.

Value of Medical Care

The attributable benefit of medical care on any one individual's or population's overall health is difficult to estimate. It has been suggested that medical care plays a highly variable and limited role compared to other determinants of health, such as behaviour, environmental exposures, socioeconomic status and genetic predisposition, in reducing years of life lost to premature death (6-8). Depending on the disease, estimates ranging from 10% to 50% of life expectancy gains since the beginning of the twentieth century have been attributed to advances in medicine. The economic costs to achieve this reduction in premature

deaths through health care appears to be disproportionate compared to the costs of investing in social and public health policies to promote healthy behaviours, alleviate poverty and minimize harmful environmental exposures, factors that may be associated with upwards of 60% of all premature deaths in some diseases (6-9). Measured in 2002 United States dollars, the average cost to reduce 1 year of premature death with medical care increased by at least 500% across all age groups from 1960 to 2000 (7). Since 1960, 90% of the life expectancy gains have been due to reductions in premature deaths from cardiovascular disease and neonatal mortality (7, 10), and this trend is not expected to change in the following decades.

Prior to 1960, reductions in premature deaths were mostly attributable to the control, prevention and treatment of infectious diseases (11). Illnesses due to infectious diseases where specific pathogens are the single causative factor for disease are uncommon among all diseases that afflict humans. With rare exceptions, the causative agents for almost all other diseases are unknown. Most diseases are due to a complex interaction of hundreds, if not thousands, of genetic predisposing factors, and harmful environmental exposures, among many other factors. Not surprisingly, treatment and preventative interventions such as antimicrobials and vaccines, respectively, that have resulted in significant individual and population-based reductions in both morbidity and mortality

have been difficult to replicate for most other health care interventions to date (7, 10-12). The "magic bullet" myth of health care cures established by the one-off success of antimicrobials and vaccines has fuelled the overly optimistic expectations about the value of health care. Combined with the "therapeutic illusion", that any intervention is better than no intervention and that all intervention effect sizes are always more beneficial and less harmful than actually reported in clinical trials, these cognitive biases have fuelled our belief that both health care and health care-related research are disproportionately vital to our health and deserving of an ever-increasing share of our limited economic resources (13-17).

Research Activity and Patient and Health Care System Outcomes

There have now been 2 separate systematic reviews summarizing the differences in outcomes between patients participating in clinical trials and those with similar conditions and baseline characteristics that are receiving identical treatment but who are not enrolled either because they refuse, are not eligible or are not invited to participate (18, 19). Gross *et al.* included 17 randomized clinical trials (RCTs) in their review, but did not preform a meta-analysis due to significant heterogeneity between effect sizes (18). They did observe that there were no differences in patient outcomes for 15 of 17 studies. In the systematic review by Vist *et al.*, both RCTs and non-RCT were included (19). Similar to Gross *et al.*, they could

not aggregate the results from the RCTs due to heterogeneity. In the 37 non-RCTs whose outcomes measured differences in mortality rates, there was no observed difference between trial and non-trial patients; however, there was low to moderate heterogeneity (I^2=33.7%, p-value<0.03) with 34 of 37 studies demonstrating no difference in outcomes. Vist *et al.* reported that the sources of heterogeneity were not obvious. Overall, both reviews concluded that participation in RCTs neither improved nor worsened outcomes compared to non-participants. An additional systematic review on the differences in outcomes between these two groups absent the inclusion criteria that the treatment be similar also demonstrated no differences in mortality and non-mortality outcomes (20). As would be expected, Fernandes *et al.* demonstrated significantly more heterogeneity in 21 studies with mortality as an outcome with I^2=84% (p-value<0.001). The reason for this was likely due to differences in treatment effects. A systematic review summarizing the differences in mortality outcomes between similar patients admitted to teaching versus non-teaching hospitals demonstrated similar outcomes (relative risk (RR) 0.96 (95% confidence interval (CI), 0.93 to 1.00) after accounting for hospital volume, along with patient severity of illness and combordities (21). In addition, in an observational study examining the association between physician group practices that were involved in conducting a clinical trial and their subsequent adherence to treatment guidelines compared with non-trial

physician group practices, no difference in guideline adherence was demonstrated (odds ratio (OR) 1.00 (95% CI, 0.84 to 1.19) (22). Assuming that the majority of patient enrolment in clinical trials occurs in hospitals that receive the majority of research awards and grants (23), these findings suggest that patients cared for in non-CAHO LCHs are not necessarily disadvantaged by the disparity in research funding and activity among Ontario's hospitals.

In contrast to the studies in the preceding paragraph, there are other studies that suggest that the intensity of institutional research activity may be associated with improved patient outcomes regardless of trial enrolment (23-27). In an observational study of 140 National Health System Trusts in England, the risk-adjusted institutional mortality from all causes was associated with research funding (23). Compared to trusts in the highest tertile for research funding, the OR of death in the lowest and middle tertile trusts was 1.05 (95% CI, 1.03 to 1.07) and 1.04 (95% CI, 1.02 to 1.05), respectively, after accounting for patient-level and hospital-level differences. In another study, mediation analysis was used to explain how institutional involvement with research might reduce mortality in ovarian cancer patients (25). The researchers estimated that the hazard ratio (HR) of death was 0.58 (95% CI, 0.42 to 0.79) for patients in trial hospitals compared to non-trial hospitals. Their mediation analysis suggested that 26% of this overall reduction in death was due to more

complete surgical debulking and increased access to adjuvant chemotherapy. The remaining 74% was due to the 'institutional effects' of research participation, a provocative observation suggesting why current knowledge translation efforts may be limited in improving patient and health care system outcomes in the absence of increasing institutional research capacity and competency.

Research for All

Up to now, I have not formally defined the term *research*. For this thesis, research is defined as an *experimental, observational or descriptive study designed to pragmatically and ethically test or generate a hypothesis with maximal accuracy, precision and validity with the intent to gain knowledge and disseminate and/or implement the results*. Intentionally omitted from this definition is any requirement that limits who should conduct research, where should it be conducted or what type of research should be most valued. This omission is critical to avoid ascribing to a particular research model an *a priori* privileged position that may have unintended consequences of limiting the production and undermining the value of all types of research (28, 29). Unfortunately, this has already happened and most public and private research funding agencies are now attempting to rectify this self-inflicted problem (29-31).

In a provocative editorial about the value of research, Dacre *et al.* posit that the sustainability of an effective and equitable health care

system requires that all health care providers become involved, in some way, in clinical research (32). They were suggesting that the traditional model of clinical research needed updating. Historically, in the majority of health care systems regardless of their funding model, health care-related research is organized into two parts; knowledge synthesis and knowledge use. Most of the time, as exemplified by our current system in Ontario, there is very little connection between those who conduct research and those who use research (33, 34). This separation has contributed to a research to practice gap that has been identified as being a significant contributor to the delayed and variable implementation of research knowledge into clinical practice (35). This has contributed to the widespread prevalence of low-value care in most health care systems (36, 37). Recent estimates suggest that low-value care may result in up to a fifth of health care spending being wasted (38, 39), along with preventable medical events being a leading cause of morbidity and mortality in hospitalized patients (38, 40, 41). To combat issues of poor medical care that compromise patient outcomes and contribute to the escalating costs of health care, new models that facilitate the integration of research into routine clinical practice, such as learning health systems (LHS), have been proposed as a solution to this system-wide problem (42-44). The LHS is based on the principle of embedding research directly into routine clinical practice so that knowledge synthesis and knowledge use are co-created

by the end-users of health care services. The idea being that evidence, context and facilitation are equally important and necessary to the successful implementation of knowledge into practice. While most health care systems have acknowledged the importance of this type of approach to improve outcomes, the models have either rarely been adopted or have been adopted with variable success and sustainability (45).

Knowledge to Action

For this thesis, *knowledge translation* (KT) is defined as *the awareness, effective use, and sustainability of evidence-based practice guidelines by knowledge users in their clinical practices* (46). KT is variably described in the literature, and has many competing frameworks that have been developed for different clinical contexts (45). In Canada, the Knowledge to Action (KTA) framework developed by Graham *et al.* has been adopted by the Canadian Institute for Health Research funding agency to guide and promote the uptake of evidence into practice (47). CIHR has also deployed specific awards and grants that require the inclusion of a KTA strategy (48). In a search of the Canadian Research Information System for 2015/2016 (*Canadian Research Information System. http://webapps.cihr-irsc.gc.ca/cris/search. Search strategy: Funding From "2015-2016" To "2015-2016" + any of the phrases: "knowledge translation" (All other fields left at default). Accessed March 27, 2017)*, there were 211 awards and grants totalling $23,923,101

distributed for KT research proposals. None of these were distributed to any of Ontario's LCHs. The vast majority were to support systematic reviews, the current preferred currency of the KTA strategy. Despite this commitment to the KTA framework by Canada's largest and most prestigious research funding agency, there has never been any study to understand how adopting the KTA framework adds value to the health care system compared to other potential frameworks or models intended to promote research uptake into practice (45, 49-51). While the CIHR has sponsored many KTA-containing proposals, a recent systematic review from 2006 to July 2013 found only 146 publications that used the KTA framework (52). Of these, only 28 (19%) publications demonstrated an important impact of the KTA framework on the research study outcomes. In addition, many of the most common tools created by KT strategies have demonstrated either no or minimal clinically important impacts on research uptake into practice (53-58), suggesting that KT strategies such as the KTA framework have so far demonstrated limited practical use and effects. Likely in response to these limitations, a modified KTA model has emerged (59). The CIHR refers to this as an *integrated knowledge translation* (iKT) model (48). According to the CIHR definition, the iKT model requires traditional knowledge creators to collaborate with traditional knowledge users to co-create research that addresses contextually relevant questions. Like the KTA framework, there has never

been any study to understand how adopting this iKT model adds value to the health care system compared to other models intended to promote research uptake into practice (59, 60). In a search of the Canadian Research Information System (*Canadian Research Information System. http://webapps.cihr-irsc.gc.ca/cris/search. Search strategy: Any of the phrases: "partnerships for health system improvement, knowledge synthesis, knowledge to action" (All other fields left at default). Accessed March 29, 2017*), there have been 274 awards and grants totalling $66,817,598 distributed for iKT proposals since 2010. None of these have been distributed to any of Ontario's LCHs. In the only published qualitative review of the CIHR iKT model, Sibbald *et al.* surveyed 173 principal investigators (PIs) who had been recipients of CIHR iKT awards and grants, along with 110 principal knowledge users whose sites had been included in these proposals (61). Of those who completed the survey and agreed to be interviewed, a purposeful sample of 24 PIs and 25 knowledge users completed a semi-structured interview. The investigators categorized these *collaborative* relationships between PIs and knowledge users as token, asymmetric or egalitarian (Table 3). Categorization was dependent on the participants' responses to the following four questions:

1) To what extent did your partnership on this study bring your expertise as a knowledge-user into the process?

2) How long did it take you to develop trust in your relationship with your partner?

3) Who was involved in the following aspects of this study?

i) Shaping the research question(s)

ii) Deciding on the methodology

iii) Data collection and tools for development

iv) Interpreting the study findings and crafting messaging around them

v) Moving the research results into practice

vi) Widespread dissemination and application

4) To what extent do you agree with this statement? “I learned a lot from my research partner while working together on this study”

Token relationships were described as researcher dominant, asymmetric relationships as researcher led with some knowledge user engagement, and egalitarian as researcher and knowledge user co-leads. A significant barrier to the success of these partnerships was the lack of clarity in roles and expectations. Both PIs and knowledge users felt the research activity was driven by PIs and knowledge users simply served as advisors. These relationships were most egalitarian when there existed a shared interest between PIs and knowledge users. In addition, a positive impact of these relationships was most evident when knowledge users were directly involved in shaping the research question and proposal. About half felt that the partnerships would remain intact after the specific research project

Table 3: Description of research relationships between PIs and knowledge users awarded CIHR iKT awards and grants

Category	Definition	PIs	Knowledge users
		Number (% of Total)	
Token	Negative responses to all questions	3 (12.5)	4 (16)
Asymmetric	Some positive and negative responses to questions	16 (66.7)	11 (44)
Egalitarian	Positive responses to all questions	6 (25)	9 (36)

Source: Adapted from (61).

was completed, and PIs expected knowledge users to sustain the project beyond the end of the research period. The study authors concluded that there is no one *best* approach to developing research partnerships, and recommended that research funders be open to supporting other models that encourage these partnerships. These findings were consistent with other reviews of iKT research that described that the complexity, time and effort needed to develop and sustain these partnerships was a rate-limiting step and potential threat to the success of the iKT model (59, 62, 63). Regardless of these limitations, other jurisdictions have adopted this model to promote research uptake (64-66). Most recently in Ontario, the CAHO launched the Adopting Research to Improve Care (ARTIC) program based on an iKT model (67). Developed in response to the limited success of traditional KT programs to improve research uptake into

practice, this program is based on CIHR's KTA framework and iKT model. One of the earliest and *most successful* projects funded by ARTIC was the Antimicrobial Stewardship Program (ASP) in Intensive Care Units (68). Funded at a cost of approximately $3.5 million dollars, this was a before-after study describing the association between the implementation of an ASP in 12 CAHO intensive care units and antimicrobial utilization (69). The study lasted 2 years and was completed in 2014. Unfortunately, neither the study protocol nor the study results have been published in a peer-reviewed journal, but CAHO reports that the study resulted in a 23% reduction in antimicrobial consumption compared to historical trends. This reduction was associated with cost savings of $300,000 in antimicrobial costs, not taking into account the program expenses which would have been considerable given the *a priori* requirements for participation being a dedicated 0.5 full-time equivalent pharmacist and a 0.2 full-time equivalent physician lead (70). There was no significant impact on patient outcomes such as reduction in *Clostridium difficile* infections, decreased length of stay or mortality. This program has apparently been funded to expand into selected non-CAHO hospitals (67) despite the fact that the original study required the ASP be staffed with a physician lead with either infectious diseases or medical microbiology specialization, a human resource infrequently found in most non-CAHO hospitals. To highlight the limitations of the ARTIC program, Moore *et al*. concluded the following:

"The evaluation and lessons learned did not consistently link the implementation projects with improved patient outcomes, and there is no comparison group that did not receive ARTIC funding…because of the program evaluation research design, we are not able to determine whether the funding model successfully improved outcomes." (67)

The Limits of Generalizability of Results from Experimental Studies

In Ontario, as in most jurisdictions, almost all funded health care-related research is generated from researchers affiliated with academic centres (71). This should not be surprising given that most funding is used to support basic scientific research (72), an endeavour that generally requires specialized facilities, scientists who are not necessarily clinicians, and research networks. As for applied clinical research, support is limited to less than 10% of the research budgets of funding agencies (72). While the "real-world" value of basic science research is rarely obvious *a priori* as benefits may accrue decades after the research has been completed, many have questioned the "real-world" value of most of the current clinical research being produced (72-74). Apart from issues due to redundant or low priority research questions, poor study design, failure to recruit and retain study participants, failure to publish, and failure to sufficiently describe interventions and study outcomes (75), the limits of generalizability of results from experimental studies may also limit the "real-world" value of even the best clinical trials (76, 77). Treatment or

intervention efficacy, as determined from an appropriately designed experimental study, is rarely ever realized in clinical practice (77-80). This efficacy to effectiveness *discount* is highly variable, but usually correlated with the complexity of the intervention or treatment; *simple* interventions such as medication treatment demonstrating the least discrepancy between efficacy and effectiveness, while complex interventions such as those that require behavioural change being the most discordant (79-81). Issues such as heterogeneity of treatment or intervention effects (79, 82), violations of the stable unit treatment value assumption (83), along with the flawed "trickle down model of how to translate research into practice" (76) that depends on the existence of a linear process between efficacy research and practice implementation (34, 76), all contribute to the efficacy to effectiveness *discount*.

For complex interventions, such as antimicrobial stewardship activities, delivered to medically complex patients in complex health care settings, the need for locally relevant effectiveness research conducted in a methodologically rigorous, ethical, pragmatic and timely fashion has been identified as being a research priority for health care systems (76, 81, 84, 85).

Entrenchment of Underperforming Ideas in Research

In their commentary, Joyner *et al.* questioned the "real-world" value of the current biomedical research focus of "personalized" medicine, and

described how commitment to this idea has hijacked resources from research funding agencies and biomedical journals (86). Their argument can be distilled to the following: due to the limits of our current experimental studies to predict which individuals might benefit from (or be harmed by) potentially beneficial (or harmful) treatments, supporting research in genomics, stem cell research and big-data will provide us with the information needed to apply research findings to individuals with less uncertainty as to their benefit (or harm). However, they argue, not only is there a paucity of evidence to support this intuitive belief about the value of this research (87, 88), but continued commitment to this research agenda will divert resources from competing research ideas, ultimately resulting in unintended but harmful consequences for the public health.

Like the commitment to the idea of "precision" medicine, Canada's research funding agencies have committed to supporting KT and iKT models of effectiveness research as a solution to a problem they created and without much evidence of their own superior efficacy or effectiveness compared to other models (60, 89, 90). The consequences of this commitment have already resulted in the centralization of research activities to academic centres, a paradoxical development given the widespread dissemination of general medical and specialist care from academic centres to LCHs. Instead of democratizing research, this commitment has resulted in the maintenance and status of preferred

researchers isolated in academic centres (91). Instead of creating local LHS whose health care providers and administrators have the research capacity and competency to both interpret and conduct research to improve the effectiveness of the care they provide to their patients, this commitment has created a workforce and public that cannot consistently interpret research findings nor deliver high-value care (14, 15, 92). Instead of valuing research for its ability to improve health, research is frequently used as a vehicle for professional advancement (91). This current model objectifies research as something that is so difficult, complex and important that it can only be done by specific people in specific places, as though it is inaccessible to the vast majority of health care providers who perform similarly complex and important tasks everyday in their clinical management of illness and health. The idea that the research to practice gap can be adequately addressed by simply modifying the research funding model to require all proposals to contain some element of a KT/iKT plan is not only flawed, but will continue to delay the necessary dissemination and democratization of research to non-academic sites that must occur to improve medical care and patient outcomes. To achieve this, vested interests with entrenched privilege in the current funding system need to be displaced by those with new ideas and no conflicts of interest who are more representative of the entire health care system. This will be a difficult task, but it must start from

outside the current research system by non-academic based researchers and administrators who make a commitment to the value of research within their own institutions. The hard work of demonstrating that local effectiveness research should be done, can be done and adds value to the health care system will initially need to be done by non-academic researchers who are currently systematically excluded from receiving research funding by the current eligibility criteria of all the funding agencies. A potential model of research that may facilitate this work is emerging, the embedded research model (34, 93).

Embedded Research as an Alternative to iKT

The health care system that has made the largest commitment to the idea that all acute care hospitals and their health care providers and patients need to be involved in clinical research to improve the value of health care has been the National Health Service in the United Kingdom (UK) (94). Starting in 2008, the United Kingdom National Institute for Health Research funded a 5-year iKT pilot program called the *Collaborations for Leadership in Applied Health Research and Care* (CLAHRCs) (64). The CLAHRCs objective was to promote the value of and facilitate the spread of applied health care research activity by funding local partnerships between academic researchers and community-based health care providers. Through these collaborative partnerships, the CLAHRCs hoped to realize an increase in the capacity and competency of

community-based National Health Service Trusts (aka acute care hospitals) to improve the value of care they deliver by closing the knowledge to translation gap. The pilot program funded 9 CHLAHRCs at a cost of £90 million that was matched by their partner organizations (94).

An evaluation of the pilot programs has revealed some important lessons to guide policy about the value and limits of this iKT model of applied health care research (94). First, the pilot program dramatically increased the external research funds available for non-academic trusts to support local research activity. In so doing, local and robust research infrastructure programs were created to support this increased research activity. Unfortunately, the sustainability of these research infrastructure programs is now dependent mostly on external funding sources such as the National Institute for Health Research that has inadvertently created pressure to conduct research that serves an agenda that is external to the local trust. In other words, research is not fully embedded within the local trusts and doesn't necessarily serve local knowledge users' needs (94). The most successful CLAHRCs are those that have decided to fund their own internal research programs so that they could fully develop their own research agendas that focus on health service innovation.

Second, successful CLAHRCs have been encouraged to develop their own research agendas, and these have been supported through dedicated research grants from national research funding agencies.

Without a commitment from research funding agencies to ensure protected space for these types of local research initiatives, the CLAHRCs would never have realized their objectives (94).

Third, while the CLAHRCs have developed their own unique models to promote knowledge mobilization, many CLAHRCs have created positions referred to as 'boundary spanners' to bridge the divide between research and practice (94). These personnel are embedded within local trusts and are responsible for facilitating the implementation of research into practice. Unlike CIHR's iKT model where KTA *experts* are external to local organizations and usually reside in academic centres, the National Health Service is planning to invest in these embedded personnel to promote knowledge mobilization across all trusts (94).

The concept of using an embedded researcher as an intermediary to promote research collaboration and knowledge co-production between academic-based and non-academic-based stakeholders is emerging as a vital strategy to overcome the limitations of the current vertical model of academic research production and knowledge users (95, 96). McGinity *et al.* defined embedded researchers as "those who work inside host organisations as members of staff, while also maintaining an affiliation with an academic institution. Their task is seen as collaborating with teams within the organisation to identify, design and conduct research studies and share findings which respond to the needs of the organisation, and

accord with the organisation's unique context and culture." (97) Unlike boundary spanners (98) or knowledge brokers (99) that are primarily focused on knowledge mobilization through *pulling* or *pushing* of evidence produced outside the host organisation, embedded researchers' main purpose is to be directly involved in research and produce knowledge relevant to the host organisation (95). In their narrative review, Vindrola-Padros *et al.* identified 17 articles that described the role that embedded researchers played in health services innovation (95). While there was significant variability in role description, some common themes emerged. Embedded researchers were most effective when they were an integral part of the host organisation. This immersion promoted effective relationships that were essential for building trust but also for making research and knowledge more relevant to stakeholders. In addition, embedded researchers were more likely to understand the research priorities of the organization, along with the obstacles to both conducting and implementing research into practice. Embedded researchers were better able to produce more rapid delivery of locally relevant research. Through their local presence, embedded researchers were actively involved in research capacity and competency building within their host organisations, thus creating cultural shifts that ensured the sustainability of incorporating research into practice. Embedded researchers that had a dual affiliation with both the host organisation and an academic institution

were better able to conduct methodologically rigorous, ethical and publishable research. As has been previously mentioned, there has been no rigorous evaluation of this KT model compared to the current KT/iKT models funded through the CIHR.

Lessons learned from the CLAHRCs

The UK Royal College of Physicians conducted a survey of its members during a 6-week period in 2015 to support its mandate to create a research-active physician workforce, and to examine the impact of the CLAHRCs on the research experiences of its members (100). The survey asked respondents to describe their research activities and interests, and probed respondents to identify barriers to entry for those interested in being involved in research. There were 1,966 respondents, 23% of whom were formally employed in a research role, while another 36% were involved in research without a formal role. Those employed in a formal role reported spending an average of 25.7 hours per week in their research activities, compared to an average of 4.7 hours per week in the other group. Over 900 respondents reported that they had either assisted with clinical research or helped to recruit patients into studies as their most common research activity over the previous 2-year period. However, when respondents were asked which research activities would they most prefer to be involved in, the most frequent response was to be a primary investigator of a study. Over 70% of respondents from both groups

reported that their research activities improved patient care and 60% felt it made them better doctors. Even after the CLAHRCs initiatives, 45% of respondents felt that the current research model was neither collaborative nor collegial. The biggest perceived barriers to becoming more involved in research were access to funding and protected time, while analytical or study design skills were infrequently mentioned as being barriers. Some of the recommendations issued by the UK Royal College of Physicians in response to the survey results included the following:

1) Trusts develop local Research & Development departments to coordinate and promote local research activity and facilitate physician involvement.

2) Research funding agencies create dedicated awards and grants to support local research activities by physicians not formally employed in a research role. These funding opportunities should be well publicised in a central hub and the application process should be simplified and made less cumbersome to better reflect the limitations of time experienced by most non-academic-based researchers.

Ontario's LCH Paradox

Despite delivering acute health care services to over 65% of Ontario's hospitalized patients, these hospitals receive less than 1% of the publicly available funds for health services research. This "1/65" gap is limiting the development of local learning health systems needed to

improve medical care. The current model of KT supported by Canada's research funding agencies focuses mostly on the production of systematic reviews by academic researchers as the most important currency of KT. Knowledge mobilization as either an end of grant KT activity or an iKT strategy appears to be an attempt to square the circle by funding agencies to deal with the difficult and refractory problem of implementation failure, while also ensuring the privileged access of academic-based researchers to limited research funds.

Scope and Objectives of the Thesis

The overall objective of the thesis was to develop the "unique skills and knowledge that learning health system researchers need to be successful and to contribute optimally to the development of health systems." (101)

In Chapter 2, a descriptive study of the research activities of Ontario's LCHs was done in an attempt to measure the impact of CIHRs iKT strategy on building research capacity and competency in these institutions.

Chapters 3 through 5 describe the results of research studies embedded into an antimicrobial stewardship program at a LCH. The studies use a stepped-wedge design to facilitate program evaluation. The outcomes measured include length of hospital stay in patients admitted

with pneumonia. To support this outcome, the researchers also measured the incidence of *Clostridium difficile* infections during the same period.

In Chapter 6, the results of a provincial survey of infection prevention and control practices was used to estimate the impact of inter-hospital patient transfers on the incidence of *Clostridium difficile* infections in both LCH and academic hospitals.

Chapters 7 through 8 describe the use a self-controlled case series design to estimate the risk of *Clostridium difficile* infection associated with antibiotic use in community-dwelling patients registered with the province's largest community-based family health team.

All of these studies contribute to understanding the impact that an embedded researcher in a research-naïve LCH can exert to help transform an acute care hospital into a learning health care system. Ultimately, the thesis hopes to provide the starting point for a conversation in Ontario about the importance and need to democratize and disseminate research participation to all parts of our health care system in the same way that highly specialized clinical services have already moved out from academic health centres into our communities with tremendous benefit to both our patients and health care system.

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Chapter 2: The Research Activities of Ontario's Large Community Acute Care Hospitals: A Scoping Review

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Declaration of Academic Achievement

GD conceived of the research study and conducted the primary literature search.

GD, JAD, ASM screened all publications for final inclusion in the study.

GD, JAD, ASM created the final variable for extraction.

GD, JAD, ASM independently reviewed the full-text publications for data extraction

GD performed all the statistical analyses

GD, JAD, ASM all contributed to writing and editing the final manuscript.

As already mentioned, Ontario's large community hospitals provide the bulk of the acute medical and surgical services to patients. Ideally, these hospitals should be conducting health services research to ensure they are consistently delivering high value care. These activities would have tremendous benefit not only for patients in their organizations, but also contribute to a more effective and efficient healthcare delivery system at the population and system level. Globally, there is recognition that the most impactful health services research is best done locally because of the complexity of healthcare systems. Even the CIHR acknowledges this through their organizational support of research models intended to improve the translation of knowledge into clinical practice. In fact, the CIHR has been advocating for these models for the last 2 decades. Presumably, if this approach were impactful we would expect to see the research capacity and competency of these large community hospitals flourish; we would expect to see independent research activities resulting in new health services knowledge generation being published in ever increasing amounts. We would expect to see previously located academic researchers migrating out to these centres to take up new research roles supported by new research grants from agencies like the CIHR. This scoping review is intended to examine if the last 2 decades of CIHR's strategy for knowledge translation has led to the realization of these outcomes.

ABSTRACT

Background

Ontario's large community hospitals (LCHs) provide care to 65% of the province's hospitalized patients, yet we know very little about their research activities. By searching for research publications from 2013 to 2015, we will describe the extent, type and collaborative nature of Ontario's LCHs' research activities.

Methods

We conducted a scoping review by searching PubMed, Embase and the Cumulative Index to Nursing and Allied Health Literature databases from January 1, 2013 until December 31, 2015 for all publication types whose author(s) was affiliated with any of the 44 LCHs. Articles were screened and abstracted by three reviewers, independently. The data were charted and results described using summary statistics, scatter plots, and bar charts.

Results

We included 798 publications from 39 LCHs and 454 authors. The median number of publications was 7 (Interquartile range (IQR) 23). Observational study design was most commonly reported in over 50% of publications. Program evaluation was the focus in 40% of publications. Primary LCH authorship was observed for 535 publications. Over 25% and 65% of the publications were attributable to 24 authors and 9 LCHs,

respectively. There was minimal collaboration both within (21.2%) and between (7.8%) LCHs. LCH size and geographic proximity to academic hospitals had minimal impact on research activity.

Conclusions

Ontario's LCHs publish infrequently, collaborate infrequently, and their role in translational research activity is not well defined. A future survey questionnaire to LCH researchers identified through this review is planned to both validate and elicit their interpretations of our study findings and opinions about LCH involvement in research.

Keywords

Knowledge translation, acute care hospitals, research activities

INTRODUCTION

Ontario is Canada's most populous province with over 13 million residents, and has a publicly funded and universally accessible hospital system that is administered by the provincial Ministry of Health and Long-Term Care (MOHLTC). Ontario's acute care hospitals are classified as small community (<100 beds), large community (>100 beds) or academic hospitals by the MOHLTC [1]. There are 44 large community hospital corporations (LCHs) that range in size from 100 to 1232 average beds in operation (median 261, IQR 237) [2]. Compared to academic and small community hospitals, approximately 55% of all hospital beds are located in LCHs, and these LCHs are responsible for the care provided to over 65%

of all medical and surgical patients annually [2]. Unlike academic hospitals, LCHs don't have a mandate to conduct research as part of their operational activities. Consequently, a consortium of 18 acute care hospitals is conducting essentially all publicly funded acute healthcare research in Ontario [3]. This research model has unintentionally contributed to either failure or delays in the implementation of evidence into practice, and knowledge translation research initiatives have been initiated by both funding agencies and academic hospitals in their attempt to ameliorate this problem [4-6]. Most of these initiatives focus on funding groups that employ an integrated knowledge translation (iKT) research model [7].

The iKT research model has traditionally been described as involving 'researchers' who collaborate with 'knowledge users' to co-create evidence that will be more readily implemented into practice [7]. Apart from the potential to reduce the time lag between knowledge synthesis and practice implementation [8, 9] and reduce the discrepancy between treatment efficacy and effectiveness that is commonly observed in 'real-world' patients [10], there are many other good reasons why 'knowledge users' and their healthcare organizations should participate in research [11]. First, there is emerging evidence that patients whose healthcare providers or institutions participate in research experience better processes of care and improved outcomes [12-15]. Second, there is an

evolving consensus that an increase in the implementation of evidence into practice will require the promotion of more practice-based evidence [16, 17].

To the best of our knowledge, the research activities of Ontario's LCHs have never been described, and so we cannot fully describe the impact of iKT on community-based research [5]. In this study, we undertake a scoping review of the published research productivity of Ontario's LCHs from 2013 to 2015. A scoping review has been defined as "a form of knowledge synthesis that addresses an exploratory research question… by systematically searching, selecting, and synthesizing existing knowledge [18-20]." The reason for our scoping review is to describe both the extent and type of published research activity being initiated and led by LCHs' researchers, and to determine the extent of collaboration with both academic and non-academic centres. In addition, we aim to document any differences in research productivity that may be secondary to LCH characteristics, such as size or location, funding opportunities, extent of collaborative research activities, and other potential explanatory variables.

METHODS

A scoping review using the methodology described by Arksey and O'Malley [18], and refined by both Levac *et al.* [19], and Colquhoun *et al.* [20] will be used to address the research question. In general, a scoping

review is an accepted method of knowledge synthesis using a pragmatic but systematic search strategy to answer an exploratory research question.

Research Question

For research articles published between 2013 and 2015 whose author(s) is affiliated with any of Ontario's LCHs, what are the extent, type and collaborative nature of Ontario's LCHs' research activities?

Search strategy and study selection

The search for research publications was limited to 3 years to ensure sufficient time periods to establish a trend, and establish a pragmatic limit to the number that needed to be reviewed. The LCHs included in the study had at least 100 beds in operation, and were not part of the Council of Academic Hospitals of Ontario during the study period, the current group of 18 hospitals designated as research centres and whose group contains only 1 large community hospital [3]. Conference abstracts, letters to the editor and book chapters were excluded, but all other publications were included to ensure that a comprehensive picture of research activity emerged. Both conference abstracts and book chapters are recognized as not having the same rigor of peer review as the other included publications, and this criterion alone was used to exclude them from inclusion in this study. The quality of the research publications was not evaluated, as is the norm for scoping reviews. Authorship order was

dichotomized as follows: first, second or last author positions were deemed to have made a 'significant' contribution to the research and are defined as primary studies, while all other author positions were deemed to be of 'lesser' significance to the research and defined as secondary studies [21-25]. Author's professional designation was not relevant to inclusion. Local LCH collaboration was defined as having two or more authors whose affiliations were from the same LCH listed in any position in the authorship order, whereas external LCH collaboration was defined as having two or more authors whose affiliations were from different LCHs listed in any position in the authorship order. In some circumstances, a research publication could have both local and external LCH collaboration. Types of publications were categorized as follows: editorial, observational study, experimental study, qualitative review, systematic review, guideline, or position paper.

PubMed, Embase and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched for research publications. One study investigator (GD) conducted a comprehensive literature search by using the following strategy: Step one: search each indexed database by the LCH name using the 'affiliation' field and the 'year' field to limit publications to 2013-2015. Step two: narrow the results by combining results from step one with the LCH address in the 'affiliation' field. Step three: for every LCH author, a modified 'snowballing' approach

using the author's full name was used to ensure maximal retrieval of all relevant publications. Step four: every publication was saved in Refworks® (http://www.refworks.com). Step five: all duplicates were removed. Step six: all the investigators independently screened each publication. All conference abstracts, letters to the editor and book chapters were discarded. Step seven: The screened lists of each investigator were compared to create the final list of relevant articles. If there was any disagreement between the lists, the publication(s) in question was included to ensure maximal sensitivity of the search.

Data charting

All three investigators contributed to the identification of variables for extraction from the publications. An Excel® (www.microsoft.com) spreadsheet was created to support the collection of data. The variables identified for extraction included the following: full author name, LCH affiliation, journal name, year of publication, authorship position, corresponding author (yes/no), total number of authors listed, same LCH collaborator (yes/no), external LCH collaborator (yes/no), funded study (yes/no), publication type, and research focus. One investigator (JAD) reviewed the full-text publications and extracted all the data variables. The other two investigators (GD and AM) independently reviewed the full-text publications and edited the extracted data from the first investigator.

The most senior investigator (GD) adjudicated any disagreement between the investigators' extracted data.

Data Analysis

Summary statistics were used to describe the number of primary and secondary studies. Scatter plots and bar charts were used to demonstrate both relationships between and distributions of variables. χ^2, ANOVA and Mood's test were used for categorical, continuous and non-parametric group comparisons, respectively. STATA/MP 14.1 for Mac was used for all statistical analyses. Research ethics approval was not required as there were no human participants.

RESULTS

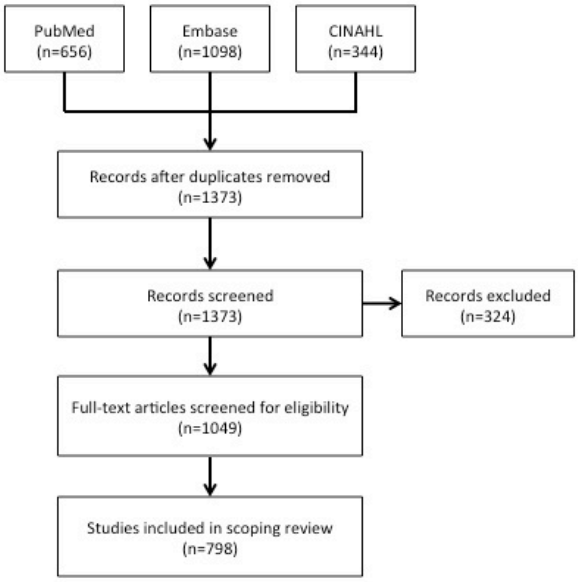
Search results

After duplicate publications were removed, the initial search strategy yielded 1 373 publications. After the first screen, an additional 324 publications were removed, leaving 1 049 publications for full text review (Figure 1). The full text review resulted in the elimination of an additional 251 publications due to the following reasons; inability to retrieve the full text article (N=49), and LCH was not in Ontario.

Research Publications

Of the 44 eligible LCHs, 39 LCHs published at least one paper over the study period. Thirty-seven LCHs produced 535 primary research

Figure 1: Flow Diagram of eligible studies



publications, while 31 LCHs produced 263 secondary research publications over the study period. The mean and median number of total research publications for LCHs was 20.4 (standard deviation (sd) 29.4) and 7 (IQR 23), respectively, over the study period. The total number of publications increased over each calendar year (Table 1). The distribution of publications across LCHs demonstrated significant heterogeneity (Figure 2). The correlation coefficient between primary and secondary publications was 0.72, with each secondary publication resulting in an average increase in 1.3 publications per LCH ($F(1,37)=39.58$, $p<0.001$, 95% CI 0.9 to 1.7).

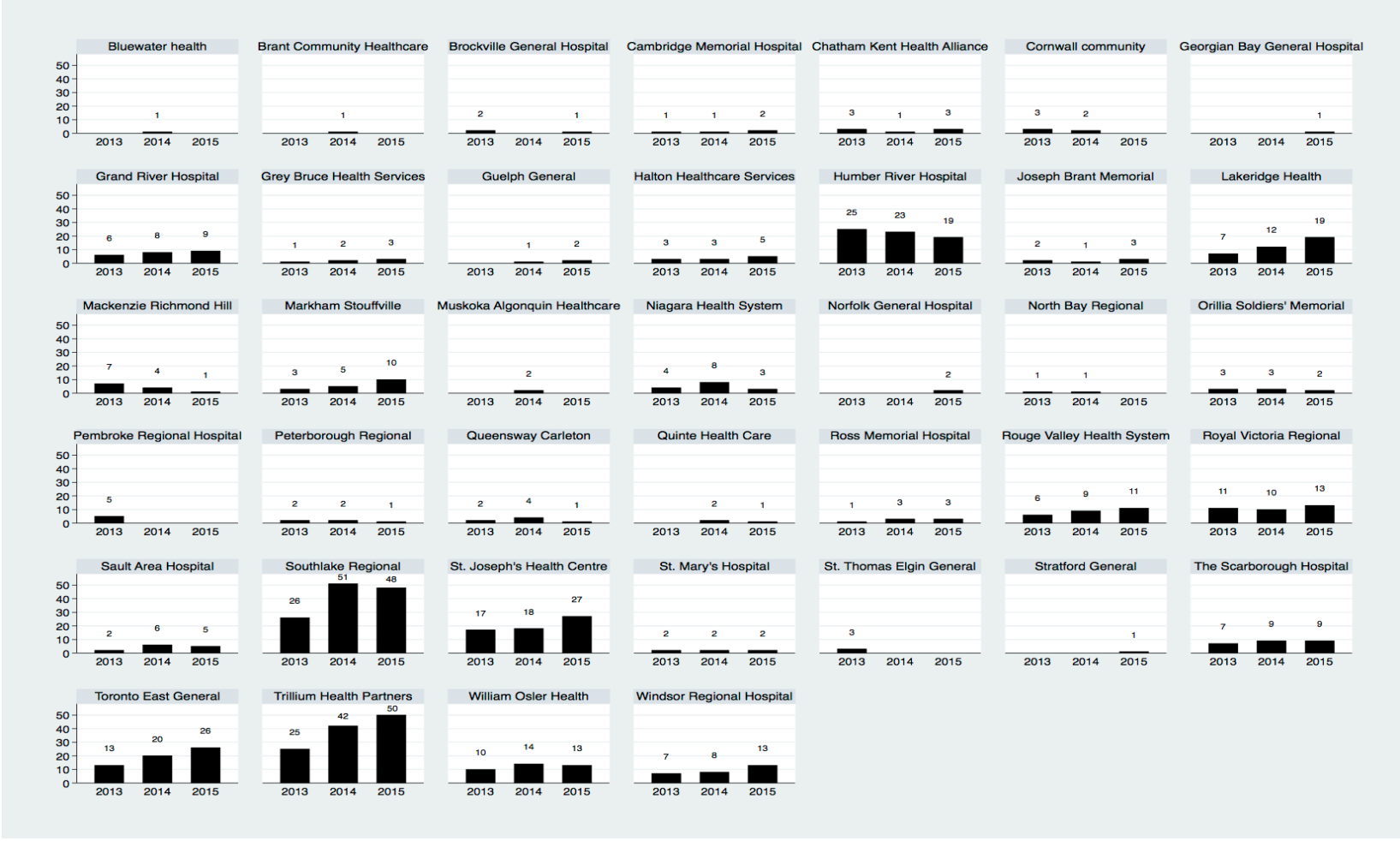
Table 1: Research publications by calendar year

Year	Publications		
	Total	Mean (sd)[1]	Median (IQR)[2]
2013	210	14.3 (9.4)	13 (19)
2014	279	23.6 (17.7)	18 (36)
2015	309	25.7 (17.4)	19 (39)

[1] One-way between year ANOVA $F(2,795)=34.23$, $p<0.001$

[2] Mood's Median $\chi^2(2)=17.89$, $P<0.001$

Figure 2: Distribution of publications by LCH



Publication Types and Topics

The type and frequency of publication types did not change over the study period (Table 2).

Table 2: Publication types by year.

Year	Publication Type[1,2]						
	1	2	3	4	5	6	7
	Publications (N, % Row Total)						
2013	16 (7.6)	9 (4.3)	5 (2.4)	139 (66.2)	2 (1)	25 (11.9)	14 (6.6)
2014	27 (9.7)	28 (10)	12 (4.3)	164 (58.8)	3 (1.1)	33 (11.8)	12 (4.3)
2015	26 (8.4)	32 (10.3)	11 (3.5)	184 (59.5)	1 (0.3)	43 (13.9)	12 (4.1)

[1] 1=Editorial; 2=Experimental; 3=Guideline; 4=Observational; 5=Position Paper; 6=Qualitative Review; 7=Systematic Review

[2] Pearson $\chi^2(12)=13.54$, $p=0.331$

Of the primary publications, 216 (40.4%) described local program evaluation and quality improvement activities. The most common publication topics were oncology (12%), cardiology (12%), nephrology (6.9%), infectious diseases (5.8%), rheumatology (4.6%) and psychiatry (4.4%).

Authorship

There were 454 unique authors responsible for the 798 publications, with 330 unique authors responsible for the primary publications and 158 responsible for the secondary publications. There were 24 authors (5.3%) that had an uninterrupted continuous publication presence over the study period [26], accounting for 215 total publications (26.9%).

The mean and median number of authors per paper was 5.6 (sd 5.7) and 4 (IQR 5), respectively, with a range from 1 to 32 authors per paper. Authorship position ranged from 1 to 31, with 22 unique values. The distribution of first, second or last authorship position is shown in Table 3.

Table 3: Authorship position by year.

Position	Year (N, % Row Total)[1]			Publications
	2013	2014	2015	Total
First	83 (29.6)	98 (35)	99 (35.4)	280
Second	37 (28.7)	43 (33.3)	49 (38)	129
Last	35 (27.8)	41 (32.5)	50 (39.7)	126

[1] Pearson $\chi^2(4)=0.77$, $p=0.94$

The correlation between authorship position and corresponding author identification was most significant for the first and last authorship positions (Table 4).

Table 4: Correlation between authorship position and corresponding author identification.

Position	Corresponding Author (N, % of Row Total)[1]		
	No	Unknown	Yes
First	55 (19.6)	23 (8.2)	202 (72.2)
Second	106 (82.2)	11 (8.5)	12 (9.3)
Last	68 (54)	10 (7.9)	48 (38.1)

[1] Pearson $\chi^2(4)=160.7$, $p<0.001$

Collaboration

Collaboration within the same LCH and between LCHs was relatively infrequent, occurring in 173 (21.7%) and 62 (7.8%) publications, respectively (Figure 3 and Figure 4). Fourteen (1.7%) publications demonstrated collaboration both within and between LCHs.

Figure 3: Distribution of collaborative research publications within the same LCH

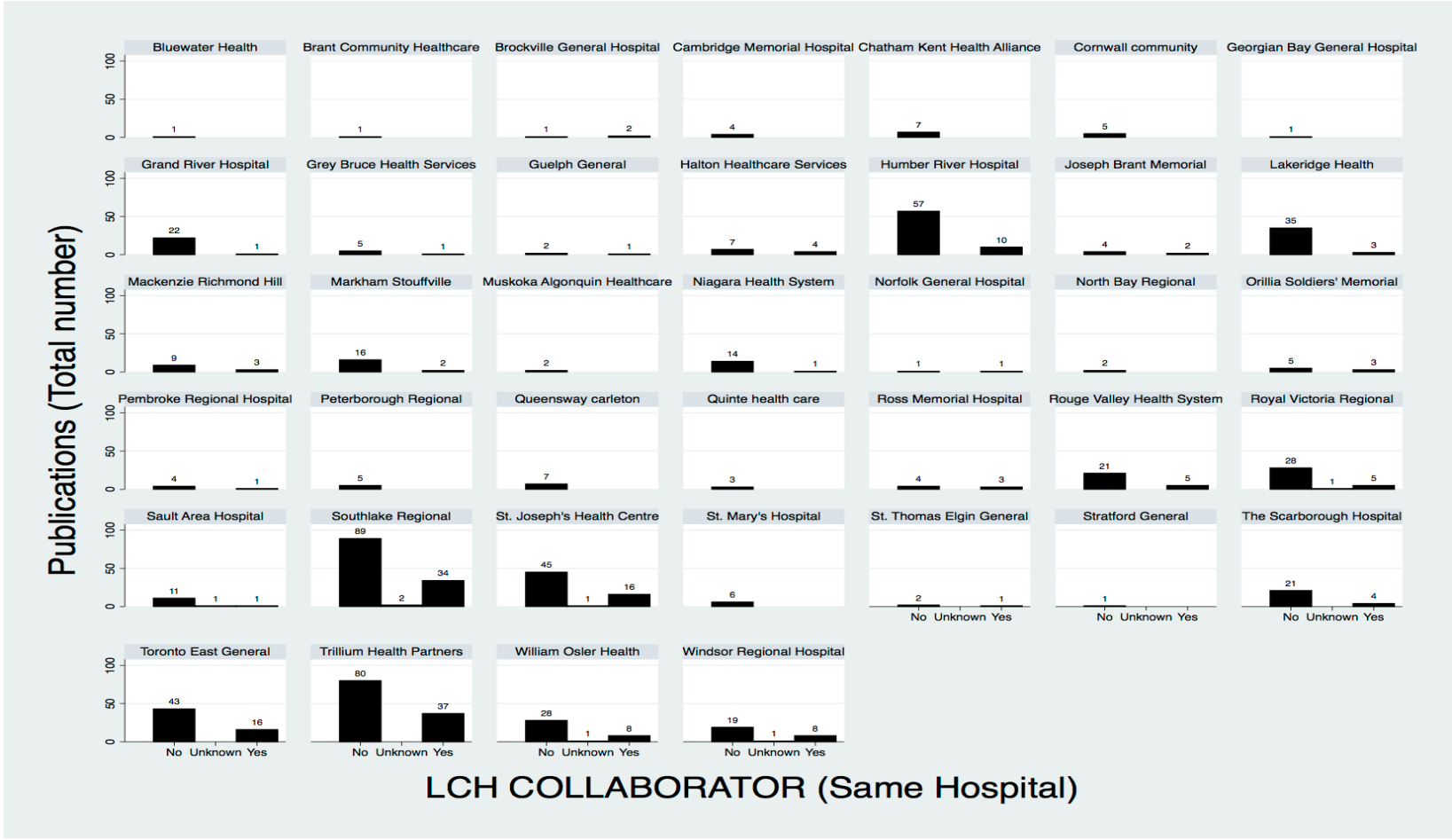
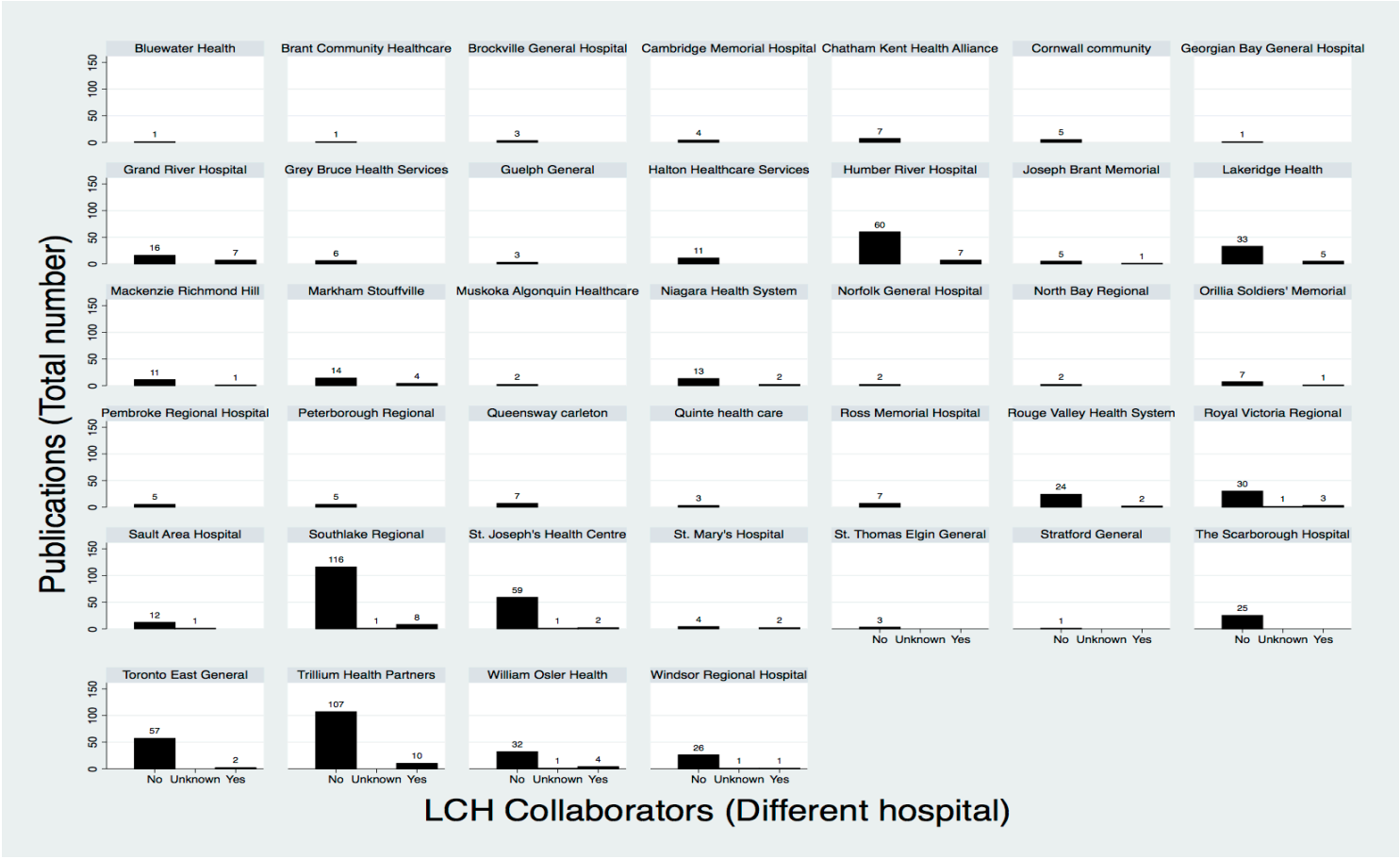


Figure 4: Distribution of collaborative research publications across different LCHs



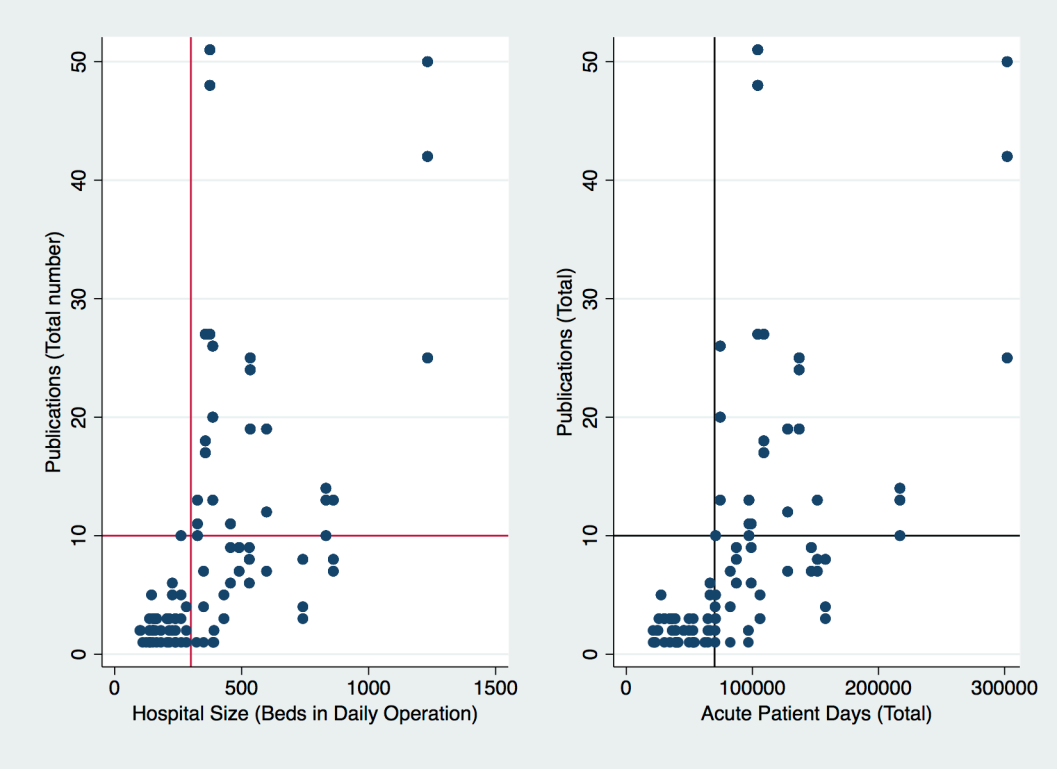
Funding

Of the primary publications, 113 (21.2%) reported receiving funding from 79 unique funding sources. A search of the Canadian Research Information system database (http://webapps.cihr-irsc.gc.ca/cris/search, accessed June 1, 2016), using each unique author name (for the primary publications only), for all grants and funds (from Canada's 12 largest research funding agencies) awarded to these researchers from 2010 to 2016 revealed that only 17 authors (3.7%) had received 24 grants (or 0.26% of the 9 198 grants and funds awarded during this time period) totaling $36 965 857 (2010 CDN) (or 1.59% of the $2 325 721 614 total grants and funds awarded during this time period). These 17 authors were affiliated with 9 unique LCHs, and were listed as either co-investigators (16 grants) or principal investigators (8 grants). None of the LCHs were listed as the research site for these grants/funds. These 17 authors accounted for 170 (21.3%) of the total number of publications, and their 9 LCHs accounted for 537 (67.3%) publications.

Hospital size and geographic location

LCHs with fewer than 300 beds and 70 000 acute patient days seemed to consistently produce fewer than 10 publications over the study period, but there did not appear to be any consistent relationship between research productivity and either bed size or acute patient days in the larger LCHs (Figure 5).

Figure 5: Relationship between research publications and (a) LCH bed size and (b) LCH acute patient days. The vertical line in (a) 300 beds and (b) 70 000 acute patient days.

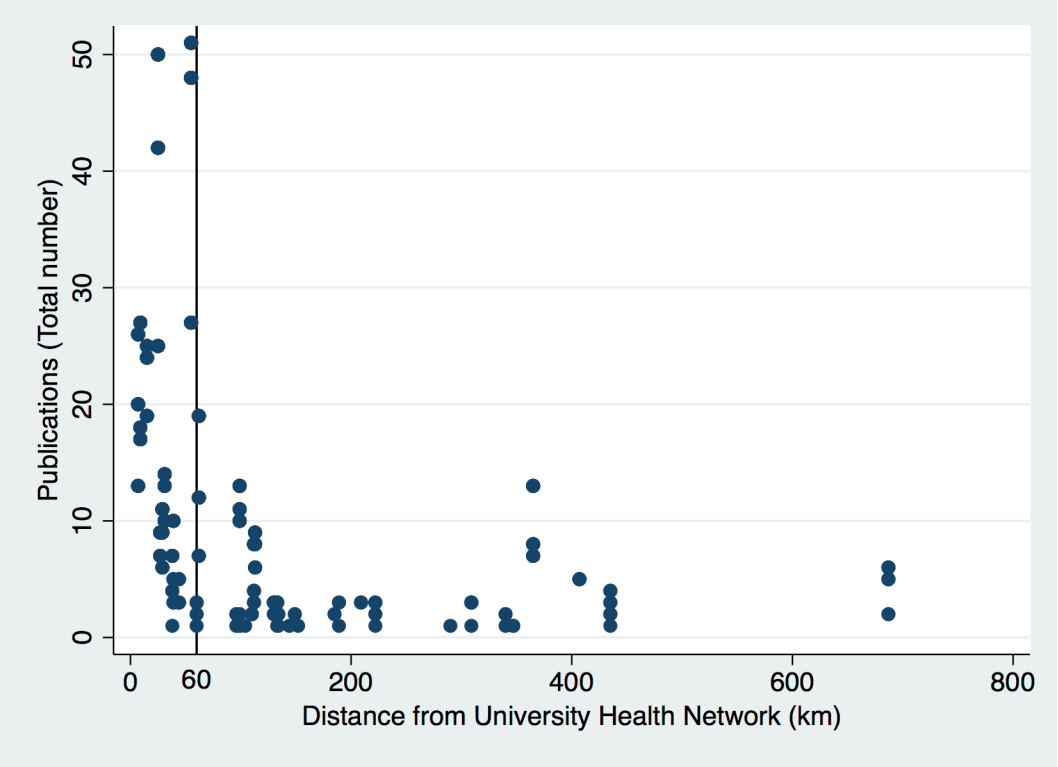


Geographic proximity to academic centres was not correlated with research publications except for those LCHs close to Toronto, Canada's largest city and healthcare network (Figure 6).

DISCUSSION

Researchers affiliated with Ontario's LCHs contributed to 798 research publications from 2013 to 2015, with 34% and 33% identified as the first author and/or corresponding author, respectively. While 40% of primary research publications were focused on locally relevant research

Figure 6: Research publications and geographic proximity to Toronto



questions, collaboration among researchers either within or between LCHs was infrequent, occurring less than 22% and 8% of the time, respectively. Most of the research publications were done by a core group of funded researchers affiliated with a few LCHs, a finding consistent with the general research community [26]. The scoping review doesn't reveal whether these core researchers are embedded within their LCHs acting to build research capacity across the entire organization or whether they are simply 'lone' researchers collaborating with external partners to pursue their own academic research interests [27].

The influence of academic centres on research productivity was only evident for those LCHs located near Toronto, more likely reflecting the positive impact of that region's population density, along with similar demographic profiles and healthcare infrastructures on facilitating the formation of research networks, an important criterion for promoting iKT [5, 28-32]. In addition, the largest LCHs were located near Toronto, suggesting that their increased participation in research was partly related to their size, a surrogate for increased research capacity.

The involvement of LCHs' researchers as contributing authors in secondary publications was correlated with an increase in publications in which they were the principal investigator, suggesting that involvement in these research studies may have led to any increased capacity to undertake independent research activities by either the researcher or their LCH. However, this observation more likely represents an epiphenomenon whereby secondary publications are simply related to an increased tendency of certain LCHs or LCHs' researchers to conduct research [29, 32].

This scoping review was mostly dependent on the accurate identification of authors' affiliations to characterize the research activities of Ontario's LCHs. Despite attempts to identify all relevant articles through multiple strategies, it is possible that we have underestimated the number of research publications involving Ontario's LCHs [33]. However, given the

consistency of findings from both year to year and within LCHs, and the comprehensiveness of the 3 indexed databases that were searched, it suggests our observations capture the vast majority of research publications associated with LCHs' researchers, and more than adequately permitted us to describe the current research activities of Ontario's LCHs and their researchers.

While the relationship between authorship order and investigator contribution remains open to interpretation [21-24], this study assumed a precedential and consistent approach to the assignment of primary and secondary research contributions, making conclusions from these classifications teleologically appropriate. We used the number of research publications as a surrogate for describing the research activity of Ontario's LCHs and LCH researchers [33], recognizing that publication is an imperfect measure for research activity [34]. In addition, this scoping review excluded other sources of program evaluation and quality improvement [35], potentially underestimating the impact of iKT on healthcare services research. The study period was only 3 years, a time frame that should have adequately, albeit imperfectly, allowed us to describe a trend. While this study included multiple sites, the findings may not be relevant to other jurisdictions outside the province of Ontario.

In Canada, the Canadian Institute for Health Research (CIHR) is the largest public research funding agency. The CIHR have created three iKT

funding opportunities: Partnerships for Health System Improvement, Knowledge Synthesis, and Knowledge to Action [36]. All three funding opportunities require that a researcher from a funding-eligible institution lead the project, but that they collaborate with community partners. Ideally, the collaboration should be structured to ensure that partners play an equal role in all aspects of the research study. Unfortunately, a recent qualitative evaluation of this approach suggested that these partnerships were rarely egalitarian; with 55% and 11% of community-based partners responding they had only an advisory capacity or a token role within the 'collaborative' partnership, respectively [36]. This is a consistent finding across other jurisdictions [30, 31]. While some Ontario studies have demonstrated the benefit of the iKT research model compared to end-of-grant knowledge translation models [37, 38], evaluations of the effectiveness of these iKT partnerships to improve knowledge translation has never been compared against any other model of community-initiated and community-led research projects conducted in the absence of academic partners, making any conclusions drawn by these funding agencies and academic hospitals highly susceptible to confirmation bias and invalid conclusions [5, 39].

Ontario's LCHs are responsible for the majority of acute healthcare services provided to the province's residents, yet these organizations seem to have minimal influential involvement in research activities; they

publish rarely and have no access to public research funds or grants. What is not clear from this scoping review is whether these organizations want to be involved in research, and if they do, what do they aspire to achieve and how do they intend to do it? What is certain is that Ontario's healthcare system needs these LCHs to become more engaged in effectiveness evaluations to ensure the sustainability of our Medicare system. How best to do this is unclear at this time. Most research agencies support academic-led iKT research models as a potential solution, but there are no clinical trials that demonstrate the superiority of this model compared to other models, such as embedding local researchers to support local research initiatives [27]. We suspect that each LCH may require a different approach, with LCHs with similar healthcare infrastructure and patient demographics to neighbouring academic centres utilizing a traditional iKT collaborative approach, whereas other LCHs in other regions without those academic relationships engaging local researchers and neighbouring LCH networks to achieve the same goals for their patients.

The optional last stage of a scoping review involves consulting stakeholders for their insight, and we intend to interview the 454 unique LCH authors identified in this study via a survey questionnaire regarding the validity of our data and their interpretations of our study findings and opinions about LCH involvement in research. By doing so we hope to

understand how to promote, build and support current and future LCH research capacity.

CONCLUSIONS

There are many drivers of poor medical care that compromise both patient outcomes and the sustainability of our healthcare systems. More research by the usual suspects supported by the same funding agencies is not the solution. What is needed is greater democratization of research funding and participation by patients and parts of the healthcare system that are currently excluded. Until that happens, no amount of tinkering with strategies such as iKT will succeed in reducing the research to practice gap.

DECLARATIONS

Ethics Approval

None required

Consent for Publication

None required

Availability of Data

The search results for all the retrieved articles are available upon request.

Competing interests

The authors declare no competing interests.

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Chapter 3: Can An Antimicrobial Stewardship Program Reduce Length Of Stay Of Immune-Competent Adult Patients Admitted To Hospital With Diagnosis Of Community-Acquired Pneumonia? Study Protocol For Pragmatic Controlled Non-Randomized Clinical Study

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Declaration of Academic Achievement

GD conceived the study, design and analytic plan, was directly involved in the implementation of the intervention, and drafted the protocol manuscript.

LM was directly involved in the implementation of the intervention, and edited the protocol manuscript

JB, MS and LT were involved in the design and analytic plan, and edited the protocol manuscript.

All authors read and approved the final manuscript.

Having established that the majority of Ontario's large community hospitals were not participating in or conducting research, we set out to establish the value of embedding research into our health services programs. We believed that if we could demonstrate the value of embedding research into our daily clinical practices, this would provide a proof-of-concept of the value of embedding research and researchers into everything we did as a health care centre. In so doing, we believed this would help with the transformation of our hospital into a learning health centre. We had an ideal opportunity in 2013 with the announcement from Accreditation Canada that antimicrobial stewardship programs would now be required organizational practices for all acute care hospitals. The Royal Victoria Regional Health Centre declared it would commit to this new Accreditation Canada standard by committing funding for a 2-year period to support a full-time pharmacist and a part-time clinician researcher. The stipulation was that the program specialists would embed a research program into this funded program to demonstrate improved outcomes by the end of the 2-year funding period. The program specialists decided that whatever research questions they asked, the results would have to lead to not only improved patient and organizational outcomes, but also new knowledge that could be disseminated to other health services programs throughout our own and other similar organizations through publication in peer-reviewed journals among other translational modalities. This recognition would be critical to the demonstration of the value of embedding research and researchers within the organization. In addition, it would establish the new standard by which all-future local health services research would be judged. In 2013, antimicrobial stewardship programs had not yet been shown to reduce length of stay of patients hospitalized with community-acquired pneumonia. In addition, evaluations had never characterized the intervention as a time-variant variable, a very practical and important confounding issue when evaluating the effectiveness of these programs in resource-limited centres. Another important outcome was the impact of our program on rates of *Clostridium difficile* infection on different wards. Up to that time, hospitals were treated as homogeneous units as opposed to wards with heterogeneous pooled risks for *Clostridium difficile,* thus potentially diluting the positive impact of stewardship activities on this hospital-acquired infection. Chapters 3 and 4 contain our publications about the impact of our stewardship activities on length of stay. Our publication about the impact of our stewardship activities on rates of *Clostridium difficile* infection are not part of this thesis document because

it represents the work done in my independent study proposal. That publication is available at:

https://doi.org/10.1371/journal.pone.0157671

Abstract

Background

Pneumonia is responsible for a large proportion of hospital admissions and antibiotic utilization. Physician adherence with evidence-based pneumonia management guidelines is poor. Antimicrobial stewardship programs (ASP) are an effective intervention to mitigate against unwarranted variation from these guidelines. Despite this benefit, ASP have not been shown to reduce the length of stay (LOS) of hospitalized patients with pneumonia. In immune-competent adult patients admitted to a hospital ward with a diagnosis of community-acquired pneumonia, does a multi-faceted ASP utilizing prospective chart audit and feedback compared with usual care reduce the LOS without increasing the risk of death or readmission at 30 days post-discharge from hospital?

Methods/Design

Starting on April 1, 2013, all consecutive immune-competent adult patients (>18 years old) admitted to a hospital ward with a positive febrile respiratory illness screening questionnaire AND a diagnosis of pneumonia by the attending physician will be eligible for inclusion in this non-randomized study. All eligible patients who fulfill the ASP review criteria will be exposed to a prospective chart audit, followed by an ASP recommendation(s) provided to the attending physician. The attending physician is responsible for implementing or rejecting the ASP

recommendation(s). Modified stepped wedge design with a baseline data collection period of three months, followed by the non-random sequential introduction of the ASP intervention on each of four hospital wards. Single community-based, academic affiliated 339-bed acute care hospital located in Barrie, Ontario, Canada. The primary outcome is hospital LOS and secondary outcomes include days and duration of antibiotic therapy, and inadvertent adverse outcomes of 30 day post-discharge mortality and hospital readmission rates. Differences in outcomes will be assessed using extended Cox regression analysis. Time to ASP intervention is included as a time-dependent covariate in the final model to account for time-dependent bias.

Discussion

By designing a pragmatic clinical trial with unique design and analytic features, we not only expect to demonstrate the effectiveness of a real-world ASP, but also provide a model for program evaluation that can be used more broadly to improve patient safety and quality of care.

Trial Registration: ClinicalTrials.gov NCT02264756. Registered 14 October, 2014.

Keywords

Pragmatic clinical trial, stepped wedge design, time-dependent bias, antimicrobial stewardship, length of stay, community-acquired pneumonia, natural experiment

Background

Community-acquired pneumonia

Community-acquired pneumonia (CAP) is defined as an acute infection of the lower respiratory tract in patients residing outside of hospital for 90 days or more before presentation (1). Residents residing in long-term care homes or nursing homes are frequently diagnosed as having a microbiologically variant form of CAP, but there is little evidence to support this classification system (2, 3). There is no gold-standard diagnostic test or criteria for CAP (4), so the diagnosis is made clinically using a constellation of clinical signs and symptoms and diagnostic tests.

In Ontario, pneumonia is the leading cause of death from bacterial infections and accounts for over 18,000 years of life lost annually due to premature mortality (5). Pneumonia accounts for the majority of antibiotic utilization in both hospital and outpatient settings (6, 7). Evidence-based guidelines for the diagnosis and management of pneumonia are available to physicians (1, 8-12). Adherence to these evidence-based guidelines is associated with both reduced mortality and antibiotic utilization (13-18).

Antimicrobial Stewardship

Antimicrobial stewardship is defined as any intervention that minimizes unwarranted variation in antimicrobial utilization from evidence-based best practice with the intent of improving patient safety and quality of care (19). Unwarranted refers to the absence of patient- or disease-specific reasons

to justify practice variation from evidence-based practice standards. Antimicrobial stewardship can be operationalized in many different ways, but prospective audit and feedback (persuasive approach) and restricted antimicrobial prescribing policies (restrictive approach) appear to be the most efficacious interventions to achieve the goals of antimicrobial stewardship (19, 20). Antimicrobial stewardship programs have demonstrated efficacy in improving antimicrobial prescribing and reducing rates of hospital-acquired infections (20). Antimicrobial stewardship programs directed to CAP patients have demonstrated reductions in mortality (15, 21), but have failed to demonstrate reductions in length of stay (20). Of note, the study by Fine *et al.* (22) used a cluster randomized controlled trial design to examine the impact of an antimicrobial stewardship program on hospital length of stay in CAP patients. This was the only study to model length of stay as a time-to-event occurrence and differences between the length of stay in the intervention and control groups was assessed by survival analysis. The intervention consisted of prospective chart audit starting on day 3 of hospitalization and physician feedback in the form of a recommendation suggesting the optimal timing of conversion from intravenous to oral antibiotics. The intervention was modeled as a time-invariant dichotomous variable in the final model despite the timing of the recommendation varied by up to 7 days from the time of enrollment. The hazard ratio for discharge was 1.16 (95% CI 0.97,

1.38) for the intervention group, suggesting a non-significant reduction in length of stay of 16%. It is unknown whether this hazard ratio would have reached statistical significance if the intervention was modeled as a time-dependent covariate in the final model as unaccounted-for time-dependent bias may have diluted the final intervention effect point estimate (23).

Research Question

In immune-competent adult patients admitted to a hospital ward with a diagnosis of CAP, does a multi-faceted ASP utilizing prospective chart audit and feedback compared to usual care reduce the length of hospital stay and days and duration of antimicrobial therapy without increasing the risk of death or readmission at 30 days post-discharge from hospital?

Methods

Setting

All participants will be admitted patients to the Royal Victoria Regional Health Centre (RVRHC), a 339 bed community-based, university-affiliated, acute care hospital located in Barrie, Ontario, Canada. The RVRHC is the only hospital serving the 128,000 residents of Barrie. Access to acute medical care for Ontario residents, including all hospital services, is publicly funded by the Ministry of Health and Long-Term Care, the provincial agency responsible for funding and oversight of Ontario's Medicare system. All patients enrolled in the study will be admitted to one of four medical wards. All study patients will be admitted to a hospitalist

service. Admission to any medical ward is controlled by bed allocation, a non-medical administrative service within the hospital responsible for patient flow and assigning patient care. Hospitalists are not assigned to any one specific medical ward, but provide care across all medical wards.

Population

Starting on April 1, 2013, all consecutive adult patients (≥ 18 years old) with the following inclusion criteria will be screened for enrollment in the study (5):

i) have a positive Febrile Respiratory Illness (FRI) screen on admission to hospital (http://www.health.gov.on.ca/fr/public/programs/emu/sars/reports/dir_122303_acute_care_nonoutbreak.pdf), AND

ii) diagnosed with pneumonia by the admitting physician (Acute exacerbations of chronic obstructive lung disease are considered within the definition of pneumonia for the purposes of this study as they are commonly treated with the same antimicrobial regimens as patients with pneumonia), AND

iii) admitted to a medical ward

All patients who meet the aforementioned criteria will be eligible for the intervention except for those with the following exclusion criteria (5):

i) hospitalized for ≥ 48 consecutive hours in the preceding 3 months, OR

ii) receiving immunosuppressants [defined as ≥ 40 mg prednisone daily (or steroid equivalent) for ≥ 2 weeks preceding hospitalization OR any other immunosuppressant used for systemic illness OR to prevent transplant rejection], OR

iii) neutropenic [defined as a polymorphonuclear count ≤ 0.5 x 10^9 cells/L] from any cause, OR

iv) immunocompromised [defined as having leukemia, lymphoma, HIV with CD4 cell count ≤ 200, splenectomy or on cytotoxic chemotherapy], OR

v) admitted to high acuity units such as intensive care units, OR

vi) require mechanical ventilation, either non-invasive or invasive, OR

vii) have a life expectancy of ≤ 3 months (palliative)

Intervention

All eligible CAP patients who meet the ASP review criteria will be exposed to the ASP intervention. The ASP intervention (ASP-i) consists of a prospective chart audit and physician feedback (persuasive) approach (24). The ASP members who conduct all the audits and make recommendations consist of an infectious diseases-trained pharmacist (LM) and an infectious diseases trained physician (GD). All patients are reviewed by both members. The ASP intervention (ASP-i) recommendations are guided by the Infectious Diseases Society of America CAP guidelines (1) and the Canadian Thoracic Society guidelines for the management of chronic obstructive pulmonary disease (25). The

possible ASP-i recommendations are based on those recommended by the National Health Service in the United Kingdom (24) and include the following:

i) No change to current care

ii) Discontinue antibiotic(s)

iii) Intravenous to oral conversion

iv) Duration of therapy

v) Dosing change

vi) Narrow or broaden spectrum of therapy

The ASP-i recommendations are not mutually exclusive. All recommendations are documented in the patient's electronic medical record and communicated directly to the attending physician by the ASP members.

Study design

This is a pragmatic controlled non-randomized clinical study intended to measure the effectiveness of a 'real world' program (26). The ASP-i will be implemented in a modified stepped wedge design (27); baseline patient data will be collected for all enrolled patients on each of the medical wards for the first three months of the study, and then the ASP-i will be introduced to each medical ward in a non-randomized sequential fashion in two month intervals until all medical wards are exposed to the intervention. This design was chosen for several reasons; the

preponderance of evidence suggests antimicrobial stewardship interventions are beneficial to patient safety and quality of care (28), human resource limitations in rolling out the program simultaneously to all wards, and the design has the advantage of a contemporaneous control group for comparison. The unit of randomization in this study could have been the four medical wards, however, randomization of the wards was not included in the design. The allocation of CAP patients to one of the four medical wards is controlled by bed allocation, an administrative branch of the hospital. Bed allocation was blinded to the study and the process of patient allocation is solely dependent on bed availability. In addition, the CAP patients, regardless of their ward location, were all admitted to the hospitalist service. The hospitalist service provides coverage across all four medical wards and has no influence on the allocation of patients to any of the wards. In essence, the patients will be 'naturally' allocated to one of the four medical wards and one of the attending hospitalists by a bed allocation process that is blinded to the intervention, so that the additional randomization of the wards themselves should provide very little benefit with respect to minimizing selection bias. In addition, the four medical wards can all accommodate CAP patients, however, one of the medical wards has historically accommodated more CAP patients than the other three. As a result, this ward was chosen as the first ward to be exposed to the ASP-i as this would ensure that the

maximal number of CAP patients would have earlier access to the ASP-i. The ethical principle of utilitarianism was used to guide the order of ward exposure to the ASP-i. The target of the intervention is the most responsible physician (hospitalist), while the unit of analysis will be individual patient outcomes adjusted for potential clustering effects within hospital wards.

Outcomes

The primary outcome is length of hospital stay (LOS) measured in minutes from the documented time of admission to the documented time of discharge (or censoring). These times are determined and entered into the patient's electronic medical record by bed allocation who are blinded to the intervention. The secondary outcomes are days and duration of antibiotic therapy. The start and stop dates corresponding to antibiotic administration while the patient is admitted to hospital are entered into the patient's electronic medical record by pharmacy assistants who are blinded to the intervention. All inpatient antibiotic administration was verified through the paper-based medical administration record by a pharmacy assistant blinded to the intervention. The days of antibiotic therapy is defined as the total number of days of all antibiotics administered to the patient both while in hospital and after discharge. The duration of antibiotic therapy is defined as the number of days that the patient received antibiotics both while in hospital and after discharge. For

example, if a patient received 2 antibiotics for 4 days over the same time period, then the days of antibiotic therapy = 8 days and the duration of antibiotic therapy = 4. The relevance of collecting both days and duration of therapy is that days of therapy is considered a valid metric for monitoring and comparing antibiotic utilization both within and across hospitals whereas duration of therapy is necessary for determining adherence with best-practice treatment guidelines (29). All antibiotic data from discharged patients will be extracted (LM or GD) from the physician discharge summary and every patient will be contacted at 30 days post discharge to verify their adherence with the prescribed antibiotic record from the discharge summary. Other secondary outcomes included the inadvertent adverse outcomes of readmission and mortality at 30 days post-discharge from hospital. Readmission to hospital is determined through telephone survey with the patient and verification through the Royal Victoria Regional Health Centre patient database. Survival is determined through telephone survey with the patient, and for those patients who cannot be reached by telephone, their status is verified through the Ontario vital statistics registry.

Participant Timeline

Enrollment of patients started on April 1, 2013. The study is expected to enroll patients until March 31, 2015. All consecutive patients that meet the inclusion criteria and have no exclusion criteria will be eligible for the

intervention. The ASP-i intervention may be implemented anytime after 48 hours post-admission in those patients who meet the criteria for ASP review. All patients who have not experienced an outcome at 14 days after admission will be censored from the study. Patients who die or are transferred from the ward (to the intensive care unit or other hospital) will also be censored. Patients who are discharged from hospital and are not censored will be contacted at 30 days post-discharge to determine their adherence with antibiotic prescription (if relevant), survival status and readmission status.

Sample Size

The sample size expected for the current study is 'fixed' and has been previously estimated to be between 400 to 500 CAP patients per calendar year (30). The accrual period will be 24 months. Assuming 70% of patients in the control arm will achieve the primary outcome of being discharged alive from hospital, and setting power = 0.8 and statistical significance (2-sided) $\alpha = 0.05$, the detectable ASP-i effect size is estimated to be up to an approximately 20% reduction in length of stay (31). The *stpower cox* command in STATA/MP 13.1 for Mac used for the calculation (32).

Recruitment

All consecutive immune-competent adult patients admitted to a hospital ward with a diagnosis of CAP will be enrolled in the study to ensure

maximum enrollment.

Assignment of Intervention

Given the 'naturally' blinded allocation process of patient admission to one of four medical wards, the pressure to demonstrate an early impact to administrators and the ethical principle of utilitarianism, the ASP-i will be implemented on the medical ward most likely to accommodate the majority of CAP patients. The remainder of the wards will be sequentially exposed to the ASP-i based on the ward most likely to care for the most to the least number of CAP patients based on historical admission patterns.

Blinding

It was not possible to blind the ASP members or the attending physicians to the ASP-i. The ASP members were not blinded to the outcome assessment, but this should have minimal risk of bias given the objective nature of the primary and secondary outcomes. The principal investigator was also responsible for data analysis given the absence of biostatistical expertise at the hospital, the absence of funding to support external biostatistical services, and the need to create quarterly reports for the hospital administrators as required by the employment contract between the Royal Victoria Regional Health Centre and the principal investigator.

Data Collection

All patient-level data will be extracted from the patient's electronic medical record by the ASP members using a standardized electronic data

collection form that is accessible on a portable tablet computer. The elements of the data dictionary defining the variables and instructions for data abstraction have been pre-programmed into each variable's respective field and can be accessed at the point of care by touching the field name. Other techniques to ensure internal validity of the data include pre-programmed data integrity constraints such as range checking and logical data edits, pre-defined value lists in drop-down menus for the vast majority of data elements and summary descriptive statistics for all continuous variables will be calculated within each patient record to permit real-time review to identify any potential outlying values. External validity of the data will be assessed by an external reviewer on a biannual basis using a random sample of 10% of the database. The data elements that will be audited by the external reviewer include only those elements that are included as either outcomes or covariates in the final statistical model and are feasible to validate against an objective source. Access to patient-level data is restricted to the ASP members. All patient-level data will be protected according to the Personal Health Information Protection Act of Ontario regulations (http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm.).

Statistical Methods

An extended Cox regression analysis that models the ASP-i as a time-variant covariate will be used to compare the primary and secondary

outcomes between the control and intervention groups (33). Violations of the proportional hazards assumption for each covariate will be identified by using the method of Schoenfeld residuals combined with the graphical method of log-log survival curve analysis (33). Results will be reported as hazard ratios with 95% confidence intervals. Patients who remain in hospital beyond 14 days will be administratively censored. Competing events such as death or transfer from a medical ward to a critical care unit will be assumed to be non-informative conditional on the covariates included in the final model (33). Time to ASP-i will be modeled as a time-variant covariate in the final model to account for any time-dependent bias (23). The ASP-i exposure will be coded as a dichotomous variable; 0=no ASP-i that switches to 1=ASP-i at the time of the ASP-i and remains 1 throughout the remainder of the follow-up time. This method treats a patient who has received an ASP-i as a non-ASP-i patient prior to the intervention. Other variables known to be associated with the primary and secondary outcomes will also be included in the final model (5), and include; age, sex, Charlson comorbidity index, CURB-65 score, time (days) to clinical resolution, and complications from pneumonia such as empyema. Fixed effects of wards on the outcomes will accounted for by including them as indicator variables in the final model. Maturation of ASP-i effect on outcomes over time will be adjusted by including a categorical time variable in the final model (time variable will be defined as

'quarter' from start of study). A dichotomous variable for acceptance or rejection of the ASP-i will be part of an interaction term with the control/intervention group variable to permit a per protocol analysis. Sensitivity analysis will be done using a competing events Cox regression model to determine the impact of the assumption of the non-informative nature of events such as death and ICU admission (34).

Monitoring

The hospital administration requires quarterly reporting of primary and secondary outcome variables. Secondary adverse outcomes such as mortality and readmission rates to hospital within 30 days after discharge will be monitored in real-time by pre-programmed calculation of relative risk ratios adjusted by the LACE score (35). Relative risk ratios > 1.2 for death or readmission at 30 days post-hospital discharge for the intervention group will be used to notify the hospital administration that an inadvertent adverse event may be due to the intervention, and an external safety monitoring committee of the Hospital Pharmacy and Therapeutics committee will be responsible for auditing the program. This relative risk ratio was chosen by the hospital administration as a reporting trigger.

Research Ethics

The study has received Research Ethics Board approval from the Royal Victoria Regional Health Centre (REB document entitled "*Intervention study of the impact of an antimicrobial stewardship program (ASP) on the*

length of stay of patients admitted to Royal Victoria Regional Health Centre with a diagnosis of community-acquired pneumonia (CAP) using a before-and-after quasi-experimental study with a control group. A waiver of informed consent was approved by the Research Ethics Board due to the nature of the pragmatic clinical trial (36, 37) based on the minimal risk of harm to patients and that any ASP recommendation that is implemented will have required that the attending physician receive informed consent from the patient as per the usual process of care. A waiver for informed consent was also granted to the ASP members to contact the patients by phone at 30 days post-discharge in order to ensure the safety of the program with respect to its impact on readmission and mortality rates. Any protocol amendments or violations will be reported to the Research Ethics Board for review.

Discussion

Pragmatic clinical trials (PCT) are designed to embed research into practice in order to reduce the delay observed in translating clinical research into practice (38). PCT not only produce results that are immediately relevant to patients and stakeholders, but these results emerge from methodologically reliable designs (39). Despite these qualities, PCT made up only 2% of the registered clinical trials in ClinicalTrials.gov in the calendar year 2013 (Search terms: “pragmatic* OR practical* OR comparative-effective*” versus “clinical trials” (accessed

July 6, 2014)). In Canada, peer-reviewed research funding agencies dispensed over 45,500 grants and awards totaling more than $12 billion from 1999/2000 to 2013/2014, but only 480 of these totaling $118 million were used to support PCT (Canadian Research Information System, http://webapps.cihr-irsc.gc.ca/cris/search; Search terms: "pragmatic, practical, comparative-effectiveness" (accessed July 6, 2014)). None of these grants and awards were used to support community-based PCT. While this PCT is designed to demonstrate the effectiveness of an ASP-i designed to reduce the length of hospital stay of CAP patients, an important finding that has yet to be published, it is also meant to demonstrate both the feasibility and value of research that is conceived and conducted by community-based healthcare providers. Given that more than 60% of all inpatients in Ontario are admitted to community-based hospitals (Healthcare Indicator Tool, Health Data Branch, MOHLTC, https://hsimi.on.ca/hdportal/ (accessed May 1, 2014)), it is essential that community-based healthcare providers are invited to conceive of locally relevant research studies that are eligible for dedicated peer-reviewed funding opportunities. This study is intended to be an example and guide for those community-based healthcare providers interested in contributing to improving their healthcare programs and systems by using PCT designs.

There are no previous studies examining the effectiveness of a prospective audit and feedback ASP-i on important patient outcomes that account for time-dependent bias. In general, these ASP-i are time-dependent interventions that have been incorrectly included as time-invariant covariates in statistical models. From an epidemiological perspective, these ASP-i are not present at the time of hospital admission but are 'acquired' at some point in time after admission to hospital. In the biased analysis, patients who are exposed to an ASP-i are analyzed as though the ASP-i had occurred at the time of hospital admission thereby increasing the denominator of the LOS hazard. The result of this mis-specification is a reduction in the LOS hazard in the ASP-i group. The resultant LOS hazard ratio will be biased and closer to 1, suggesting the absence of any beneficial ASP-i effect (23). This study is the first to account for time-dependent bias by including ASP-i as a time-variant covariate in the final statistical model.

This study has several challenges to its internal and external validity. First, the absence of medical ward randomization could introduce selection bias. However, the allocation of patients to the ward and their medical provider is determined through a 'natural' allocation process that is blinded to the study, thus minimizing this potential source of bias. Secondly, the ASP members are not blinded to the intervention, outcomes assessment or data analysis. However, the likelihood of introducing bias

is minimal because the primary and secondary outcomes are stringently defined and objective. Thirdly, the risk of contamination is significant given that the hospitalists provide coverage across the 4 medical wards. It is conceivable that their behaviour will change over time as they become conditioned to the ASP-i and that this behaviour change may then precede the ASP-i as the study evolves over the 2 year period. The consequence of this contamination would be to bias the outcome hazard ratios toward a value of 1 or no ASP-i effect. However, a recent Cochrane review of the impact of audit and feedback on physician behaviour demonstrated only a 4.3% (IQR 0.5% to 16%) absolute increase in adherence with best practice (40), suggesting that the risk of contamination in this study may be small given the inherent resistance of physicians to changes in behaviour. In addition, the rate of ASP-i consults per month (defined as the ratio of the number of ASP-i consults to the number of eligible patients) will be modeled as time series data, and an assessment using regression analysis and the Durbin alternative test will be used to detect any serial correlation between the previous month(s)' ASP-i and the subsequent rate of ASP-i consults. Evidence of serial correlation between preceding ASP-i and subsequent rates of ASP-i consults would suggest possible contamination. Of course, contamination in this study may simply represent that the ASP was able to effectively change physician behaviour in a positive manner; a desirable impact for patient care albeit with some

undesirable effects on exposure-outcome evaluation. Fourth, the timing of the ASP-i at ≥ 48 hours after admission restricts the option of recommending earlier conversions from intravenous to oral antibiotics in eligible patients. Previous studies have suggested that earlier conversions might reduce LOS (41, 42). If the causal mechanism for reducing LOS is through this earlier conversion, then this study may not be able to detect this ASP-i effect. As a single hospital site study, the applicability of the results to other hospitals and programs is unknown. However, a multi-site study using the same design, intervention and analysis is currently being planned. Submissions of the proposal have been made to each participating hospital's Research Ethics Board. The anticipated start date of this multi-site study is May 1, 2015.

We believe that the ASP-i will lead to shorter lengths of hospital stay for CAP patients and reduced exposures to unnecessary antibiotics, both of which should result in reduced rates of hospital-acquired complications and healthcare costs. In addition, this study offers a model for community-based healthcare providers to conceive of and conduct PCT for the purpose of programmatic evaluation. By involving community-based hospitalized patients and their healthcare providers in translating research into practice, access to improvements in our healthcare system will finally be more equitably distributed and shared.

Trial Status

The study has enrolled 582 patients. The study will continue to enroll patients until March 31, 2015.

List of abbreviations

ASP, Antimicrobial Stewardship Program

ASP-i, Antimicrobial Stewardship Program intervention

LOS, Length of Stay

CAP, Community-acquired pneumonia

RVRHC, Royal Victoria Regional Health Centre

FRI, Febrile Respiratory Illness

Competing interests

None to declare.

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Chapter 4: Evaluating The Impact Of An Antimicrobial Stewardship Program On The Length Of Stay Of Immune-Competent Adult Patients Admitted To A Hospital Ward With A Diagnosis Of Community-Acquired Pneumonia: A Quasi-Experimental Study

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Declaration of Academic Achievement

GD conceived the study, design and analytic plan, was directly involved in the implementation of the intervention, and drafted the protocol manuscript.

LM was directly involved in the implementation of the intervention, and edited the protocol manuscript

JB, MS and LT were involved in the design and analytic plan, and edited the protocol manuscript.

All authors read and approved the final manuscript.

Abstract

Objective: Demonstrate an antimicrobial stewardship intervention can reduce length of stay for patients admitted to hospital with community-acquired pneumonia (CAP).

Study Design: Starting April 1, 2013, consecutive adult patients with CAP admitted to an acute care community hospital in Barrie, Ontario, Canada, were eligible for enrollment until March 31, 2015. Antimicrobial stewardship intervention was a prospective audit and feedback recommendation implemented in a stepped wedge design across 4 wards. The primary outcome was time to hospital discharge and secondary outcomes included time to antibiotic discontinuation and a composite outcome of 30-day readmission or all-cause mortality. Intervention effect was estimated by survival (time to discharge and antibiotic discontinuation) and logistic (30-day re-admission or all-cause mortality) regression analyses.

Results: Complete data was available for 763 patients. Primary outcome was observed in 196 (82%) control and 402 (77%) intervention patients. Length of stay was reduced by 11% (95% CI -9% to 35%). Time to antibiotic discontinuation was shortened by 29% (95% CI 10% to 52%). Odds ratio for 30-day readmission or all-cause mortality was 0.79 (95% CI 0.49 to1.29).

Conclusions: A prospective audit and feedback intervention did not significantly reduce length of hospital stay in CAP patients despite reducing overall antibiotic utilization.

Keywords: community-acquired pneumonia; antimicrobial stewardship; prospective audit and feedback; stepped wedge design; time-variant survival analysis; length of stay

Running Title: *Antimicrobial stewardship impact on length of stay in pneumonia patients*

1. Introduction

In the province of Ontario, Canada, pneumonia is the leading cause of death from bacterial infections and accounts for over 18,000 years of life lost per annum (1). Pneumonia accounts for the majority of antibiotic utilization in both hospital and outpatient settings (2, 3). Evidence-based guidelines for the diagnosis and management of pneumonia are available to physicians (4, 5). There exists significant unwarranted variation from these guidelines that is associated with both increased mortality and antibiotic utilization (6-10). Unwarranted variation refers to the absence of patient- or disease-specific reasons to justify practice variation from evidence-based guidelines. Antimicrobial stewardship interventions (ASi) are defined as any intervention that minimizes unwarranted variation in antibiotic utilization from evidence-based practice with the intent of improving patient safety and quality of care (11). ASi can be

operationalized in different ways, but prospective audit and feedback (persuasive approach) and restricted antimicrobial prescribing policies (restrictive approach) appear to be the most effective interventions to achieve the goals of antimicrobial stewardship (11-13).

ASi directed to community-acquired pneumonia (CAP) patients have failed to demonstrate reductions in length of hospital stay (12, 13). Length of hospital stay accounts for the majority of costs for CAP compared to any reductions in antibiotic utilization attributable to ASi (14) Given the high operational costs of antimicrobial stewardship programs that use prospective audit and feedback interventions, it is important to demonstrate that these programs can minimize the costs of caring for CAP patients. Of the three randomized controlled trials in CAP patients, only the study by Fine *et al.* modeled length of stay as a time-to-event occurrence (15-17). In this study, the ASi consisted of a prospective chart audit starting on day 3 of hospitalization and physician feedback in the form of a recommendation suggesting optimal timing of conversion from intravenous to oral antibiotics. The intervention was modeled as a time-invariant exposure in the final model despite the timing of the recommendation varied by up to 7 days from the time of enrollment. The hazard ratio for discharge was 1.16 (95% CI 0.97, 1.38) for the intervention group, suggesting a non-significant reduction in length of stay of 16%. Not accounting for time-variant bias may have diluted the ASi

effect toward a value of HR = 1 (18). In addition, Fine *et al.* did not use a competing risks model potentially leading to a biased ASi effect estimate (19).

Quasi-experimental, or observational, study designs are commonly used to evaluate real-world programs. This study design is at risk for estimating a biased average treatment effect due to the absence of investigator controlled treatment assignment and frequent absence of contemporaneous controls. The problem of contemporaneous controls can be minimized by using a stepped wedge study design(20) This design provides investigators with the opportunity to implement an intervention in a sequential manner over a number of time periods across all units (clusters). Not only does this provide a contemporaneous control group both within and across units, but all patients will ultimately receive the intervention which is important for those interventions in which a preponderance of evidence suggests overall patient benefit. The problem of treatment assignment ignorability can be minimized by using a matching strategy such as propensity score analysis that attempts to condition the average treatment effect on observable random variables used to minimize selection bias (21).

In the present study, we estimated the effectiveness of an ASi utilizing a prospective audit and feedback intervention to reduce the length of stay for patients admitted to hospital with CAP. The ASi was implemented on 4

wards in a single hospital using a stepped wedge design to ensure contemporaneous controls, and the time to hospital discharge was modeled using survival analysis. In addition, the ASi was modeled as a time-variant exposure variable, and outcomes such as death were treated as both censored and competing events.

2. Materials and Methods

The study protocol has been published elsewhere (22).

2.1 ***Setting.*** Single site, 339 bed community-based, university-affiliated hospital located in Barrie, Ontario, Canada. This is the sole hospital serving 128,000 Barrie residents. Patients admitted to 4 medical wards were enrolled in the study. All study patients were admitted to the hospitalist service.

2.2 ***Participants.*** Consecutive adult patients (≥ 18 years old) were enrolled for a 2 year period starting on April 1, 2013. Inclusion criteria for enrollment were diagnosis of pneumonia by the admitting physician, length of hospital stay ≥ 48 hours and prescribed either an oral second/third generation cephalosporin, any oral respiratory fluoroquinolone or any intravenous antibiotic ≥ 48 hours. Exclusion criteria included recent hospitalization in the preceding 3 months, receiving immunosuppressants, neutropenia, immunocompromise, admission to an intensive care unit or life expectancy ≤ 3 months.

2.3 ***Intervention.*** ASi consists of a prospective chart audit and physician feedback persuasive approach (23). The ASi occurred anytime after 48hrs post-admission. An infectious-diseases trained pharmacist (LM) and infectious-diseases trained physician (GD) conducted every ASi. The ASi recommendations were consistent with the Infectious Diseases Society of America CAP guidelines (4) and the Canadian Thoracic Society guidelines for the management of chronic obstructive pulmonary disease (24). All ASi recommendations were documented in the patient's electronic medical record and communicated directly to the attending hospitalist. All patients were contacted by telephone at 30 days post-discharge for follow-up of antibiotic use, and to determine 30-day re-admission and all-cause mortality events.

2.4 ***Design.*** This is a quasi-experimental stepped wedge controlled study intended to measure the effectiveness of a 'real world' program (25). The ASi was implemented in a non-randomized stepped wedge design across 4 medical wards (Figure 1) (20). The target of the ASi was the hospitalist, while the unit of analysis was individual patient outcomes adjusted for potential clustering effects within hospital wards.

Figure 1. Sequential implementation of ASi across 4 medical wards over the 24 month study period.

Ward	Type	Period																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
		2013m4	2013m5	2013m6	2013m7	2013m8	2013m9	2013m10	2013m11	2013m12	2014m1	2014m2	2014m3	2014m4	2014m5	2014m6	2014m7	2014m8	2014m9	2014m10	2014m11	2014m12	2015m1	2015m2	2015m3
3GA	Medicine	c	c	c	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
3GC	Medicine	c	c	c	c	c	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
4GC	Medicine	c	c	c	c	c	c	c	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
3SA	Medicine	c	c	c	c	c	c	c	c	c	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	c=control period (N=24); x=intervention period (N=96)																								

2.5 ***Sample size.*** Sample size for the study was 'fixed' and had been previously estimated at 400 to 500 eligible patients per calendar year (14). This study enrolled 763 patients, and 78.3% experienced the primary outcome (N=598 events). Setting power = 0.8 and statistical significance (2-sided) α = 0.05, the estimated ASi effect needed for detection was $\geq$ 20 % reduction in length of stay (26).

2.6 ***Outcomes.*** Primary outcome is length of hospital stay (LOS). Patients are administratively censored at 14 days post admission. Potential competing outcomes are death, transfer from the ward to an intensive care unit or transfer from the ward to another hospital. The secondary outcome was antibiotic discontinuation measured using days (DOT) and duration (DUT) of antibiotic therapy. DOT is defined as total number of days of all antibiotics administered to the patient both while in hospital and after discharge, while DUT is defined as number of days that

the patient received antibiotics both while in hospital and after discharge. For example, if a patient received 2 antibiotics for 4 days over the same time period, then DOT = 8 and DUT =4. The other secondary outcomes include 30-day re-admission or all-cause mortality determined through telephone survey or the hospital patient database.

2.7 ***Data Collection.*** Patient-level data was prospectively collected by LM and GD starting at the time of admission and continued until discharge, censoring or other event. The following variables were collected and considered for inclusion in the regression models; ASi (yes/no), ASi recommendation acceptance/rejection, Charlson comorbidity score (27), CURB-65 score (28), time to clinical resolution of pneumonia symptoms/signs (Halm's criteria) (29), gender, age at admission, presence or absence of clinical and radiographic criteria for pneumonia (30), duration of intravenous antibiotic therapy, complicated pneumonia (yes/no), LACE score (31), day of the week of hospital admission, and ward location.

2.8 ***Statistical methods.*** All variables were tested for time-variant effects using the method of Schoenfeld residuals combined with the graphical method of log-log survival curve analysis. ASi, time to clinical resolution of Halm's criteria, and duration of intravenous antibiotic therapy were time-variant (data not shown). Extended semi-parametric (Cox) and flexible parametric (Royston-Parmar) models were compared to determine best fit

to the observed data. Royston-Parmar parametric model was superior (data not shown) and was subsequently used to compare ASi effect on the primary and secondary outcomes (time to hospital discharge and time to antibiotic discontinuation, respectively) (32). Screening for equivalence of variables by ASi condition (yes/no) was done using the normalized difference score (21). Propensity scores for receiving treatment were estimated by including variables with a normalized difference score ≥ 0.25 in a logistic regression model. Likelihood ratio test of nested models was used to select the final model. The propensity scores were included as a continuous variable in the primary outcome survival analysis. The optimal degrees of freedom for both the time-invariant and time-variant variables of the Royston-Parmar model were determined by comparing the Akaike Information Criterion (AIC). Variables were tested for inclusion in the final model if univariate survival analysis demonstrated a p-value ≤ 0.2. The final model was built using step-wise forward selection using ascending p-values to determine the order of variable testing. Variables were retained if there was a significant likelihood ratio test p-value ≤ 0.05 compared to the nested model. Multicollinearity between variables in the final model was assessed using variance inflation factor. ASi effect is reported as a hazard ratio (HR) with 95% confidence intervals. Hazard ratio > 1 is interpreted as a shorter LOS for ASi-exposed patients, HR = 1 means no difference between the two groups, and HR < 1 means ASi-exposed

patients have longer LOS. To check for contamination or maturation of ASi effect, an interaction term between ASi and calendar quarter was tested for significance in the final model. To check for an ASi effect on duration of intravenous antibiotics, an interaction term was created between these two variables and tested for significance in the final model. Per protocol analysis was done by including a dichotomous variable for acceptance or rejection of ASi as part of an interaction term with ASi exposure. Sensitivity analysis for non-informative censoring assumption was done by comparing ASi effect estimate to a competing events Fine-Gray survival model (19, 33). The ASi effect is reported as a subdistribution hazard ratio (SHR) with 95% confidence intervals. SHR > 1, SHR = 1, and SHR < 1 is equivalent to the HR interpretation. ASi effect on secondary outcome of DOT and DUT was analyzed using the same survival models as for LOS. ASi effect on secondary outcome of composite of 30-day re-admission and all-cause mortality was analyzed by logistic regression analysis using the LACE score as the sole independent variable (31). Stata/MP 13.1 for Mac (64-bit Intel) was used for all analyses.

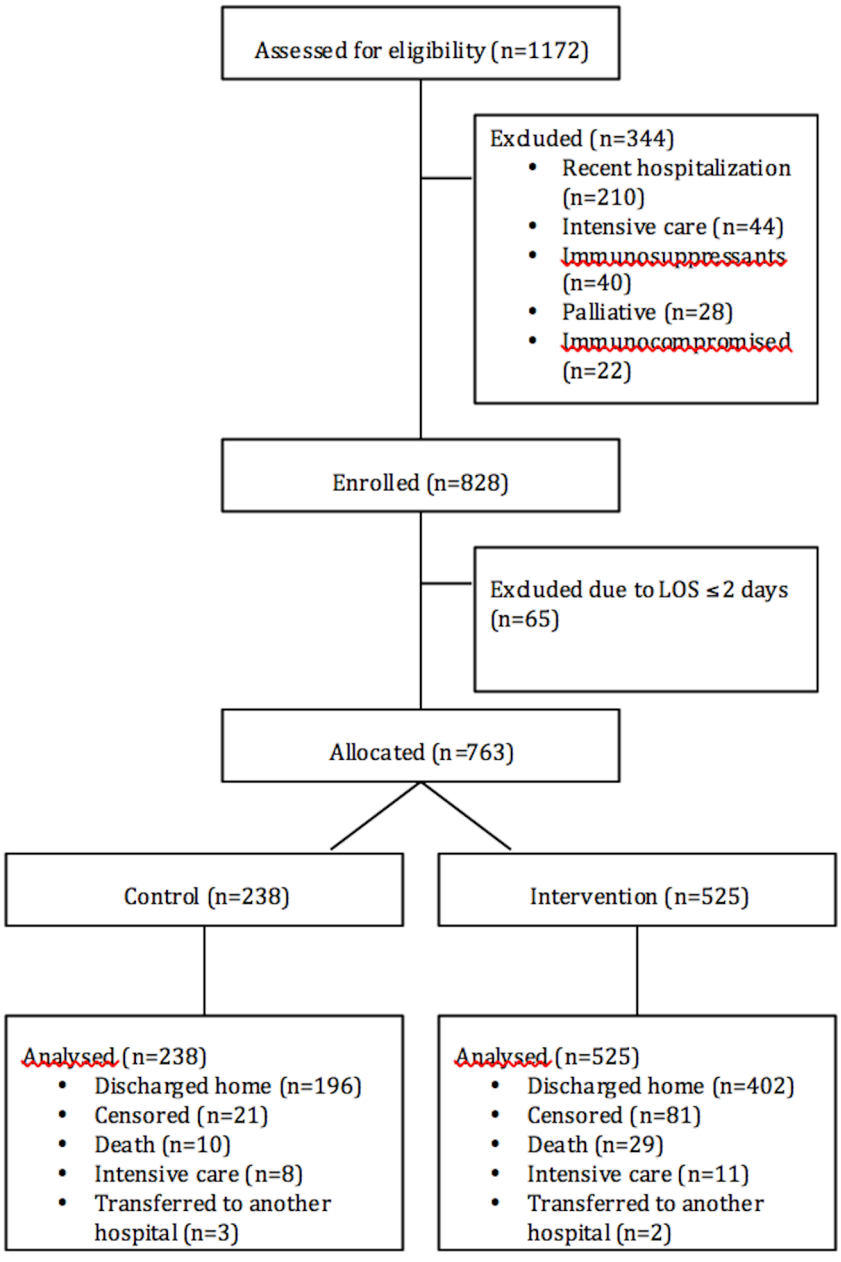
2.9 ***Research ethics.*** This study received research ethics approval from the Royal Victoria Regional Health Centre to begin patient enrollment on February 3, 2013. Annual re-approval by the research ethics board was granted to continue patient enrollment and follow-up ending on January

21, 2016. As the target of the ASi was the hospitalist, a waiver of informed consent was approved by the Research Ethics Board due to the nature of the quasi-experimental trial based on the minimal risk of harm to patients and that any ASP recommendation that was implemented will have required that the attending physician receive informed consent from the patient as per the usual process of care. A waiver for informed consent was also granted to the ASP members (LM and GD) to contact the patients by phone at 30 days post-discharge in order to ensure the safety of the program with respect to its impact on readmission and mortality rates.

3. Results

3.1 ***Patient characteristics.*** A total of 763 patients contributing 5,165.7 hospital days were included in the final analysis (Figure 2). Comparison of their baseline characteristics by ASi allocation using normalized difference scores ≥ 0.25 suggested potential imbalances in the CURB-65 score, gender, Halm criteria, and age at admission. Probability of ASi assignment conditioned on these covariates demonstrated only CURB-65 score (b_1=0.324, p<0.001) and gender (b_2=0.465, p=0.007) to be significantly predictive. Likelihood ratio test of nested models resulted in the exclusion of age (b_3=-0.005, p=0.46) and Halm criteria (b_4=0.019, p=0.86) from the final propensity score model.

Figure 2. Total number of patients screened, enrolled, and included in the analysis.



3.2 ***Time to ASi.*** Mean time to ASi was 2.84 days (sd 1.03). There was no significant difference in time to ASi across calendar quarters (χ^2=49.3, p=0.20) or wards (χ^2=20.1, p=0.51).

3.3 ***ASi Recommendations.*** 396 (75.4%) ASi recommended treatment change, and 356 (89.9%) were accepted. Of the 129 ASi recommendations for no change to treatment, 93 (72.1%) were accepted. The overall acceptance rate was 85.5%. Neither acceptance (χ^2=8.91, p=0.18) nor treatment change (χ^2=11.41, p=0.08) differed across calendar quarters. Neither acceptance (χ^2=2.72, p=0.44) nor treatment change (χ^2=1.28, p=0.73) differed across wards.

3.4 ***Length of stay.*** The null Royston-Parmar model with the best fit to the observed data included restricted cubic splines with 3 degrees of freedom for both the time-invariant and time-variant variables. Apart from ASi variable, no other variables demonstrated time-dependency. Regardless of the model used (Royston-Parmar or Fine-Gray), the ASi was not associated with a significant effect on LOS (Table 1).

Table 1. Comparative multivariate analysis of ASi effect on LOS using the Royston-Parmar proportional hazards model and the Fine-Gray competing risks model.

Effect	**Royston-Parmar**		**Fine-Gray**	
	Hazard Ratio	95% CI	SHR	95% CI
ASi (Time-independent)	0.65	0.54 to 0.78	1.11[a]	0.91 to 1.35
ASi (Time-dependent)		1.07 to 1.39		
Propensity score	0.38	0.12 to 1.26	0.20	0.06 to 0.70
Duration intravenous antibiotic therapy (day of therapy)	0.85	0.82 to 0.89	0.92	0.88 to 0.95
Age (every 10 year increment over 20 years old)	0.91	0.86 to 0.96	0.92	0.86 to 0.99
Complicated pneumonia (present)	0.77	0.62 to 0.96	0.63	0.50 to 0.79
Halm's criteria	0.81	0.79 to	0.88	0.86 to

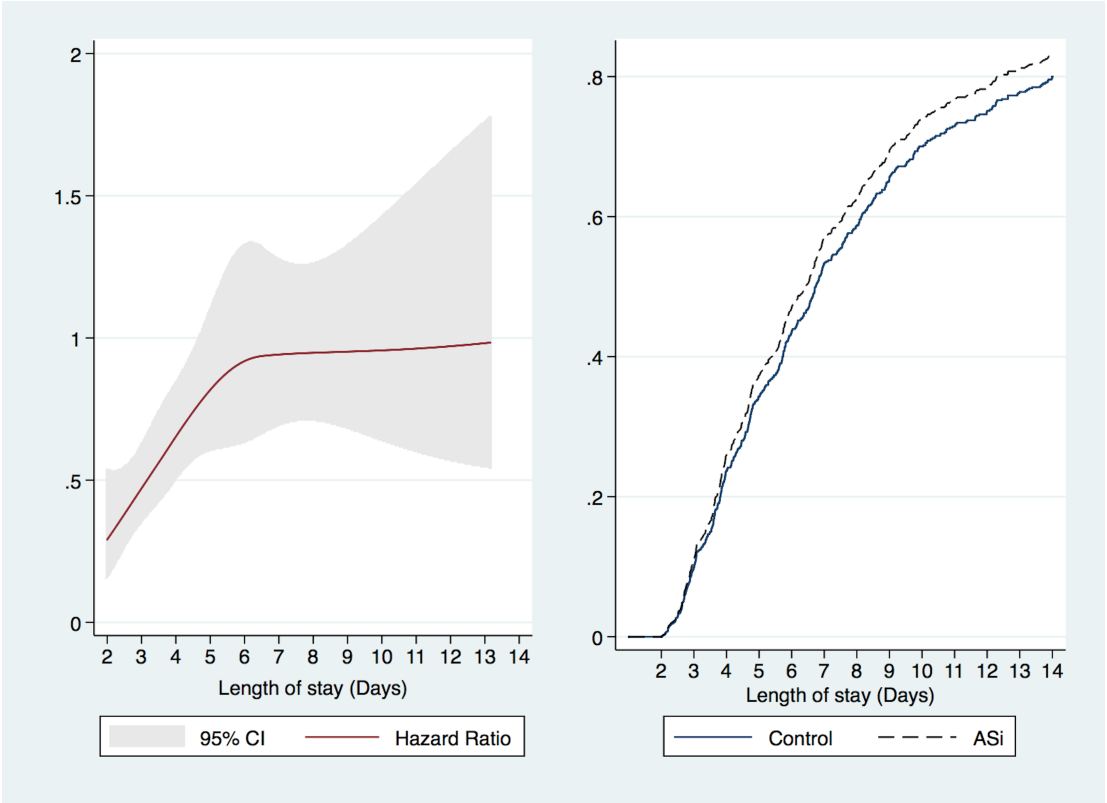
(duration in days)		0.84		0.90
Diagnostic criteria (present)	1.48	1.24 to 1.78	1.24	1.01 to 1.51
Admission day (Sunday reference)				
Monday	NS		1.80	1.23 to 2.64
Tuesday	NS		NS	
Wednesday	NS		1.61	1.12 to 2.31
Thursday	NS		NS	
Friday	NS		1.47	1.01 to 2.14
Saturday	NS		1.84	1.30 to 2.62

[a] Data split into 2 entries for each patient exposed to ASi at time of ASi, so each patient contributes to 2 risk periods (ASi = no and ASi = yes) to final analysis.

SHR=subdistribution hazard ratio; ASi=antimicrobial stewardship intervention; NS=not significant

The Royston-Parmar model had both time-variant and time-invariant ASi effects (Figure 3).

Figure 3. Left panel: Royston-Parmar multivariate model estimate of hazard ratio. Right panel: Fine-Gray multivariate model estimate of cumulative incidence functions. Ratio of cumulative incidence functions = subdistribution hazard ratio



There was disagreement between the two models, however, in the first 4 days of hospitalization with the Royston-Parmar model suggesting shorter LOS in patients not exposed to ASi. Neither model demonstrated any difference in the ASi effect by calendar quarter or ward (data not shown). Per protocol analysis did not demonstrate any differences in ASi effect in those patients who had rejected recommendations compared to accepted recommendations regardless of the type of ASi recommendation (data not shown).

3.5 ***Secondary outcomes.*** Over the entire study period, total antibiotic utilization was 7,999 DOT and 5,911 DUT. Distribution of DOT and DUT was right-skewed. Comparison of ASi effects estimated by Royston-Parmar and Fine-Gray models using similar covariates from LOS model demonstrated relative agreement, with both models estimating shorter DOT (average reduction of 24 versus 29%) and DUT (average reduction of 34 versus 65%) in the ASi groups, respectively (Table 2).

Table 2. Comparison of ASi effects by multivariate model.

Effect	Royston-Parmar		Fine-Gray	
DOT	**HR**	**95% CI**	**SHR**	**95% CI**
ASi (Time-independent)	1.24	0.99 to 1.56	1.29	1.10 to 1.52
ASi (Time-dependent)				
γ_1	0.99	0.80 to 1.22		
γ_2	1.02	0.87 to 1.20		
γ_3	0.91	0.83 to 1.01		
DUT[a]				
ASi (Time-Independent)	1.34	1.07 to 1.69	1.65	1.41 to 1.93
ASi (Time-dependent)				
γ_1	1.27	1.02 to 1.58		
γ_2	1.22	1.06 to 1.41		

[a] Restricted cubic splines with 2 degrees of freedom were used.

SHR=subdistribution hazard ratio; DOT=days of therapy;

ASi=antimicrobial stewardship intervention; DUT=duration of therapy

For intravenous therapy, antibiotic utilization was 3,129 DOT and 2,479 DUT. Estimated ASi effects demonstrated reduced antibiotic utilization for intravenous DOT between days 3 and 7, but no significant ASi effect on intravenous DUT. At 30-days follow-up, there were 85 unique composite outcomes with 56 in the ASi group and 29 in the control group. There was no difference in the composite 30-day re-admission and all-cause mortality with odds ratio 0.79 (95% CI 0.49, 1.29) for the ASi group.

4. Discussion

Our quasi-experimental study demonstrated the feasibility of implementing a community-based hospital program supported by a methodologically robust evaluation of its effectiveness. The stepped wedge design was necessary for practical implementation due to human resource limitations, but also provided a contemporaneous control group for analysis. Time-dependent bias can dilute effect estimates toward neutrality (18). This study modeled time to ASi as a time-variant variable since it was not present at the time of admission but occurred at some unique point in time later in a patient's hospitalization. Despite enrolling the required number of patients to demonstrate a clinically meaningful reduction in LOS, ASi did not significantly reduce the time to discharge despite having a substantial impact on reducing total antibiotic utilization. There are several possible explanations. In our study, the average LOS for patients who were discharged alive was 5.7 days (sd 2.9) suggesting it

may be difficult to further impact this already short LOS. Also, the majority of our ASi occurred after 48 hours of hospitalization possibly missing a critical period for early ASi. This may explain why our ASi did not appear to have a significant impact on intravenous antibiotic utilization. However, a recent study did not demonstrate any effect on LOS from early ASi (34). Another study has suggested that the only conservable days in pneumonia patients is timely discharge after achieving clinical stability since the risk of death and/or deterioration is < 1% after achieving clinical stability compared to 15% before this clinical endpoint (29, 35). In their observational study published in 1998 (29), Halm EA *et al.* demonstrated that the median time to clinical stability was 3 days (IQR 2 to 4) while the median stay in hospital after achieving clinical stability was 4 days (IQR 2 to 7). Contrast this to the findings from our study that demonstrated a median time to clinical stability of 3 days (IQR 1 to 4) while the median stay in hospital after achieving clinical stability was only 1 day (IQR 0 to 3) in both the control and intervention groups, demonstrating the significant reductions in LOS that have already occurred over time without any ASi. Our study did not directly measure the ASi effect on time to discharge after achieving clinical stability as an *a priori* outcome, but this will be reviewed as a secondary analysis. Lastly, ASi may need to be bundled with a comprehensive care plan that includes early patient mobilization,

aggressive weaning of supplemental oxygenation and home care supports to ensure optimal timing of hospital discharge (36).

Validity of survival analysis is dependent on the assumption of non-informative censoring. The study was designed to left-censor patients at 14 days after admission since stays in hospital beyond this time are unlikely to be due to CAP but rather due to hospital-acquired pathology (37). While left-censoring is non-informative, treating events such as death or intensive care unit admission as censored at the time of the event may result in informative censoring and bias the exposure effect estimate (19). Since there is no formal statistical test to validate the assumption of non-informative competing event censoring, the investigators collected data on an *a priori* established set of predictor variables related to death and severe illness requiring intensive care admission in order to attempt to condition these competing events as non-informative. In addition, there were only 63 total competing events in the study likely making their impact on the ASi effect minimal. Comparison of ASi effect estimates with a competing risks survival analysis was done using Fine-Gray model. The results for ASi effect were consistent across models suggesting that the non-informative assumption of censoring competing events was satisfied.

Strengths of the study included meeting its target sample size to detect a clinically meaningful ASi effect, including a propensity score weight for possible selection bias as a result of the absence of treatment

assignment, completeness of the data collected for analysis with no loss to follow-up including post-discharge antibiotic utilization, internal validity and reliability of the data collected by the 2 members of the program (LM and GD) using an electronic data collection tool with pre-programmed data integrity constraints and pre-defined value lists, presence of contemporaneous control patients by using a stepped wedge design, use of objective end points for both primary and secondary outcomes to minimize bias by un-blinded study design, inclusion of temporal interaction terms with ASi in the final model to rule out contamination or maturation effects, accounting for time-dependent bias by using extended statistical models, and inclusion of competing events and assessment for bias from non-informative censoring.

Limitations included single-site study making external validity of results unknown. Patients were allocated to wards by hospital administrators who were blinded to the study and according to bed availability. The absence of ward randomization should not have contributed to a biased average treatment effect given that the hospitalists caring for patients on these wards also cared for similar patients on the other wards and had no input into the allocation of patients to any of the wards included in the study. In addition, unobserved ward-level effects on both selection bias and outcome were accounted for in the final model. The ward-level effects on both primary and secondary outcomes were not

significant conditioned on the final model variables. Also, we included patients admitted with a history of chronic obstructive pulmonary disease in our study. While these patients may be considered to represent a distinct population from pneumonia patients, from a clinical standpoint, all of them receive antibiotic regimens similar to pneumonia patients and treatment guidelines are well established making this group very amenable to ASi within hospitals. The inclusion of this group of patients in CAP studies is commonly reported in the literature (37). In addition, this patient population was evenly distributed with 243 and 124 patients in the ASi and control group, respectively (p=0.136).

By using a well-designed quasi-experimental study, a small community hospital was able to evaluate the effectiveness of its ASi targeted at CAP patients. Despite the absence of effect on LOS, the ASi was able to reduce overall antibiotic utilization without compromising patient safety and quality of care. Antimicrobial stewardship activities vary across institutions, frequently limited by both financial and human resources especially in community-based hospitals, and studies such as ours are critical in establishing how these resource-limited programs should focus their activities in addition to providing guidance on how to evaluate program effectiveness in research-naïve institutions.

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Chapter 5: Transition From A Dedicated To A Non-Dedicated, Ward-Based Pharmacist Antimicrobial Stewardship Program Model In A Non-Academic Hospital And Its Impact On Length Of Stay Of Patients Admitted With Pneumonia: A Prospective Observational Study.

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Declaration of Academic Achievement

GD conceived the study, design and analytic plan, was directly involved in the implementation of the intervention, and drafted the protocol manuscript.

LM was directly involved in the implementation of the intervention, and edited the protocol manuscript

After the initial 2-year funding expired, our stewardship program was not only renewed, but there was a request for further expansion of the program into other hospital wards that were not initially involved in the start of the program. The success of our program, both from a research and clinical outcomes perspective, created a new problem, as we had no increased funding to expand our services. Having demonstrated the program's effectiveness in reducing rates of healthcare-associated infections and antimicrobial utilization, we decided to conduct a quality improvement study to determine the impact of transitioning to a ward-based pharmacy model from our previous model. Like all our previous studies, we designed a methodologically rigorous study to answer this question. This paper was the featured paper in BMJ Open Quality for the December 2017 issue, with the editor commenting "DiDiodato and colleagues provided a compelling estimate of the impact of transitioning to a ward-based pharmacist indicating a 19.4% relative reduction in length of stay for patients admitted with community-acquired pneumonia. Such efforts to design improvement work in a way that allows an estimate of the impact relative to a comparison group remain uncommon in the published improvement field. DiDiodato and colleagues should be congratulated on designing and carrying out this type of study."
(http://bmjopenquality.bmj.com/content/6/2/e000255).

From effectiveness to quality improvement research, our stewardship program benefitted from the presence of an embedded researcher in a manner that would never have been realized through any other model. In addition, the conduct of these studies in our hospital would be critical to informing an embedded researcher about the barriers to conducting and implementing research, and would be used to assist in the design and implementation of the foundational elements needed to transform our hospital into a learning health centre.

Abstract

Pharmacists play an integral role in antimicrobial stewardship (AS). Some AS programs employ dedicated pharmacists, sometimes with Infectious Diseases training, while others employ ward-based pharmacists. The role and impact of both is under investigation.

This study compares the length of stay (LOS) of patients admitted to hospital with community-acquired pneumonia (CAP) after the implementation of an AS program initially led by a dedicated ID-trained pharmacist, and then transitioned to a ward-based pharmacist.

Starting April 1, 2013, all adult patients admitted with CAP were prospectively reviewed by the AS program. The control period (phase 0) lasted 3 months. Thereafter, AS was implemented in each of 4 medicine wards at 2-month intervals in a staggered fashion. During this period (phase 1), an ID-trained pharmacist and physician performed daily prospective audit and feedback. After 24 months, ward-based pharmacists assumed this AS role (phase 2).

Over the 36 month study period, 1 125 CAP patients were entered into the AS database, with 518 and 247 patients receiving an AS audit and feedback in phases 1 and 2, respectively. The acceptance rate for AS recommendations was similar for phases 1 and 2, each exceeding 82%. After accounting for secular trends, the overall reduction in LOS was

19.4% (95% CI 1.4% to 40.5%). There was no difference in LOS between phases 1 and 2.

This study demonstrated an AS audit and feedback intervention reduced median LOS in CAP patients by approximately 0.5 days regardless of pharmacist model. However, fewer patients were exposed to the AS intervention in phase 2, suggesting dedicated AS pharmacists may be necessary to realize the full benefits of AS.

Problem

Since April 2013, our 339-bed acute care community-based hospital located in Barrie, Ontario, Canada, has had an AS program led by a dedicated 0.8 full-time equivalent (FTE) ID-trained pharmacist and a 0.2 FTE ID-trained clinician researcher. We modeled our approach after the "Start Smart-Then Focus" AS program employed across acute care trusts in the National Health Service [1] . In addition, we embedded two research projects *a priori* into the AS program to ensure that we could evaluate the effectiveness of our approach in reducing both the length of stay (LOS) in patients admitted to hospital with community-acquired pneumonia (CAP) and incidence rate of *Clostridium difficile* infection [2, 3] . Like other AS programs, ours has continued to evolve. The biggest change has been the transition from one where both the ID-trained pharmacist and physician were responsible for every AS audit on each medical ward, to one where the AS audits were done by the ward-based pharmacists as part of their daily routine. This transition was done out of necessity to accommodate the expansion of our AS program to the surgical wards in the hospital. Our concern was that the gains our AS program had achieved in reducing antibiotic utilization without negatively impacting on LOS, mortality rates or 30-day readmission rates might be lost in the transition. This study examines the impact of this transition on CAP LOS.

Background

Accreditation Canada, Canada's hospital accreditation organization, declared that antimicrobial stewardship (AS) should be a required organizational practice for acute care hospitals in 2013 [4]. As a result, hospitals must implement an AS program to promote optimal antimicrobial use to be eligible to receive Accreditation Canada's highest award [5]. This singular change in hospital accreditation policy was likely the tipping point in convincing previously reticent hospital administrators to fund AS programs [6]. While Accreditation Canada doesn't endorse any specific AS model, the Society of Infectious Disease Pharmacists (SIDP) and the American Society of Health-System Pharmacists (ASHP) have recently suggested that all AS pharmacists should ideally be Infectious Diseases (ID)-trained, or at the very least, have AS-specific training [7] despite the absence of evidence to support these recommendations [8-10]. More importantly, the combination of *dedicated time* to target *uncomplicated* issues, such as the duration of treatment for common clinical syndromes like pneumonia, are more likely to be relevant to pharmacist-led AS program success than any formalized training requirements or attempted AS interventions in highly complex patients such as those admitted to intensive care units [11-13].

Measurement

For the entire 3 year study period, both the ID-trained pharmacist and physician collected the following patient data on admission; age group (deciles), sex (male/female), Charlson comorbidity score [14] (score based on presence of 12 possible comorbidities, and predictive of all-cause mortality 1 year after hospital discharge), CURB-65 score [15] (score based on presence of **C**onfusion, elevated **U**rea, elevated **R**espiratory rate, low **B**lood pressure and age $\geq$ **65** years, and predictive of in-hospital pneumonia-related mortality), presence of acute radiologic changes (yes/no as interpreted by radiologist), presence of Halm's criteria [16] (yes/no for each of fever, hypoxia, tachypnea, hypotension, and confusion), medical ward of admission, date, day and time of admission. Each patient record was reviewed daily until hospital discharge, censoring (at 14 days after admission) or other competing outcome (death, admission to an intensive care unit, or transfer to another acute care hospital). The following patient data was collected after admission; AS audit and feedback (yes/no), date of AS intervention, AS recommendation acceptance by attending physician (yes/no), intravenous days of antimicrobial therapy (DOT; every day that an intravenous antibiotic was administered to the patient regardless of dose or frequency was counted as 1 DOT; if two different antibiotics were delivered intravenously on the same day, then each antibiotic contributed 1 DOT to the total), time to clinical stability (days from admission when every abnormal Halm's criteria

had normalized), time to oral intake (days from admission when patient consumed ≥50% recommended caloric intake), presence of complications (lung abscess, empyema or pleural effusion needing drainage), date and time of outcome.

The primary outcome was LOS for patients discharged alive from hospital (=date and time of discharge – date and time of admission). LOS was modeled as a time to event outcome. Administrative censoring at 14 days after admission was decided *a priori.* Competing events were included in the model. Competing events were defined as events that preclude the occurrence of the primary outcome and included admission to an intensive care unit after being admitted to a ward, death or transfer to another acute care facility. Competing risks semi-parametric survival analysis was used to estimate the average effect of the AS intervention on LOS.

Time to AS intervention (=date of AS intervention – date of admission) was modeled as a time-varying covariate by splitting the observation period of each patient record with an AS intervention into two segments; one before and one after the AS intervention. For example, if a patient was admitted to hospital on day 0, and had an AS intervention on day 4, and was discharged alive on day 10, then this record would be divided into 2 segments: segment 1 extends from day 0 to day 4 with the outcome recorded as censored, and segment 2 extends from day 4 to day 10 with the outcome recorded as discharged alive. This splitting ensures that only

those patient days at risk after an AS intervention are used to calculate the AS intervention hazard rate for live discharge, thus reducing the chance of a false negative result. Time to clinical stability and time to oral intake were also modeled as time-varying covariates in the final model. Secular trends for LOS for each medical ward were included in the final model by using an interaction term between each ward and time (number of months) since April 2013. Given the observational nature of the study and the risk of selection bias as a result of confounding by indication, propensity scores (PS) to estimate the conditional probability of exposure to the AS intervention for each patient were calculated using a logistic regression model that included the following variables; CURB-65 score, Charlson comorbidity index, age group, sex, Halm's criteria, radiologic changes, empiric use of intravenous antibiotics, day of week of admission, and an interaction term between ward of admission and phase of study (1, 2 or 3). The propensity scores were then used to calculate the inverse probability of the treatment weights (IPWs) for the treated (1/PS) and untreated (1/(1-PS)) patients [17] . Variables included in the final model were the same variables included in the logit propensity score model, except the interaction term between ward of admission and phase of study was replaced by the secular trend variables, to ensure a "doubly robust" analysis to guard against model misspecification [18] . In addition, interaction terms between AS exposure and total days of intravenous

therapy and AS exposure and AS recommendation acceptance were tested for inclusion in the final model using the Akaike's information criterion (AIC) and Bayesian information criterion (BIC).

The average AS intervention effect is reported as a subhazard ratio (SHR) that is interpreted as the ratio of the probabilities of hospital discharge in patients exposed to AS compared to those not exposed and in whom a competing event has not yet occurred [19] . A SHR > 1 means that LOS is reduced in AS-exposed patients compared to unexposed patients as a result of an increased *hazard rate* of hospital discharge in the AS-exposed group, whereas a SHR < 1 means that AS-exposed patients have a longer LOS than unexposed patients, and a SHR =1 means there was no difference in LOS between the two groups [19] . Comparisons between continuous and categorical summary statistics by AS exposure status were done using a t test or Pearson's chi squared (χ^2) test, respectively.

The secondary outcome was total DOT per patient. DOT was right skewed, with a range from 1 to 58. DOT was log-transformed and modeled using simple linear regression. The final model included all the following variables chosen *a priori*: CCM, CURB-65 score, time to clinical stability, CAP criteria, ward of admission, age, sex, antimicrobial stewardship intervention, and presence of complicated CAP.

Design

The methodology for this study has been published elsewhere [2] . Briefly, all adult patients (≥18 years old) admitted to hospital with a diagnosis of CAP by their attending physicians were prospectively identified and followed by the AS program. CAP was defined as a lower respiratory tract infection in a patient who had not had any previous hospitalization of ≥48 consecutive hours in the prior 3-month period [20] .

Audit and feedback was the primary AS intervention used throughout the study. Basically, the AS team identified CAP patients, collected data prospectively, and audited patients Monday to Friday starting at ≥ 48 hours after admission if the patients met the following criteria: i) were admitted to a ward, and ii) were receiving any intravenous antibiotics ≥ 48 hours, or were receiving any oral fluoroquinolone (moxifloxacin or levofloxacin), oral quinolone (ciprofloxacin), or oral cephalosporin (cefprozil or cefuroxime) for ≥ 48 hours, or were receiving ≥ 5 days of any antibiotic. The AS team then made recommendations to the attending physician; these were documented in the electronic medical record, along with documenting the recommendations in the physician order section of the patient's paper chart as suggestions that required attending physician agreement and sign off prior to implementation, and direct verbal communication with the attending physician whenever possible or deemed necessary. Agreement was considered to have occurred if the attending physician signed off on the AS recommendations

within 24 hours. The AS recommendations could be any one or more of the following: i) no change to current therapy, ii) intravenous to oral conversion, iii) discontinue antibiotic therapy, iv) change in duration or dose, v) de-escalation or escalation of antibiotic therapy [1] . These recommendations were not mutually exclusive, and it was common for the AS team to make more than one recommendation for the same patient.

Strategy

From April 1 to June 30, 2013, all CAP patients admitted to hospital served as strict controls (phase 0). Over the next 8 months, each of the 4 medical wards was exposed to AS using a staggered implementation at 2-month intervals. This staggered implementation was done for both pragmatic human resource limitations but also to provide contemporaneous controls for the AS-exposed patients during this phase. By January 1, 2014, all 4 wards were exposed to AS, and this phase continued until March 31, 2015 (phase 1). An ID-trained pharmacist and ID-trained physician were responsible for every AS audit and feedback in phase 1. From April 1, 2015 to March 31, 2016 (phase 2), ward-based pharmacists became responsible for AS audit and feedback to permit the dedicated AS team members to expand their activities onto the surgical wards (Figure 1).

Figure 1: Stepped-wedge implementation of the antimicrobial stewardship program over a 36-month study period.

Ward	Phase													
	0			1										2
	Month													
	1	2	3	4	5	6	7	8	9	10	11	12	13-24	25-36
3GA	x	x	x	AS	AS	AS	AS	AS	AS	AS	AS	AS	AS	AS
3GC	x	x	x	x	x	AS	AS	AS	AS	AS	AS	AS	AS	AS
4GC	x	x	x	x	x	x	x	AS	AS	AS	AS	AS	AS	AS
3SA	x	x	x	x	x	x	x	x	x	AS	AS	AS	AS	AS
AS= intervention X= no intervention (control intervals)														

In advance of phase 2, the ward-based pharmacists were provided with the IDSA CAP treatment guidelines and instructed on their rationale and interpretation by the AS team. In addition, a series of web-based teaching vignettes were provided on a monthly basis for the pharmacists to complete. The pharmacists were required to complete the questions associated with the vignettes, and then were provided with feedback from the AS team. In total, there were 6 vignettes. Beyond this, these ward-based pharmacists had no extra-training or dedicated time to

support their AS activities, but they had the option of reviewing their AS audits and recommendations on a daily basis with the dedicated ID-trained pharmacist and ID-trained physician.

This study received approval from the Royal Victoria Regional Health Centre Research Ethics Board, who waived the need for informed consent given the AS program had already been approved for implementation by the hospital, there was minimal risk of harm to the patient, and every AS recommendation would necessarily require the attending physician to receive informed consent from the patient prior to implementation as per the usual process of care.

Stata/MP 14.1 was used for all statistical analyses.

Results

Over the 3 year study period, 1 698 patients were screened for eligibility and 1 125 CAP patients were enrolled into the AS database. The enrolled CAP patients contributed 7 420.2 patient days at risk, with 890 patients being discharged alive. During the study, 765 patients were exposed to AS and 360 patients who were not exposed served as controls. Their baseline characteristics are presented in Table 1.

Table 1: Baseline characteristics of AS-exposed and non-exposed CAP patients.

Variable	AS Exposure		P-value
	No (n=360)	Yes (n=765)	
Age Group			P=0.467
<20	3	4	
20-39	6	10	
30-39	10	22	
40-49	16	33	
50-59	41	57	
60-69	65	157	
70-79	77	170	
80-89	94	223	
90-99	45	87	
≥100	3	2	
Sex			P=0.163
Male	168	390	
Female	192	375	
Charlson comorbidity score	1.68 (sd[1] 1.85)	1.74 (sd 1.76)	P=0.61

CURB-65 score	1.82 (sd 1.17)	2.02 (sd 1.13)	P<0.01
CAP criteria			P=0.082
Yes	131	320	
No	229	445	
Empiric Intravenous antibiotics			P<0.01
Yes	284	654	
No	76	111	
Ward			P<0.001
3GA	152	469	
3GC	43	112	
3SA	33	61	
4GC	69	122	
ER	64	0	
Day of week			P=0.595
Sunday	40	104	
Monday	55	109	
Tuesday	57	117	
Wednesday	60	104	
Thursday	54	122	

Friday	50	96	
Saturday	44	113	
Propensity score	0. 657 (sd 0.100)	0. 691 (sd 0.074)	P<0.001

[1] sd=standard deviation

The primary outcome of live discharge was observed in 79.1% of patients (Table 2).

Table 2: CAP patient outcomes.

	AS Exposure		P-value
	No (n=360)	Yes (n=765)	
Outcome			P=0.014
Live discharge	292	598	
Censored	31	109	
Death	20	41	
Intensive care unit admission	13	15	
Transfer to another acute care hospital	4	2	

The overall AS recommendation acceptance rate was 84.3%, with no significant difference between phase 1 (441 of 518 recommendations

accepted) and phase 2 (203 of 247 recommendations accepted) (p=0.246). The time to AS audit and feedback was slightly earlier in phase 2 compared to phase 1 (Table 3).

Table 3: Time-varying variables.

Variable	AS Exposure		P-value
	No (n=360)	Yes (n=765)	
Time to clinical stability (days)	3.54 (sd[1] 3.34)	4.75 (sd 3.80)	P<0.001
Time to oral intake (days)	2.14 (sd 2.06)	2.39 (sd 1.90)	P=0.054
	Phase 1 (n=517)	Phase 2 (n=248)	
Time to AS intervention (days)	2.87 (sd 1.11)	2.59 (sd 1.67)	P=0.016

[1] sd=standard deviation

Over the 3 year study period, there were 11 269 total days of antimicrobial therapy, of which 4 413 were administered intravenously. Compared to the control group mean total DOT=12.12 (sd 7.98), the mean total DOT for phase 1 and 2 were 10.30 (sd 5.85) and 9.00 (sd 5.25) (χ^2 (68)=106.08, p=0.002), respectively. After controlling for confounding, the mean reduction in total DOT in phase 1 and 2 was 0.8 days (95% CI 0.7 to 0.9) and 0.71 days (95% CI 0.62 to 0.81), respectively, compared to the control

group. Almost all this reduction was due to shorter courses of intravenous antimicrobials, with a mean reduction in intravenous DOT in phase 1 and 2 being 0.63 days (95% CI 0.51 to 0.78) and 0.73 days (95% CI 0.58 to 0.91), respectively. There were no differences in the mean reductions between phases 1 and 2 in either total DOT or intravenous DOT after accounting for confounding.

After accounting for selection bias and other confounding variables, the SHR for the average AS intervention effect was 1.194 (95% CI 1.014 to 1.405) (Table 4). There was no improvement in either AIC or BIC when ASP exposure interaction terms with either total days of intravenous therapy (SHR 1.003, 95% CI 0.961 to 1.048) or AS recommendation rejected (SHR 1.078, 95% CI 0.823 to 1.413) were tested, so these were not included in the final model.

Table 4: Estimation of SHRs from competing risks survival regression analysis.

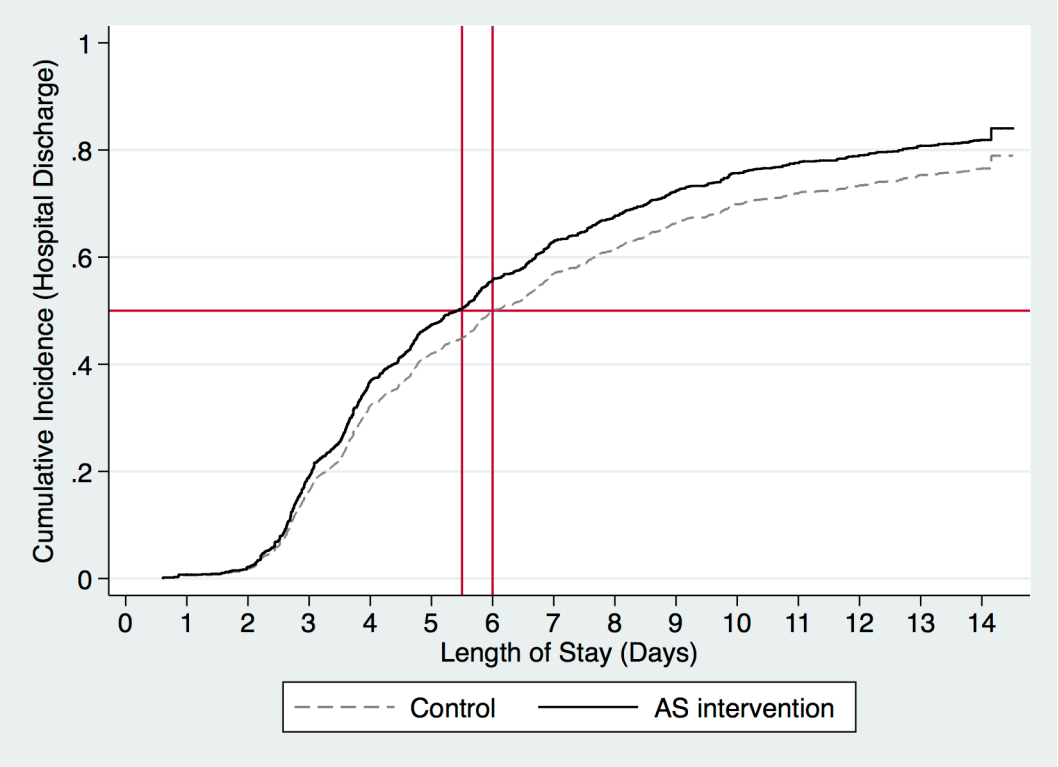
Variable	SHR	95% Confidence Interval	
		Lower Limit	Upper Limit
AS intervention (compared to no AS intervention)	1.194	1.014	1.405
Secular trend by ward and month			

(compared to ER)			
3GA	1.010	1.001	1.018
3GC	0.995	0.988	1.002
3SA	0.998	0.994	1.001
4GC	0.997	0.995	1.000
Age group (for each decile group above <20 baseline comparator)	0.939	0.880	1.002
Sex (compared to female)	0.807	0.689	0.949
Charlson comorbidity score (for every 1 unit increase in score)	0.956	0.910	1.005
CURB-65 score (for every 1 unit increase in score)	0.889	0.816	0.969
CAP criteria (compared to no)	1.040	0.876	1.233
Complicated CAP	0.702	0.567	0.870

(compared to no)			
Total days of intravenous therapy (for every extra 1 day of antibiotic)	0.947	0.925	0.969
Time to clinical stability (for every extra 1 day)	0.990	0.987	0.994
Time to oral intake (for every extra 1 day)	0.985	0.978	0.992

The cumulative incidence functions for hospital discharge in AS-exposed and non-exposed patients demonstrated a reduction in median LOS of approximately 0.5 days in AS-exposed patients (Figure 2). There was no difference in average AS intervention effect between phases 1 and 2 (SHR phase 2/phase 1 = 1.111 (95% CI 0.846 to 1.460). However, the proportion of CAP patients audited in phase 1 (518/640) exceeded the proportion audited in phase 2 (247/367) ($p<0.001$).

Figure 2: Cumulative incidence functions for live hospital discharge in AS-exposed and non-exposed patients.



Lessons and Limitations

In this study, an AS daily prospective audit and feedback intervention decreased the LOS (increased the probability of hospital discharge) in CAP patients by an average of 19.4% resulting in a decreased LOS by 0.5 days regardless if the AS intervention was delivered by an AS-dedicated, ID-trained pharmacist/physician or non-AS-dedicated, ward-based pharmacist with access to dedicated AS staff. However, 13.6% (95% CI 7.9% to 19.3%) fewer CAP patients were exposed to AS in phase 2, suggesting that AS interventions that rely on

non-dedicated AS personnel may be just as effective for common infectious diseases syndromes with well established diagnostic and treatment guidelines as AS programs with dedicated and/or AS-trained staff, but that fewer patients will likely benefit due to the competing clinical priorities of ward-based pharmacists. The mediator(s) for this observed reduction in LOS is unclear even though it might be tempting to associate this shorter LOS to the AS intervention-mediated reduction in intravenous DOT in both phases 1 and 2. Our observed reduction in LOS compares favourably with a recent Cochrane review that determined AS interventions *probably* reduce LOS by 1.12 days (95% CI 0.7 to 1.54), albeit this was not solely observed in patients with CAP [10] .

Previously, we had estimated that our 2 year stepped-wedge observational study should have been able to detect an AS intervention effect exceeding a 20% reduction in LOS [2, 3] . The sample size calculation used for that study might not have sufficiently accounted for the loss of power due to clustering both within wards and within similar time periods across wards given the cross-sectional nature of the study design [21] . The extension of that study by 1 year not only permitted us to evaluate the impact of the transition between two different AS pharmacy models, but likely provided us with a large enough sample size to detect a difference in that *a priori*-established primary outcome.

To the best of our knowledge, this is the only observational study of AS intervention effects in CAP that has accounted for time-dependent bias. AS interventions are generally episodic, usually occurring at different times in patients' hospital admissions. AS interventions need to be modeled as time-varying covariates in the final statistical model, otherwise the result will be to reduce the hazard rate in the exposed group and increase the hazard rate in the unexposed group culminating in a biased effect estimate [22] . For our study, this time-dependent bias could lead to a false negative SHR, meaning that we would underestimate the AS intervention effect on LOS and, possibly, conclude that our AS program had no effect on this primary outcome.

Another strength of our study included the use of a "doubly robust" model specification for both exposure and outcome. By using this approach, we not only reduced the risk of a biased effect estimate, but it also permitted us to estimate the causal AS intervention effect from this observational study [18] . However, like all observational studies, there always exists the possibility of unmeasured confounders that are not directly related to the included variables in the model, leading to misspecification and biased effect estimates. In addition, the results from this single-site study may not be relevant to other AS programs.

Conclusions

While AS has been deemed a required organizational practice for Canadian hospitals, there appears to be significant heterogeneity in the structures, processes and outcomes used and measured by the different AS programs. This may simply be a reflection of AS programs focusing on local issues and needs. Regardless, local AS programs should be involved in research to ensure their approach to improving patient safety and quality of care is effective. With this in mind, we have undertaken this study to evaluate the impact of a change in the structure of our hospital's AS program on an important patient and healthcare system outcome. Our results suggest that our prospective audit and feedback intervention reduces the LOS of patients admitted to hospital with CAP, and that this benefit has not been compromised by the transition from a dedicated ID-trained pharmacist AS model to a non-dedicated, ward-based pharmacist AS model. While the observed downside of this structural change appears to be that fewer patients are exposed to the AS intervention, we did not measure whether other ward-based pharmacy responsibilities were compromised as a result of this new responsibility. In addition, the ward-based pharmacists still had full access to the dedicated AS team members, so it is not clear whether an AS model that exclusively uses non-dedicated personnel will be able to realize the same benefits. Also, the non-dedicated personnel assumed responsibility for a program that had already been implemented for a period of almost 2 years, further

adding to the uncertainty of benefit for an AS program that begins with non-dedicated personnel.

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Chapter 6: Inter-Hospital Patient Transfers between Ontario's Academic and Large Community Hospitals Increase the Risk of *Clostridium difficile* Infection.

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Declaration of Academic Achievement

GD conceived the study and survey questions, design and analytic plan, contacted all the infection prevention and control personnel, and drafted the protocol manuscript.

LM was directly involved in the implementation of the intervention, and edited the protocol manuscript

In addition to our patient-level and organizational-level research activities, the embedded researcher model was extended to study outcomes at the population-level (Chapter 7 and 8) and system-level (Chapter 6). A further demonstration of the added value of such a model, this research was done to expand the design and analytical experience of the embedded researcher, but also to demonstrate to funding agencies that seem to systematically exclude community-based researchers from funding opportunities that their decisions are not consistent with the quality or importance of the research that is being done outside these traditional environments. In addition, these research activities are important for raising the profile of embedded researchers who might not otherwise be invited to participate in health services planning and policy setting by the usual suspects.

Abstract

Background: To determine the impact of inter-hospital patient transfers on the risk of *Clostridium difficile* infection (CDI).

Methods: The number of inter-hospital patient transfers and CDI cases for 11 academic and 40 large community hospitals (LCHs) were available from 2010 to 2015. These data were used to compute a CDI score for each sending facility as a measure of CDI pressure on the receiving facility. This CDI score was included as a variable in a multi-level mixed effect poisson regression model of CDI cases. Other covariates included year, CDI testing strategy, antimicrobial stewardship program (ASP), and criteria used for patient isolation. Hospital-specific random effects were estimated for the baseline rate of CDI (intercept) and ASP effect (slope).

Results: The CDI score ranged from 0 to 103, with mean 20.4 (standard deviation 21.8). Every 10-point increase in the CDI score was associated with a 4.5% increase in the incidence of CDI in the receiving academic hospital (95% confidence interval (CI) 0.9 to 8.5) and 3.6% increase in the receiving LCHs (95% CI 0.3 to 7). The random components of the model varied significantly, with a strong negative correlation of -0.85 (95% CI, -0.94, -0.65).

Conclusions: Our results suggest inter-hospital patient transfers increase the risk of CDI. ASPs appear to reduce this risk, however, these ASP effects demonstrate significant heterogeneity across hospitals.

Background

A previous study demonstrated an increased risk of *Clostridium difficile* infection (CDI) associated with inter-facility patient transfers(1). In this retrospective observational study from 2005 to 2011 using data from 480 hospitals in California, this impact was measured by incorporating measures of centrality, determined using network analysis, in the final model to estimate their effect on CDI cases. The study estimated for every increase of 1 in log (weighted indegree), there was a 3.3% (95% CI 1.5 to 5.2) increase in CDI incidence, where weighted indegree is a measure of the total number of patients transferred between hospitals. The study did not attempt to determine the mechanism through which this increased risk was transferred, that is, they did not know whether the increased risk was due to transferred patients who had CDI or by some other indirect mechanism.

In a subsequent study that measured the impact of inter-facility patient transfers on the risk of CDI in long-term care facilities (LTCF), the incidence rate ratio (IRR) for the importation of cases of acute care CDI per doubling of the LTCF-associated CDI rate was 1.23 (95% CI 1.14 to 1.33) conditional on both patient-level and regional-level covariates such as antibiotic use (2). This study hypothesized that the increased incidence of CDI importation coupled with facility-level antibiotic use were

responsible for 75% of the variation seen in the increased incidence rates of CDI among residents in LTCFs.

In Ontario, Canada's most populous province with over 13 million residents, there are 12 academic and 45 large community hospitals (LCHs) (3). These hospitals account for over 95% of all acute inpatient days among adults over 18 years of age(4). These hospitals are part of a provincial network of hospitals that are publicly funded and universally accessible under Canada's Medicare program. As a result, there are a significant number of inter-hospital patient transfers, sometimes affecting up to 3% of all inpatients (5). Since 2008, there has been mandatory hospital reporting of hospital-associated CDI (HA-CDI) rates(6). This study will explore the association between inter-hospital patient transfers and incidence rates of HA-CDI while taking into account hospital-level infection prevention and control (IPAC) practices and policies relevant to the control of CDI.

Methods

IPAC policies and practices survey

A survey was mailed to every academic and LCH IPAC program manager. The survey was focused on IPAC practices and policies relevant to MRSA, VRE, ESBL$^+$, and CRE, along with infections due to *Clostridium difficile*. The survey questionnaire consisted of 20 questions to be answered for each calendar year from 2010 to 2015 in order to determine both the

current IPAC practices and policies and how these had changed over time. The survey was initially sent out in June 2016; non-responders were resent the survey monthly for the following 6 months or until they responded. The survey questions and their range of responses relevant to CDI are available upon request. In January 2017, the IPAC managers were contacted a second time to validate their responses.

Inter-hospital patient transfers

In Ontario, all non-emergent inter-hospital patient transfers require the sending hospital to register a medical transfer authorization number prior to transfer. All of these registered numbers are stored in the Provincial Transfer Authorization Centre, a database maintained by the Ministry of Health and Long-Term Care (MOHLTC) and Ornge, the province's emergency medical transfer service(5). The database was established in 2003. The database is not externally validated, meaning there is no validation done to ensure that patients were actually transferred after being registered for a medical transfer authorization number. The database identifies the sending and receiving facilities for each patient transfer. There is no patient-level data that is stored in the database.

CDI cases

The MOHLTC receives the number of HA-CDI cases (attributable to that hospital) and the number of patient days at risk for HA-CDI every month from every academic and LCH in the province. This data is publicly

available from Health Quality Ontario, an agency of the MOHLTC responsible for the public reporting of mandatory patient safety indicators(6). While the data submitted is not validated by the MOHLTC, the database has been shown to be consistent when compared against both the MOHLTC Public Health Laboratory CDI database and the Canadian Institute of Health Information administrative database (7). The monthly data was summed for each calendar year to coincide with the IPAC survey response frequency.

CDI Score

The CDI score was developed to account for *Clostridium difficile* disease pressure from the sending hospital, an established risk factor for HA-CDI (8,9). *Clostridium difficile* disease pressure is defined as the number of HA-CDI cases present in the sending hospital in that calendar year. The CDI score represents a modification of the weighted indegree measure of connectivity used by Simmering *et al.* (1). It is a measure of connectivity that combines the total number of patients transferred into a hospital with the total number of HA-CDI cases from that sending hospital. The CDI score is a more efficient measure of connectivity compared to weighted indegree since in a regression analysis that must include separate variables for weighted indegree and HA-CDI disease pressure, along with an interaction term between the two variables, the CDI score can account for this in a single variable. Unlike measures of connectivity calculated

from social network models, no special statistical analyses are required to calculate the CDI score, making it a much more accessible measure of connectivity (10). The CDI score was calculated for every calendar year for each hospital. The steps involved in the calculation of the CDI score are represented in Table 1 for a hypothetical case.

Table 1: Calculation of the CDI score for a hypothetical case. In this example, a receiving facility accepts a total of 228 patients from 4 sending facilities, each of whom transfers out a variable number of patients (Y). The score is weighted by the transfers from each sending facility as a percentage of the total transfers into the receiving facility (W).

Sending Facility	**Receiving hospital**	**Total (Sender)**	**HA-CDI Cases (Sender)**	**% Total Transfers (Receiving)**
	Patient Transfers			
n	**X**	**Y**	**Z**	**W**
1	129	1018	154	56.6
2	68	1018	154	29.8
3	9	789	198	3.95
4	22	52	56	9.65
CDI Score	Σ^n [(X/Y)*Z]*W = 16.45			

The linearity relationship between the CDI score and CDI cases was assessed using a scatterplot, and this was compared against the log-transformed CDI score. There was no significant difference in linear fit between the versions of CDI score and CDI cases, so the native CDI score was included in the final model to simplify the interpretation of the regression output.

Study Design and Outcomes

A multi-level, mixed-effects poisson distribution was used to model the mean number of HA-CDI cases for each hospital by calendar year. The predictor variables included in the baseline model were an indicator for calendar year (2010 to 2015), *Clostridium difficile* stool assay, criteria used for isolation, and presence of an antimicrobial stewardship program (ASP). The CDI score was added to the baseline model to determine if this improved goodness of fit. Goodness of fit was tested using the Akaike information criterion (AIC) and the likelihood ratio (LR) test. An AIC change of ≥ 2 units and a LR test statistic with a p-value ≤ 0.05 were used to identify improved model fit with the inclusion of the CDI score variable. Patient days at risk for each calendar year were included as the exposure to control for hospital size and permit the interpretation of the outcome as the incidence rate of HA-CDI. The model included a random component for the baseline incidence of HA-CDI (intercept) and the effect size for the antimicrobial stewardship program variable (slope) to detect heterogeneity

between hospitals. The correlation between the random components was assessed with a Pearson correlation coefficient. STATA/MP 14.2 for Mac (64-bit Intel) was used for all statistical analyses. As no personal health information was used in this study, research ethics board approval was not required.

Results

IPAC survey

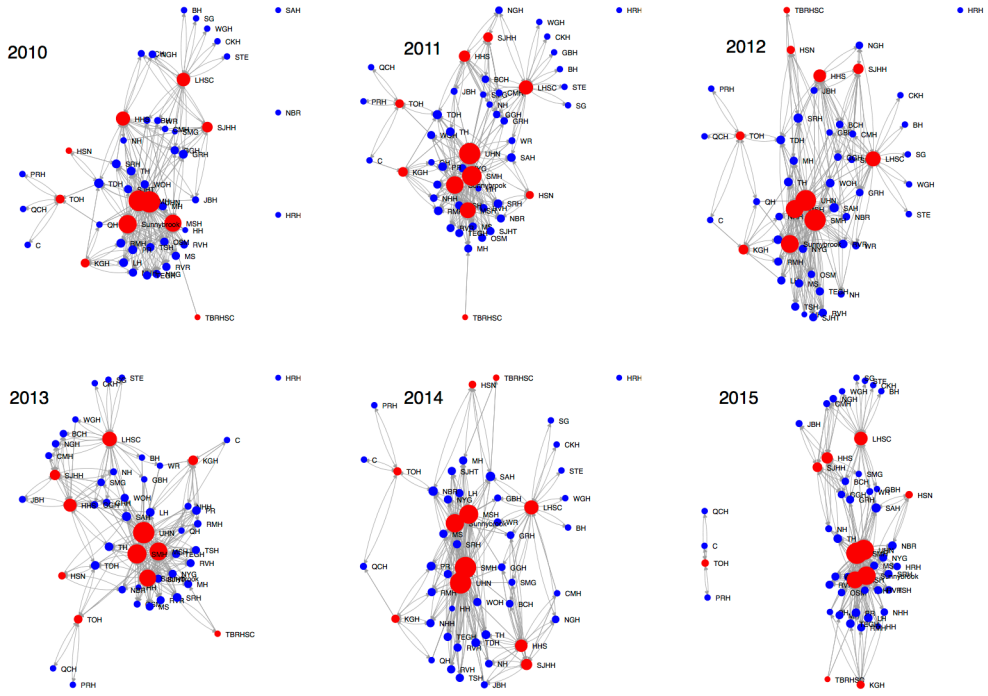
The response rate was 94.7% (54 out of 57 hospitals), with complete surveys from 51 of 54 hospitals. There were 11 academic and 43 LCH that responded to the survey. There is a total of 315 annual observations, with 251 from LCHs and 64 from academic hospitals. The questions relating to the duration of CDI precautions and the type of CDI precautions were not included in the final model due to lack of variability in responses from year to year; over 90% of all time periods in both hospital types reported using additional precautions plus private rooms, and over 92% of all time periods in both hospital types reported discontinuing precautions only after symptoms had resolved for $\geq$ 48 hours. In 2010, over 70% of LCH used toxin A/B immunoassay-based testing only, compared to 64% in academic hospitals. By 2015, the predominant testing strategy was a single step nucleic acid amplification in 49% and 64% of LCHs and academic hospitals, respectively. In 2010, only 22% of LCHs had ASPs, and this increased to 74% in 2015. Among academic hospitals, 36% had

ASPs in 2010 and this increased to 82% by 2015. The predominant trigger for isolation was the presence of ≥ 3 loose stools in 2010 for both hospital types, but by 2015, the predominant trigger was the presence of ≥ 1 loose stool in both hospital types.

Inter-hospital patient transfers

The total numbers of patients assigned a medical transfer authorization number being received into and transferred out of hospitals included in this study were 167,020 and 167,040, respectively. There is not a perfect correlation because this study did not account for transfers between small community hospitals and other hospital types, or between LCHs. Both of these types of patient transfers would constitute an insignificant proportion of the overall inter-hospital patient transfers and would not affect the results of this analysis. Network maps for each calendar year demonstrate that there were minimal changes from year to year between the academic and LCH transfer networks, both with respect to numbers of transferred patients but also composition of the network (Figure 1).

Figure 1: Network map of academic (Red) and LCHs (Blue) and their transfers (black arrowheads), by calendar year. The size of the nodes (circles) correlates with the in-degree score (in-degree is a centrality index calculated using network analysis and measures the number of patients each hospital receives).



CDI Score

The CDI score ranged from 0 to 103, with a mean score 20.4 (sd 21.8) and median score 13.5 (IQR 3.1 to 27.7). The academic hospital CDI mean score 41.7 (sd 21.1) was significantly greater than the LCHs CDI mean score 14.5 (sd 18.1) (p-value < 0.001).

Outcomes

Complete data was available for 50 hospitals, and 288 observations were included in the final combined analysis (Table 2). Both the Δ AIC > 2 and LR test statistic were significant, suggesting that adding CDI score to the baseline model improved the fit.

Table 2: Regression output for combined (academic and LCHs) analysis, with baseline model and baseline model plus CDI score.

Variable	Incidence Rate Ratio (IRR)	95% Confidence Interval		AIC	LR test statistic (p-value)
		Lower limit	Upper limit		
Baseline Model (N=288 observations, n=50 hospitals)				2488.68	N/A
ASP	0.88	0.78	0.99		
Year					
2010	0.93	0.86	1.01		
2011	1.11	1.04	1.17		
2012	1.08	1.02	1.15		
2013 (Comparator)					
2014	0.86	0.81	0.92		
2015	0.85	0.80	0.90		
Baseline Model + CDI Score				2486.59	4.09

					(p=0.043)
CDI Score (Δ+10 units)	1.025	1.001	1.049		

A separate analysis was conducted for both the LCHs and academic hospitals to determine if the CDI score effect was consistent in size and direction across hospital types (Table 3).

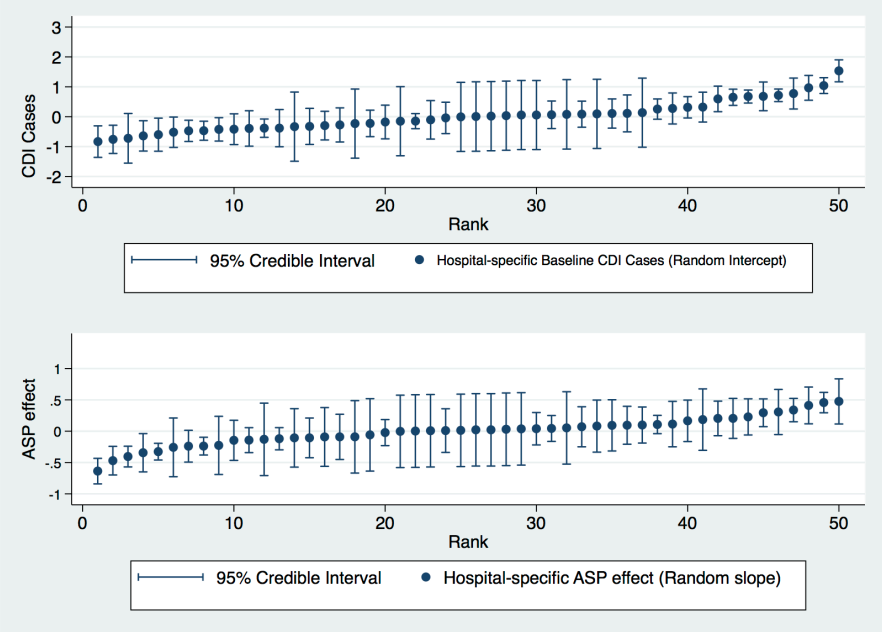
Table 3: Regression output for each hospital type, with baseline model and baseline model plus CDI score.

	Academic (N=64 observations; n=11 sites)		LCH (N=224 observations; n=39 sites)	
	Models			
	Baseline	CDI Score (Δ+10 units)	Baseline	CDI Score (Δ+10 units)
Incidence Rate Ratio (IRR)		1.047		1.036
IRR 95% CI		1.009 to 1.085		1.003 TO 1.070
AIC	656.34	652.43	1830.92	1828.48
LR test		5.92		4.44

statistic (p-value)		(p=0.015)		(P=0.035)

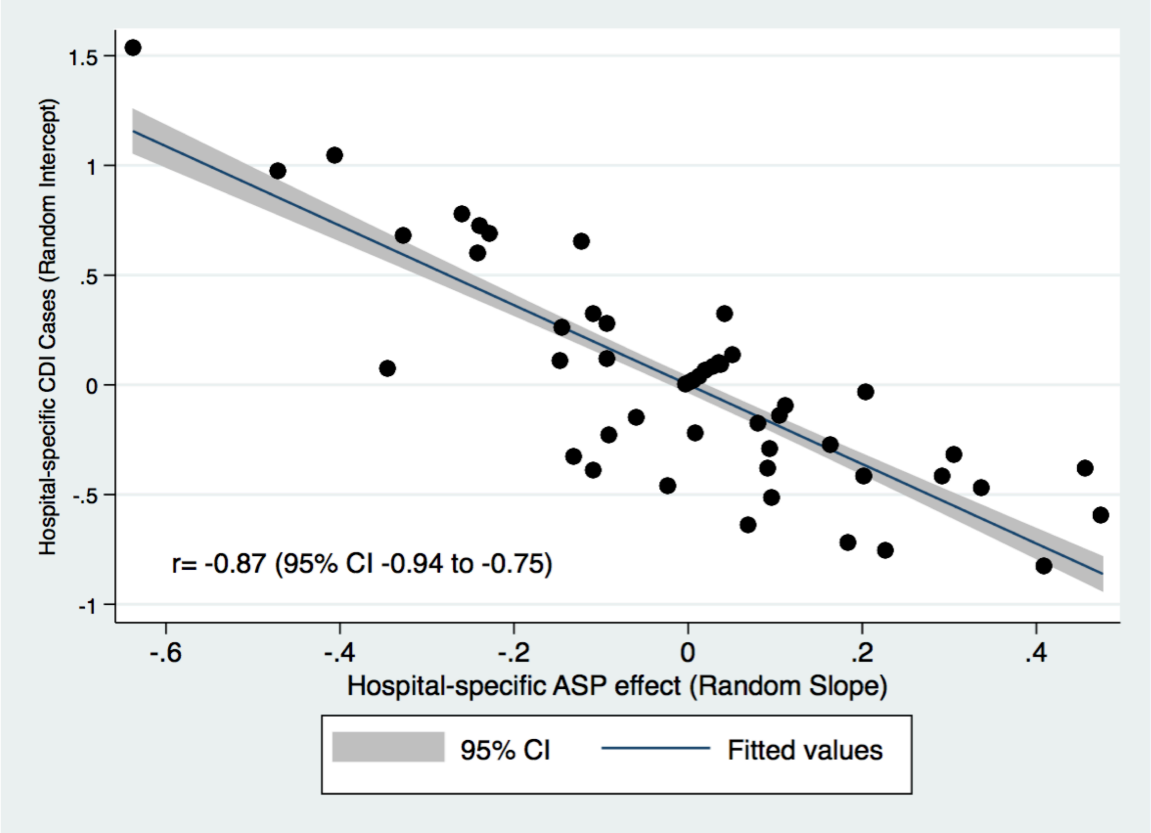
The random intercept standard deviation estimate for the variation between the hospitals' baseline HA-CDI cases is 0.61 (95% CI 0.46 to 0.81), and the random slope standard deviation estimate for the variation between the hospitals' ASP effect is 0.30 (95% CI 0.22 to 0.41). The estimated Bayes predictions for the random coefficients for each hospital and their rank, along with their corresponding confidence intervals, are presented in Figure 2.

Figure 2: Empirical Bayes predictions for the random coefficients (intercept and slope) for each hospital, ranked by medians.



There was a strong negative correlation between the random intercept and random slope (Figure 3).

Figure 3: Correlation between random intercept and random slope



Discussion

This study is the first to demonstrate that the HA-CDI colonization pressure at another hospital is associated with an increased incidence of HA-CDI at a separate hospital that receives transferred patients from that sending facility after accounting for differences in IPAC practices and policies and *Clostridium difficile* diagnostic testing strategies. Simmering *et al.* demonstrated the impact of the number of patients transferred from a

sending to a receiving hospital on the incidence of CDI by including two centrality indices (indegree and weighted indegree) in their regression model (1); this study advances those findings by also incorporating the HA-CDI colonization pressure in the model.

Despite demonstrating an association between patient transfers and an increased HA-CDI risk, the mechanism by which this risk is realized is unclear. The most intuitive explanation would be that either patients with symptomatic CDI or asymptomatic colonization with *Clostridium difficile* are the vectors for disease transmission (2,11), however, there may exist other explanations for this increased risk. For example, transferred patients could be at higher risk for CDI due to increased exposure to antibiotics at the sending facility, exposing this higher risk population to increased risk of HA-CDI at the receiving facility (12,13).

The importance of IPAC policies and practices, their effectiveness, and their differential implementation across network hospitals may also be critical to explaining the risk associated with inter-hospital patient transfers. In this study, the effectiveness of a hospital's ASP was inversely correlated with their HA-CDI. While the direction of association cannot be determined from this retrospective observational study, other studies have demonstrated that importance of ASPs on reducing HA-CDI rates (14).

The model used in this study has many limitations beyond ecological fallacy. Patient transfer data extracted from the PTAC database were not validated against other administrative databases, and so we could not verify whether these patient transfers occurred. In addition, we did not characterize hospital antibiotic usage patterns, perhaps the most important patient-level and hospital-level predictor for HA-CDI (2,13,15).

Conclusions

Despite the study's limitations, we demonstrated that inter-hospital patient transfers are associated with an increased risk of CDI at the receiving hospital due to HA-CDI colonization pressure in the sending facility. While we don't know how this risk is transmitted, the study suggests that ASPs across hospital networks have important roles to play in minimizing this risk. Other IPAC policies and practices beyond ASPs may also be important for more accurately characterizing this risk, especially diagnostic strategies that employ a two-step algorithm that results in fewer false-positive results. Finally, the study demonstrated significant variation in ASP effectiveness across hospitals, suggesting an area for improvement that can be approached on a regional network level.

Acknowledgments

None to declare.

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Chapter 7: Antibiotic Exposure And Risk Of Community-Associated *Clostridium Difficile* Infection In Adult Patients Registered With Ontario's Largest Family Medicine Health Team: A Study Protocol For A Self-Controlled Case Series Analysis.

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Abstract

Objective

By using a unique observational study design that can account for both observed and unobserved time-invariant confounders, the association between antibiotic exposure and subsequent risk of community-associated *Clostridium difficile* infection (CA-CDI) will be estimated.

Rationale

CA-CDI is an infectious gastrointestinal illness whose incidence is estimated to be between 10 to 61 cases per 100 000 population, with up to 50% of cases requiring hospitalization due to the severity of the disease. While antibiotic exposure and age≥65 years are known risk factors for healthcare-associated *Clostridium difficile* infection (HA-CDI), the importance of antibiotic exposure in CA-CDI is less well defined. In addition, previous case-control studies have demonstrated a potential association between antibiotic exposure and subsequent risk of CA-CDI, they did not account for important time-invariant confounders because of the limitations of matching potentially leading to a biased estimate of the antibiotic-CA-CDI association.

Design

This is a retrospective, analytical observational study using a self-controlled case series (SCCS) design. This design permits cases to act

as their own control by comparing the relative incidence rate of CA-CDI in antibiotic exposure periods to all other times in the observation period.

Methods

Cases are defined as any incident case of CA-CDI that also had an antibiotic exposure during the observation period for any patient registered with the Barrie and Community Family Health Team from January 1, 2011 to December 31, 2016. The observation period for each case will be divided into exposed and non-exposed intervals, with exposed intervals starting 2 days after an antibiotic prescription and continuing for the following 60-day period. The association between antibiotic exposure and subsequent risk of CA-CDI will be reported as the relative incidence rate ratio (IRR) for CA-CDI between exposed and non-exposed intervals. Conditional poisson regression analysis will be used to estimate the relative IRR.

Relevance

Antibiotics, along with immunization, have transformed the public health by reducing premature deaths due to infectious diseases. Over 80% of all antibiotics prescribed for human illness occurs in outpatient settings, and it is estimated that up to 50% of these prescriptions are medically unnecessary and contribute to the emergence of antibiotic resistance. By demonstrating the potential harm associated with antibiotic exposure, this study may help nudge physician prescribing behaviour and result in

improved antibiotic utilization, better patient outcomes, and reduction in the emergence of antibiotic resistance.

Background

Clostridium difficile is a toxin-producing, spore-forming bacterium that can cause mild to severe and life-threatening diseases of the intestine (1). *Clostridium difficile* infection is the most common healthcare-associated infection, but recent epidemiologic studies have demonstrated a significant burden of disease even among patients with no obvious healthcare-related exposures (2, 3). These cases are referred to as community-associated *Clostridium difficile* infection (4). Since 2009, the surveillance definition of CA-CDI has been a patient with diarrhea whose stool specimen tests positive for *Clostridium difficile* toxin or culture in the community or within 3 days after admission to hospital in the absence of either any overnight stay in any healthcare facility during the previous 12 weeks or a previous CDI diagnosis during the previous 8 weeks (3). The estimated incidence of CA-CDI ranges from 10.0 to 60.5 cases per 100 000 population, accounting for 25% to 35% of all CDI cases (2, 3). Unlike HA-CDI, antibiotic exposure is not consistently associated with CA-CDI with up to 46% of CA-CDI cases reporting no antibiotic exposure in the 3-month period preceding the diagnosis (5, 6).

In 2 recent meta-analyses, 5 and 8 observational studies, respectively, were used to calculate a pooled odds ratio (OR) to estimate the

association between antibiotic exposure and CA-CDI (7, 8). All CA-CDI cases were diagnosed using either a positive stool assay for *Clostridium difficile* toxin or International Statistical Classification of Diseases and Related Health Problems (ICD-9 008.45) coding on hospital admission. The observation period started from 0 days (same day as antibiotic prescription) up to 2 days after antibiotic prescription, and continued for the following 30 days up to 180 days. All studies were retrospective and either case-control or nested case-control studies. The number of CA-CDI cases ranged from as low as 40 to as high as 1,223, with the ratio of cases to controls ranging from 1:2 to 1:10. The matching criteria varied significantly between studies but were limited to age, clinic site, date of diagnosis, comorbidities, and/or medications used for gastric acid suppression. The quality scores ranged from 3 to 7 (out of a maximum score of 7). The study periods reported cases from 1994 to 2007. The pooled OR from each study was 3.55 (95% CI 2.56 to 4.94) and 6.91 (95% CI 4.17 to 11.44), respectively, with significant heterogeneity of effect sizes (I^2 = 90.6% and I^2 = 95%, respectively) demonstrated between studies in both meta-analyses. By stratifying the results by antibiotic class, overall effect heterogeneity was reduced by 55% but this reduction varied across antibiotic classes. For example, effect heterogeneity remained high for clindamycin (I^2 = 76%), cephalosporins (I^2 = 97%), penicillins (I^2 = 85%), and macrolides (I^2 = 42%). For other antibiotic

classes, effect heterogeneity was eliminated (fluoroquinolones, sulfonamides and tetracyclines). The antibiotic classes with the strongest association with CA-CDI included fluoroquinolones (OR=5.50; 95% CI 4.26 to 7.11 and OR=5.65; 95% CI 4.38 to 7.28, respectively), clindamycin (OR=16.80; 95% CI 7.48 to 37.76 and OR=20.43; 95% CI 8.5 to 49.09, respectively), and cephalosporins (OR=5.68; 95% CI 2.12 to 15.23 and OR=4.47; 95% CI 1.60 to 12.50, respectively). Only tetracyclines did not demonstrate any association with CD-CDI, and the weakest positive association was seen with sulfonamides/trimethoprim (OR=1.81; 95% CI 1.34 to 2.43 and OR=1.84; 95% CI 1.48 to 2.29). Comparing these antibiotic class effect ORs for CA-CDI to their corresponding ORs for HA-CDI demonstrates significant differences between effect sizes. For example, for clindamycin exposure and subsequent incidence of HA-CDI, the estimated OR = 2.31 (95% CI 1.84 to 2.91) which is less than 15% of the effect size seen for CA-CDI (9). This is a consistent finding among all the other antibiotic classes, with antibiotic class ORs for CA-CDI being significantly greater than for HA-CDI, suggesting confounding bias may be inflating the association between antibiotic exposure and CA-CDI.

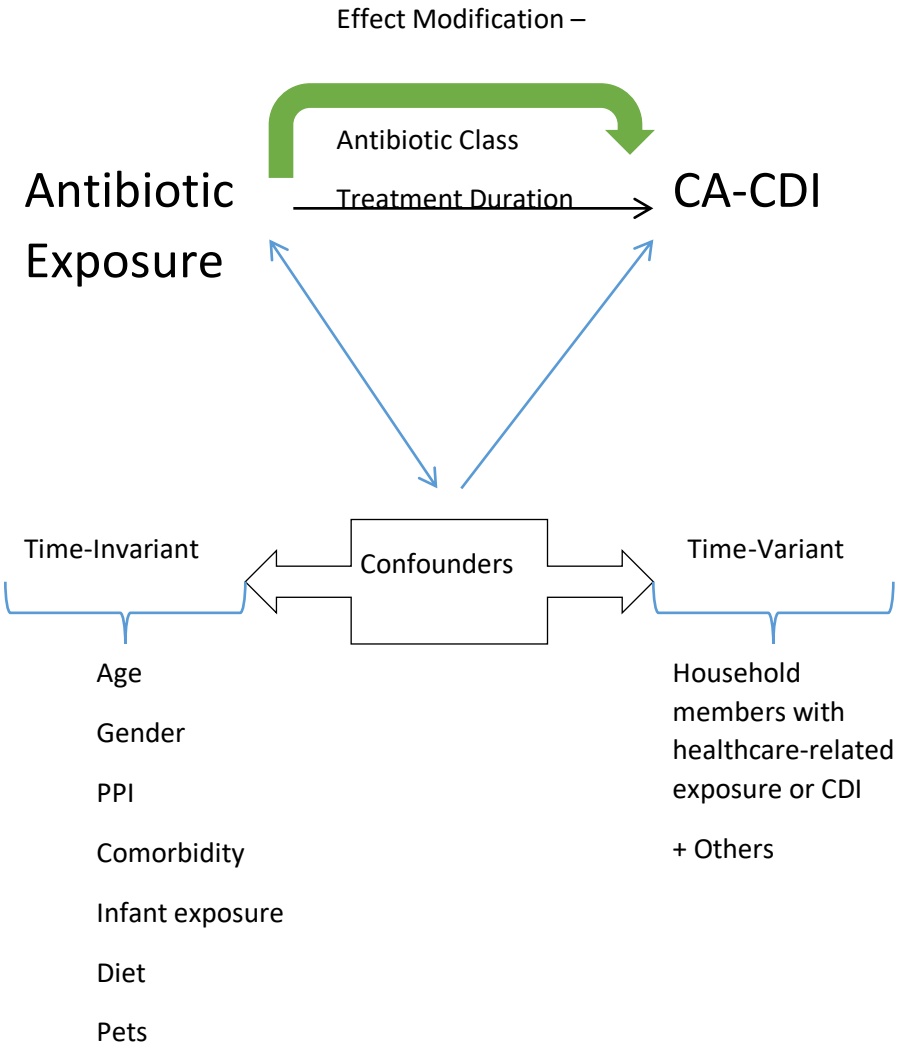
The evidence for other risk factors in CA-CDI is equivocal and has been recently reviewed (5). Unlike HA-CDI, CA-CDI cases appear to be younger in age and have fewer comorbid illnesses. The role of proton pump inhibitors (PPI), a class of broadly prescribed therapeutics used for

gastric acid suppression, may be less important in CA-CDI compared to their weak but established association in HA-CDI (10). Exposure to infants ≤ 2 years old, who are frequently asymptomatically colonized with *Clostridium difficile* and believed to be potential reservoirs in the community, has been associated with CA-CDI, especially in younger women without any other risk factors. Other potential risk factors include exposure to household pets colonized with *Clostridium difficile*, ingestion of retail meats that have been shown to be contaminated with *Clostridium difficile* spores, and contact with household members who have had healthcare-related exposures or previous *Clostridium difficile* infection. Apart from this last exposure, all the other potential risk factors are assumed to be time-invariant because they would tend to remain unchanged over the period of observation commonly used for case-control studies (Figure 1).

Research Question

For adult patients (≥18 years old) registered with the Barrie and Community Family Health Team who were diagnosed with community-associated *Clostridium difficile* infection and exposed to antibiotic therapy between January 1, 2011 and December 31, 2016, was the 60-day exposure-risk period after antibiotic prescription associated with an increased risk of *Clostridium difficile* infection compared to the remainder of the observation period for each case?

Figure 1: Antibiotic exposure and subsequent risk of CA-CDI accounting for potential confounders and effect modification.



Study Design

Target Population

Target

1) an incident case of CA-CDI is defined as any patient with diarrhea whose stool specimen tests positive for *Clostridium difficile* toxin or culture in the community or within 3 days after admission to hospital in the absence of either any overnight stay in any healthcare facility during the previous 12 weeks or a previous *Clostridium difficile* infection diagnosed during the previous 8 weeks, and

2) antibiotic exposure is defined as any antibiotic prescription ≥ 1 dose that is documented in a patient's medical record

Accessible Population

All adults (≥18 years old) diagnosed with an incident case of CA-CDI who have been exposed to antibiotics, and

1) are registered patients with the Barrie and Community Family Health Team (BCFHT) in Barrie, Ontario, Canada, and

2) met the inclusion criteria between January 1, 2011 and December 31, 2016

The Barrie and Community Family Health Team is composed of 86 physician practices, six allied health clinics and four walk-in clinics. As of June 30, 2016, there were 139,670 registered BCFHT patients. Since 2011, the BCFHT has utilized the *Accuro*® electronic medical record system for all registered patients. For identification of adult patients with an incident case of CA-CDI and antibiotic exposure, the database will queried by the system administrator. In general, CA-CDI cases will be

identified using the public health laboratory (PHL) reports directly inputted into the EMR since all stool testing for *Clostridium difficile* infection is done by the PHL. Healthcare-exposure in the 12 weeks preceding the diagnosis of CA-CDI will be available through a link between the BCFHT and Royal Victoria Hospital (RVH) databases. The RVH is a 399-bed acute care, large community hospital, and is the only hospital in Barrie, Ontario.

Model

This is a retrospective, analytical observational study using the self-controlled case series model. Self-controlled case series (SCCS) method represents "an alternative epidemiologic study design" that can be used "to investigate an association between a transient exposure and an outcome event" (11). By dividing each case's observation period into exposure-risk and non-exposure-risk periods, a relative incidence rate ratio for outcome between exposed and non-exposed periods can be determined while taking into account the effect of time-varying confounders.

The advantages of this design include the following:

1) no separate matched controls are needed for the cases because comparisons are made within individuals and not between individuals.

2) time-invariant confounders are automatically accounted for in the design because they cancel out of the final model.

3) time-variant confounders, such as season or year, can be included in the model through further division of the observation periods according to these potential confounders.

4) multiple exposure-risk periods of varying length can be included in the model.

5) all exposure periods occurring within the observation period are included in the model regardless of their temporal relationship to the outcome since patients are not censored at the time of the outcome event, potentially leading to a less biased exposure effect size.

The assumptions of the SCCS model include the following:

1) occurrence of any *Clostridium difficile* infection does not affect the probability of subsequent antibiotic exposure. This assumption will likely be violated since physicians' tendency to prescribe antibiotics after an episode of either HA-CDI or CD-CDI will be restrained. For this reason, a pre-exposure period will be incorporated into the model to offset this potential source of bias.

2) after accounting for time-variant confounders, such as season, year of diagnosis, or effect modifiers, such as antibiotic class or treatment duration, event rates are assumed to be constant within each defined interval.

3) recurrent CA-CDI cases are independent. Only incident CA-CDI cases (see surveillance definition) will be included as outcome events in this

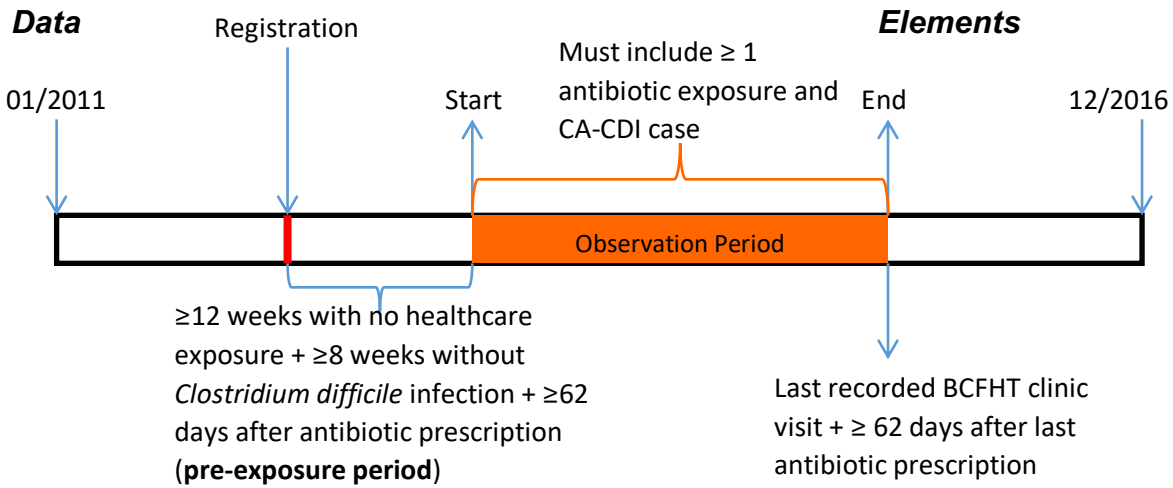
study since recurrent CA-CDI ≤ 8 weeks of an incident CA-CDI are assumed to be related.

Methodology

Data Collection Period

The BCFHT database will be the source of all patient data. The data collection will be limited to January 1, 2011 to December 31, 2016. Healthcare exposure will be determined by linking the BCFHT database to the Royal Victoria Hospital (RVH) database. The RVH is the sole hospital in Barrie, Ontario, and is assumed to be the primary site of acute healthcare for all the BCFHT patients. The observation period is not fixed, but will be determined by the period of patient registration with the BCFHT, along with healthcare exposure and *Clostridium difficile* infection (Figure 2).

Figure 2: Schematic of the observation period (start and end points) for a hypothetical patient.



The data elements, their descriptions and their definitions are described in Table 1. Antibiotic exposure will be categorized *a priori* as "high risk", "low risk" and no exposure (3 categories). Specifically, "high risk" antibiotic exposure includes any prescriptions for fluoroquinolones (moxifloxacin, levofloxacin or ciprofloxacin), clindamycin or cephalosporins (cephalexin, cefprozil, or cefuroxime). These antibiotics have been categorized as "high risk" from their estimated effect size ORs from the 2 previous meta-analyses (7, 8). They have been combined into a

single “high risk” exposure category on the assumption that their effect sizes overlap given their estimated 95% confidence intervals (7, 8). The same rationale was used to create the “low risk” exposure category.

Table 1: Data dictionary

Variable	**Definition**	**Type**	**Categories**
CA-CDI	PHL positive assay + no healthcare exposure ≥ 12 weeks + no previous *Clostridium difficile* infection ≥ 8 weeks	Outcome	0=no; 1=case
CA-CDI Date	Date of CA-CDI diagnosis	Outcome	DDMMYY
Antibiotic	Any prescription ≥1 dose	Exposure	2 = high risk (fluoroquinolones, clindamycin, cephalosporins); 1 = low risk (penicillins,

			amoxicillin, amoxicillin-clavulinate, macrolides, sulfonamides, tetracyclines, nitrofurantoin, fosfomycin, metronidazole); 0 = none
Antibiotic Date	Date of prescription	Exposure	Start and end dates (DDMMYY)
Duration	Days of antibiotic prescription	Effect modifier	0=less than 5 days; 1=5 days or more
Age	Years at time of diagnosis	Confounder	0=younger than 65 years old; 1=65 years and older
Season	Season at time of diagnosis	Confounder	Winter, spring, summer, fall
Year	Year at time of diagnosis	Confounder	2011-2016

Sample Size Calculation

Sample size calculations for SCCS are dependent on the effect size, and the ratio of the duration of exposure to non-exposure periods (12). In addition, the exposure variable has two independent categories ("high risk" vs none and "low risk" vs none) that will require separate hypothesis testing resulting in a multiplicity effect that may inflate the Type I error rate (13). As a result, multiplicity adjustments using the Hochberg procedure will be applied to preserve the error rate at the nominal Type I error rate = 0.05 (13). This multiplicity adjustment requires that the sample size calculation be estimated using a Type 1 error rate (α) = 0.05/2. Assuming a conservative effect size OR of 1.8 (7, 8), the number of CA-CDI cases needed to detect this effect are estimated in Table 2.

Table 2: Estimated sample sizes needed to detect an effect size OR of 1.8 for different ratios of exposure:non-exposure risk periods, powers, type I error rate and the multiple hypothesis testing problem (12, 13).

Power (%)	**Type I error (α)**	**Ratio (exposure/Non-exposure)**	**Sample size (CA-CDI cases)**
90	0.025	0.6	161
90	0.025	0.4	148
90	0.025	0.2	203
90	0.025	0.1	344

90	0.025	0.05	636
80	0.025	0.6	121
80	0.025	0.4	114
80	0.025	0.2	159
80	0.025	0.1	274
80	0.025	0.05	509

A preliminary screen of the BCFHT identified approximately 2,000 *Clostridium difficile* cases from January 2011 to December 2016, suggesting that 500 to 700 CA-CDI cases will be available for analysis (assuming 25% to 35% of all *Clostridium difficile* infections are due to CA-CDI).

Data Analysis

Conditional poisson regression analysis will be used to estimate the overall relative incidence rate ratio (IRR) for the risk of CA-CDI following exposure to antibiotics. The overall relative IRR is a ratio of the incidence rate of CA-CDI in the exposure period compared to the incidence rate of CA-CDI in the non-exposure period. The exposure period is defined as the interval starting 2 days after an antibiotic prescription (date of prescription in EMR) and continuing for the next 60 days. The non-exposure periods are defined as the remaining intervals in the observation period [=Total observation period (days) – exposure period (days)]. The observation period start date is defined as the day after the pre-exposure

period ends (Figure 2). The pre-exposure period is defined as the time after patient registration with BCFHT that is also ≥ 12 weeks after any healthcare-related exposure and ≥ 8 weeks after a previous case of *Clostridium difficile* infection and ≥ 62 days after any antibiotic prescription. The observation period end date is defined as the day of the last recorded BCFHT clinic visit regardless of the reason (eg, death versus moving out of the BCFHT catchment area) (Figure 2). The observation period end date must also be ≥ 62 days after the last antibiotic prescription to ensure that the entire exposure period is accounted for in the analysis (Figure 2). The SCCS design permits multiple exposure periods and incident CA-CDI cases to be included in the final model. An IRR > 1 implies an increased risk of CA-CDI following antibiotic exposure, an IRR < 1 implies a reduced risk of CA-CDI following antibiotic exposure and an IRR = 1 implies no difference in risk of CD-CDI following antibiotic exposure. Antibiotic exposure will be categorized as "high risk", "low risk" and no exposure. The null hypothesis for the high-risk antibiotic exposure category (IRR=1) will be rejected, according to the Hochberg procedure, if $p_{High\ Risk} \leq \alpha/2$ OR ($p_{High\ Risk} \leq \alpha$ and $p_{Low\ Risk} \leq \alpha$), where $\alpha=0.05$ (Type I error rate) (13). The null hypothesis for the low risk antibiotic exposure category (IRR=1) will also be rejected, using Hochberg's procedure, if $p_{Low\ Risk} \leq \alpha/2$ OR ($p_{Low\ Risk} \leq \alpha$ and $p_{High\ Risk} \leq \alpha$), where $\alpha=0.05$. Duration of antibiotic therapy will be incorporated as an effect modifier in the final model by creating an

interaction term with antibiotic exposure and including this interaction term as a separate variable. Temporal trends will be accounted for by the season variable given the known seasonal variation that exists with *Clostridium difficile* infection (14). In addition, the laboratory tests used for the diagnosis of *Clostridium difficile* infection have changed over the years of the study from those based on enzyme-linked immunosorbent assays to DNA-based assays (15). The DNA-based tests are more sensitive than their predecessors, and have been demonstrated to increase the detection of *Clostridium difficile* toxin by up to 2-fold (16). The year variable (Table 1) will be included as a confounder in the final model to account for this temporal change in laboratory tests. While age will be included as a time-variant confounder, it is unlikely that any significant proportion of the cases will transition between the dichotomous categories during the observation period, thus making age more similar to a time-invariant confounder that will be eliminated as a result of the SCCS design.

Expected Outcomes

Given the results from the previous observational studies, the investigator expects that the “high risk” antibiotic exposure category will be associated with an increased risk of CA-CDI but the effect size will be much more moderate (IRR 2-3). This less biased effect size is expected because the SCCS design should reduce the bias associated with both observed and unobserved time-invariant confounders, given that they are eliminated in

the final model. In addition, the investigator expects that the "low risk" antibiotic exposure effect size will trend to the null, and may eventually demonstrate no association with CA-CDI. The investigator also expects that prolonged courses of antibiotic treatment duration will increase the risk of CA-CDI, regardless of the risk category of antibiotic exposure. Both of these findings should nudge physician-prescribing behaviour to promote the use of less risky antibiotics for shorter treatment durations, both of which have been recommended to reduce the risk of adverse patient outcomes and minimize the emergence of antibiotic resistance.

In the future, it would be ideal to conduct a prospective observational study using the SCCS design and incorporating the time-invariant confounder of household member exposure to any healthcare facility so that the effect size of this potential risk factor could be estimated. These results could be used to develop a simple screening risk tool that could be validated for predicting the risk of CA-CDI given both antibiotic exposure and household member exposure, and subsequently used by both family physicians and their patients to help make informed decisions about treatment. In addition, the impact of preventative measures such as probiotic administration or environmental cleaning strategies for the household could be tested in randomized controlled studies for those patients who require antibiotic treatment with a high-risk class antibiotic

and are exposed to household members who increase their risk of CA-CDI.

Study Limitations

This is an observational study, so we cannot be certain that any association that may be demonstrated to exist between antibiotic exposure and CA-CDI is causal in nature. We are assuming that an antibiotic prescription implies medication compliance, thus potentially leading to definition bias. Because of its retrospective design, the potentially important confounder of exposure to household members who may have had or have ongoing healthcare exposure or who were diagnosed with *Clostridium difficile* infection will remain unobserved, potentially leading to unobserved confounder bias. Detection and selection bias may be important limitations given that only patients who present to the BCFHT with diarrheal symptoms may be diagnosed with CA-CDI, thus potentially underestimating the true incidence of disease in this target population. In addition, given the change in diagnostic testing strategies, this may also contribute to detection bias with a lower incidence of CA-CDI expected in the early years of the study period compared to the more contemporaneous period even after accounting for year of diagnosis. Definition bias may result from limiting the definition of healthcare exposure to the Royal Victoria Hospital, given that these CA-CDI cases may have had healthcare exposures in other acute healthcare facilities.

Assumptions of the SCCS design may be violated (see ***Model*** section), leading to concept bias. The sample size calculations assume a consistent exposure:non-exposure ratio for each case, but this ratio is likely to be quite variable across cases and may result in underestimation of the required number of cases needed, potentially leading to an underpowered study and false negative effect size. In addition, the power to detect antibiotic class effect sizes may not be possible due to an insufficient number of cases, thus limiting conclusions about associations between exposure and cases to groups of antibiotic classes. While the exposure risk period has been defined to include the majority of CA-CDI cases associated with antibiotic exposure, there may be cases that occur within 90 to 180 days after antibiotic exposure that may be misclassified as non-exposure-related CA-CDI cases, thus contributing to definition bias.

Ethics

The study requires both examination of personal health information and database linkage across healthcare institutions, and so research ethics approval will be required. However, a complete waiver of informed consent will be requested from both the BCFHT research ethics board and the Royal Victoria Hospital research ethics board on the basis that this is a retrospective study that involves no more than minimal risk to the subjects, the waiver would not adversely affect the rights and welfare of the

subjects, and the research could not practicably be carried out without the waiver given informed consent would have to be sought from each registered BCFHT patient from 2011 to 2016 who met the inclusion criteria, thus potentially requiring the investigator to contact hundreds, perhaps even thousands, of patients.

Database Security

While cases will only be identified using a unique random number and none of the data elements are direct identifiers, given the limited number of cases, the CA-CDI date variable may be considered a quasi-identifier (17). Despite the absence of any other quasi-identifiers, it is likely that each case will represent an equivalence class of size one (17), potentially increasing the risk of re-identification. To this end, only the investigator will have access to the database through a data sharing agreement with the BCFHT, and the database will be kept on a password-protected USB memory stick that will be stored in a locked cabinet in a locked office. Once the study is complete, the USB memory stick will be returned to the BCFHT to be kept in a secured environment for 10 years, subsequent to which the data will be permanently erased.

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Chapter 8: Antibiotic Exposure and Risk of Community-associated *Clostridium difficile* Infection: A Self-Controlled Case Series Analysis

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Declaration of Academic Achievement

GD conceived the study, design and analytic plan, and drafted the protocol manuscript.

LLF was directly involved in the analytic plan and edited the protocol manuscript.

ABSTRACT

We estimated the association between antibiotic exposure and community-associated *Clostridium difficile* infection among 139,000 patients registered to the Barrie Family Health Team from January 1, 2011 to May 1, 2017 using a self-controlled case series (SCCS) design. Poisson regression analysis was used to estimate the incidence rate ratio (IRR) between antibiotic exposure versus non-exposure periods within individuals. Antibiotic exposure was categorized as either high risk (fluoroquinolone, clindamycin or cephalosporin) or low risk (all other antibiotic classes). Year of diagnosis was included to account for unobserved time-varying covariates. The interaction between proton pump inhibitor use and infection was included in the model. The final analysis included 189 cases. The pooled IRR for high risk antibiotics was 2.26 (95% confidence interval (CI): 1.29, 3.98) and 2.03 (95% CI: 1.19, 3.47) for lower risk antibiotics. There was no difference between high risk and lower risk antibiotics (IRR 1.11, 95% CI: 0.53, 2.36). Proton pump inhibitor use was not an effect modifier. The IRRs were smaller than the odds ratios reported in previous case control studies, suggesting a less biased estimate because SCCS designs control for time-invariant confounders. Compared to case control studies, SCCS designs are underutilized in infection prevention and control studies.

Clostridium difficile is an anaerobic bacterium that has been associated with mild to life-threatening diseases of the intestine (1). The most consistently reported risk factors are age over 65 years, prolonged hospitalization and recent antibiotic exposure (2). Research has suggested that these risk factors disrupt the intestinal flora and predispose patients to opportunistic infections with *Clostridium difficile* (1). The estimated incidence of community-associated *Clostridium difficile* infection (CA-CDI) ranges from 10.0 to 60.5 cases per 100,000 populations, accounting for 25% to 35% of all *Clostridium difficile* cases (3, 4). Unlike hospital-associated CDI (HA-CDI), antibiotic exposure is not as consistently associated with CA-CDI with up to 50% of cases reporting no exposure in the 3 month period preceding the diagnosis (5, 6).

Two recent meta-analyses estimated odds ratios (ORs) for the association between antibiotic exposure and CA-CDI (7, 8). The pooled ORs were 3.55 (95% CI 2.56, 4.94) and 6.91 (95% CI 4.17, 11.44). The antibiotics with the strongest association were fluoroquinolones (ORs 5.50 and 5.65), clindamycin (ORs 16.8 and 20.43) and cephalosporins (ORs 5.68 and 4.47). These ORs are several-fold larger than the corresponding ORs for HA-CDI. For example, the OR for clindamycin use and risk of HA-CDI was estimated to be 2.31 (95% CI 1.84, 2.91), or 15% of the effect seen for CA-CDI (9). This discrepancy is a consistent finding across all

antibiotic classes, with ORs for CA-CDI far exceeding those for HA-CDI, suggesting confounding bias may be inflating the association between antibiotic exposure and CA-CDI.

Case control studies have been used to estimate these ORs. Like all observational studies, case control studies cannot account for unobserved confounders resulting in significant bias in OR estimates. SCCS designs represent "an alternative epidemiologic study design" that can be used "to investigate an association between a transient exposure and an outcome event" (10). Unlike case control studies, SCCS designs can account for unobserved, time-invariant confounders because each individual acts as their own control. By dividing each case's observation period into exposure-risk and non-exposure-risk periods, an incidence rate ratio (IRR) can be estimated. The advantages of SCCS over case control designs include the elimination of the need for separate matched controls, time-invariant confounders are automatically accounted for in the design, time-varying confounders can be included in the model, multiple exposure periods within the same individual can be included and there is no requirement that the exposure must precede the outcome, only that the observation includes both the exposure and outcome (10).

The primary objective of this study was to estimate the strength of association between antibiotic exposure and CA-CDI and compare this to ORs estimated from case control studies.

METHODS

Study setting and population

The Barrie and Community Family Health Team (BCFHT) is the largest integrated community-based primary practice in Ontario, Canada's most populous province. The BCFHT consists of 86 physician practices with over 139,000 registered patients. The BCFHT serves the city of Barrie with a population of 146,000. The Royal Victoria Regional Health Centre is the only hospital in Barrie. From January 1, 2011 to May 1, 2017, all adults over 18 years old registered with the BCFHT who were diagnosed with CA-CDI and exposed to any antibiotic therapy were eligible for inclusion. An incident case of CA-CDI was defined by a positive stool culture or any diagnostic test for *Clostridium difficile* in the community or within 3 days of admission to a healthcare facility, with no previous history of an overnight stay in any healthcare facility in the preceding 12 weeks, and with no previous CDI in the preceding 8 weeks(4). Antibiotic exposure was defined as any antibiotic prescription ≥ 1 dose that was documented in the patient's electronic medical record.

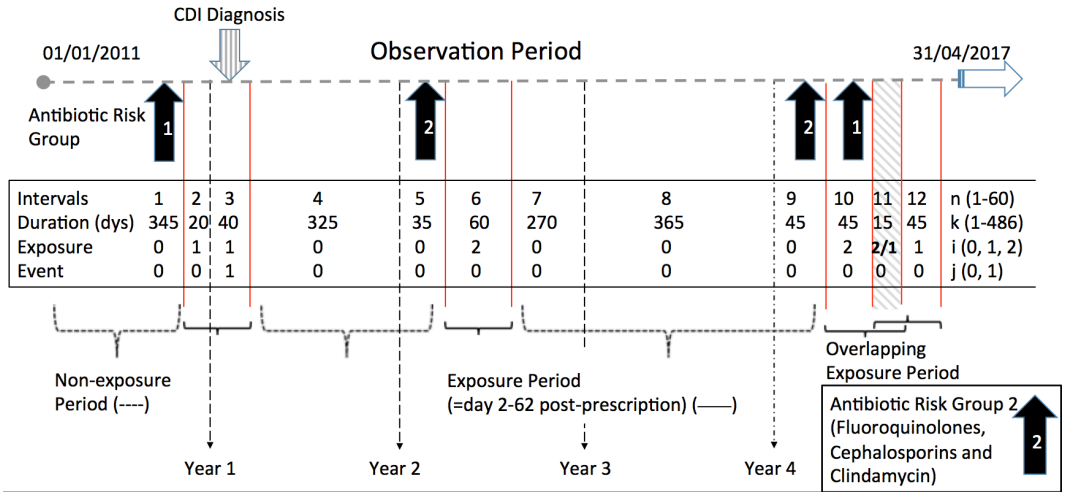
Since 2011, the BCFHT has utilized the *Accuro*® electronic medical record system for all registered patients. For identification of adult patients with an incident case of CA-CDI and antibiotic exposure, the system administrator queried the database. CA-CDI cases were identified using the public health laboratory reports directly inputted into the electronic

medical record. All stool testing for *Clostridium difficile* infection is done by the public health laboratory. Healthcare-exposure in the 12 weeks preceding the diagnosis of CA-CDI was available through a link between the BCFHT and Royal Victoria Regional Health Centre databases. Research ethics approval was obtained from the institutional review boards of both the Royal Victoria Regional Health Centre and the BFCHT.

Study design and outcomes

This was a retrospective, observational study using the SCCS design. The SCCS design divided each CA-CDI case's observation period into antibiotic-exposure and non-exposure periods (Figure 1).

Figure 1: Schematic of observation period for a hypothetical CA-CDI case (See main text for a detailed explanation of the design).



The start of each CA-CDI case's observation period was defined as January 1, 2011 if the patient was registered prior to this date and was also ≥ 12 weeks after any healthcare-related exposure and ≥ 8 weeks

after a previous case of *Clostridium difficile* infection and ≥ 62 days after any antibiotic prescription. For those patients registered at a later date, this date was defined as the start date as long as all the other aforementioned conditions were met. The observation period end date was defined as the day of the last recorded BCFHT clinic visit regardless of the reason (eg, death versus moving out of the BCFHT catchment area) and ≥ 122 days after the last antibiotic prescription to ensure that the entire exposure period was accounted for in the analysis. The antibiotic exposure period was defined as starting 2 days after an antibiotic was prescribed and continued until 62 days after that prescription. This interval was chosen as it represents the highest risk period for CDI after antibiotic exposure and was consistently included in previous case control studies (7, 8). In addition, to account for unobserved time-varying confounders, the observation period was further divided into yearly intervals (Figure 1). The final number of intervals (n) and interval lengths for each CA-CDI case (j) was unique and dependent on the duration of the observation period (k), the number of antibiotic prescriptions, and the yearly intervals (Figure 1).

Antibiotic exposure was categorized *a priori* as “high risk”, “low risk” and no exposure (i) (3 categories: high risk=2; low risk=1; no exposure=0). Specifically, “high risk” antibiotic exposure included any prescriptions for fluoroquinolones (moxifloxacin, levofloxacin or ciprofloxacin), clindamycin

or cephalosporins (cephalexin, cefprozil, or cefuroxime). These antibiotics were categorized as "high risk" from their estimated effect size ORs from the 2 previous meta-analyses (7, 8). They were combined into a single "high risk" exposure category on the assumption that their effect sizes overlapped given their estimated 95% confidence intervals (7, 8). The same rationale was used to create the "low risk" exposure category. If there were overlapping intervals due to multiple antibiotic exposures, the intervals were categorized as the higher risk antibiotic exposure. For example, if a patient had received a low risk antibiotic, but 32 days after this prescription they were prescribed another course of antibiotics with a high risk agent, then the last 30 days of the first low risk antibiotic exposure interval were categorized as a high risk exposure interval (Figure 1).

Proton pump inhibitor (PPI) use was included as a covariate in the final model, along with its interaction with antibiotic exposure to detect evidence for effect modification of the association between antibiotics and CA-CDI. Patients prescribed any PPI (omeprazole, esomeprazole, lansoprazole, rabeprazole, or pantoprazole) at any time during the observation period were categorized as having been exposed to PPIs.

Statistical analysis

Conditional poisson regression analysis was used to estimate the overall incidence rate ratio (IRR) for the risk of CA-CDI following exposure

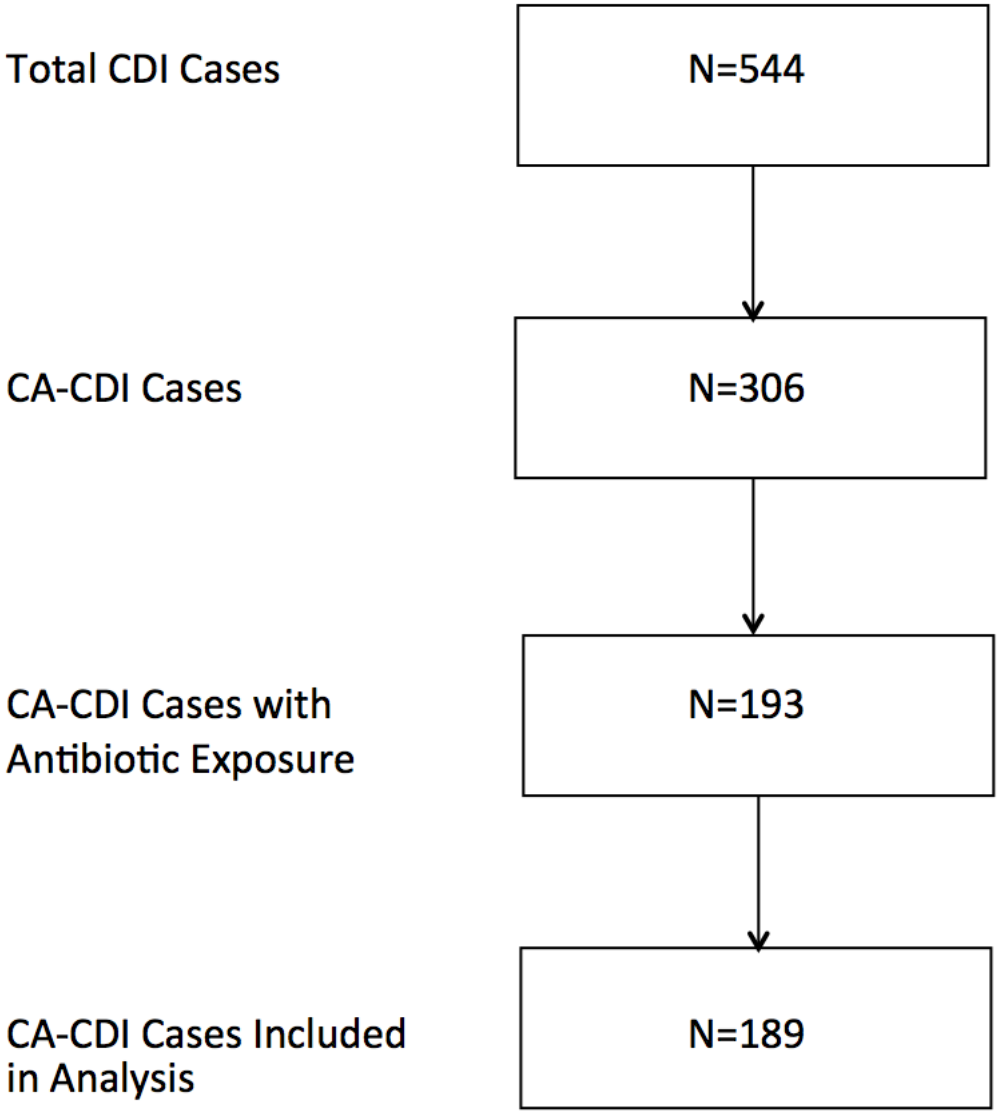
to antibiotics (10). The overall IRR is a ratio of the incidence rate of CA-CDI in the exposure period compared to the incidence rate of CA-CDI in the non-exposure period. The SCCS design permits multiple exposure periods and incident CA-CDI cases to be included in the final model. An IRR > 1 implies an increased risk of CA-CDI following antibiotic exposure, an IRR < 1 implies a reduced risk of CA-CDI following antibiotic exposure and an IRR = 1 implies no difference in risk of CD-CDI following antibiotic exposure. In addition, the laboratory tests used for the diagnosis of *Clostridium difficile* infection have changed over the years of the study from those based on enzyme-linked immunosorbent assays to DNA-based assays (11). The DNA-based tests are more sensitive than their predecessors and have been demonstrated to increase the detection of *Clostridium difficile* toxin by up to 2-fold (12). The year variable was included in the final model to account for possible confounding bias due to this temporal change in laboratory tests and to account for changes in patient age. In addition to estimating the IRR, the attributable proportion of CA-CDI due to antibiotic exposure was estimated by using the following formula = [(IRR – 1)/IRR]*100%, along with 95% confidence intervals. Sample size needed to demonstrate an IRR 2 with 90% power and type 1 error rate of α=0.025 was calculated as 172 CA-CDI cases for a ratio of exposure to non-exposure risk period durations of 0.1 (13). To test the SCCS independence assumption between outcome and subsequent

exposure, we will estimate the marginal difference in the mean interval lengths (days) between CD-CDI-antibiotic exposures versus antibiotic-antibiotic exposures using non-parametric regression analysis using the *npregress* command in STATA 15.0. The standard error will be estimated using resampling and adjusted for clustering within individuals. STATA/MP 15.0 for Mac (64-bit Intel) was used for all statistical analyses.

RESULTS

There were 189 CA-CDI cases included in the final analysis (Figure 2). The average age was 57.5 years, (standard deviation (SD) 18.0), with females accounting for 75% of cases. The number of antibiotic prescriptions ranged from 1 to 13 per individual, with an average of 2.7 (SD 2.1). The intervals between antibiotic courses ranged from 1 to 2,162 days, with a median of 249 days (interquartile range (IQR) 113 to 492). The number of intervals per patient's observation period ranged from 1 to

Figure 2: Flow Diagram for CA-CDI Cases



60. These interval durations ranged from 1 to 486 days, with a median of 60 days (IQR 34 to 338). The total duration of all the observation periods was 415,338 days, with 10.2% of the days apportioned to exposure periods. Approximately 25% of patients were prescribed a PPI.

The IRR for high risk versus low risk antibiotic exposure was estimated to be 1.11 (95% CI: 0.53, 2.36) (Table 1).

Table 1. Incidence Rate Ratio (IRR) Estimates for High and Low Risk Antibiotic Exposures

Antibiotic Exposure Group	**IRR**	**95% Confidence Interval**	**P-value**
0	Baseline	N/A	N/A
1	2.03	1.19, 3.47	0.009
2	2.26	1.29, 3.98	0.005

There was no evidence for any effect of PPI use on increased risk of CA-CDI in any antibiotic risk category. The attributable proportion of CA-CDI due to antibiotic exposure exceeded 50% (Table 2) for both antibiotic classes.

Table 2. The Attributable Proportion of CA-CDI due to Antibiotic Exposure (Using IRR estimates and 95% Confidence Intervals from Table 1)

Antibiotic Exposure Group	**Attributable Proportion (%)**	**95% Confidence Interval**
0	Baseline	N/A
1	50.7	16.0, 71.2
2	55.7	22.5, 74.9

In a sensitivity analysis using an exposure risk interval of 120 days (starting 2 days after prescription and continuing until 122 days after

prescription) to account for both prolonged courses of antibiotic use or prolonged periods of risk, the results remained relatively unchanged, with a non-statistically significant trend to lower IRRs for each antibiotic risk category (Table 3).

Table 3. Incidence Rate Ratio (IRR) Estimates Using an Exposure Risk Interval of 120 Days (instead of 60 days) After Antibiotic Prescription.

Antibiotic Exposure	**IRR**	**95% Confidence Interval**	**P-value**
0	Baseline	N/A	N/A
1	1.61	1.00, 2.57	0.048
2	2.12	1.32, 3.41	0.002

The overall mean interval between outcome-exposure and exposure-exposure was approximately 156 days (95% CI: 143, 170). The marginal difference between the mean interval lengths between CA-CDI-antibiotic exposures and antibiotic-antibiotic exposures was estimated at approximately 5 days (95% CI: 3, 8) longer in the CA-CDI-antibiotic exposure group.

DISCUSSION

Compared to the ORs from the previous case control studies, the IRRs estimated using the SCCS design were significantly different and suggested a much weaker association between antibiotic exposure and CA-CDI. Unlike previous case control studies, the IRRs for high risk and

low risk antibiotic exposures estimated by the SCCS design did not demonstrate any statistically significant differences with both groups increasing the overall risk of CA-CDI by approximately 2-fold. This may represent an important finding that may help inform antimicrobial stewardship efforts in primary care practices, suggesting that there may not be such a thing as a "safer" antibiotic class for minimizing the risk of CA-CDI. This might help "nudge" physicians to be more prudent in prescribing antibiotics to patients with minimal symptoms because they may feel less reassured by the notion that there is a "safer" antibiotic alternative. More prudent prescribing may also lead to a reduction of 50% of CA-CDI cases in the population according to our results.

These IRRs are much more consistent with previous ORs estimated for HA-CDI associated with antibiotic exposure. Many methodological issues plague the results from the 2 meta-analyses. In these meta-analyses, 5 and 8 observational studies, respectively, were used to calculate a pooled OR to estimate the association between antibiotic exposure and CA-CDI (7, 8). All the individual studies were either case control or nested case control studies. The matching criteria varied significantly between studies but were limited to age, clinic site, date of diagnosis, comorbidities, and/or medications used for gastric acid suppression. The quality scores of the included studies ranged from 3 to 7 (out of a maximum score of 7). There was significant heterogeneity of

effect sizes (I^2 = 90.6% and I^2 = 95%, respectively) demonstrated between studies in both meta-analyses (7, 8). Even after stratifying the results by antibiotic class, overall effect heterogeneity was reduced by 55% but this reduction varied across antibiotic classes. For example, effect heterogeneity remained high for clindamycin (I^2 = 76%), cephalosporins (I^2 = 97%), penicillins (I^2 = 85%), and macrolides (I^2 = 42%). For other antibiotic classes, effect heterogeneity was eliminated (fluoroquinolones, sulfonamides and tetracyclines).

The advantages of the SCCS design over case control studies include improved efficiency due to the elimination of the need for separate controls. SCCS designs are also able to control for all unobserved time-invariant confounders, while still being able to incorporate time-varying confounders in the model. This is especially important for the case of CA-CDI because there are many non-traditional risk factors that are hypothesized to contribute to an increased risk of disease, such as diet, exposure to infants less than 2 years of age, and job occupation(5).

This is an observational study, so we cannot be certain that any association demonstrated to exist between antibiotic exposure and CA-CDI is causal in nature. We are assuming that an antibiotic prescription implies medication compliance. SCCS designs assume that the outcome will not affect subsequent exposures. We examined this independence assumption by comparing the marginal difference in mean interval lengths

(days) between CA-CDI-antibiotic exposures versus antibiotic-antibiotic exposures. While the mean interval lengths were longer in the CA-CDI-antibiotic exposures group compared to the antibiotic-antibiotic exposures group, the difference of 5 days is unlikely to be clinically significant given this represents less then 3% of the overall mean length of the intervals. However, we cannot be certain that the independence assumption has not been violated given these results. Because of its retrospective design, the potentially important confounder of exposure to household members who may have had or have ongoing healthcare exposure or who were diagnosed with *Clostridium difficile* infection will remain unobserved, potentially leading to unobserved confounder bias. We only had data on healthcare facility exposure for the Royal Victoria Regional Health Centre, so it could be possible that some of these cases had other healthcare-related exposures that we would not have detected.

In summary, we demonstrated that the association between antibiotic exposure and CA-CDI estimated from case control studies may be upwardly biased and may be more consistently measured by using a SCCS design. The SCCS design is a relatively novel epidemiologic model that provides infection prevention and control practitioners the opportunity to test hypotheses using observational data in a more efficient and consistent manner than is currently available through case control studies.

The SCCS design should be incorporated as a standard feature in the education curriculum for IPAC practitioners and epidemiologists.

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PRESENTATIONS

This work was presented at the Infectious Diseases Conference of America (IDWeek) 2017 conference in San Diego, California on Friday, October 6 at Poster Abstract Session 150: HAI: C. difficile Risk Assessment and Prevention, Poster #1300; *Antibiotic Exposure and Risk of Community-associated Clostridium difficile infection (CA-CDI): A Self-Controlled Case Series Analysis*

POTENTIAL CONFLICTS OF INTEREST

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

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13. Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Stat Med. 2006 Aug 15;25(15):2618-31.

Chapter 9: Conclusion

Before 2013, the Royal Victoria Regional Health Centre resembled every other large community hospital in the province of Ontario. It is a large acute care institution, with an operational budget of approximately $400 million dollars, provides care to about 20,000 medical and surgical patients on a yearly basis, and is a regional referral centre to a population of 400,000 residents. The hospital is well administered, provides good clinical care and sporadically, a health care provider conducts some kind of research study that might be published but that everyone else would be otherwise impervious to its results. On occasion, academic researchers come knocking at our door to see if they could entice us to help them recruit patients for their studies; studies that answer their pre-specified questions, studies that we have no involvement in designing, and studies that have no space for either our or our patients' input, and are thus rarely transformational to the care we provide in our organizations or in the building of our own independent research capacity and competency. This research model is most recently referred to as integrated Knowledge Translation (iKT) by academic researchers and their partner research funding agencies such as the Canadian Institute for Health Research (1). Those of us in non-academic centres simply refer to the iKT model as a misguided attempt to rectify the known pandemic of wasted research

activities that this system has unintentionally created (2, 3), at least as it pertains to health services research.

In 2013, the Royal Victoria Regional Health Centre decided to do something quite unique among non-academic hospitals. The hospital committed to embedding research *a priori* into a new antimicrobial stewardship program. More than that, it committed to embedding a local researcher into the program. What was the rationale for the organization to commit to this novel way of implementing health services within the organization? The organization came to the realization that the organizations that provide the best patient care and health services are those that embed research into their daily clinical activities. In my experience, here are the ten steps that are needed to transform any community hospital into a learning health centre.

Step 1

It is not any more complicated than having the right person (embedded researcher) available at the right time (new Accreditation Canada requirement of practice for antimicrobial stewardship programs). This is the first lesson of this thesis; in organizations like the Royal Victoria Regional Health Centre, identifying the right person to lead the transformation into a learning health centre is the first and most important step. In these organizations, the impact that a single embedded researcher can have on the organization is enormous and unique to non-

academic centres. The key is that the embedded researcher is someone local, with tremendous influence as a result of established clinical relationships.

Step 2

These influential people need to have the research capacity and competency to support health services research within the organization (4) That means organizations that have identified the right person should do everything they can to support their research education. Organizations need to invest in the education of these local embedded researchers if they don't already possess this expertise. That means not only subsidizing their post-graduate educational fees, but also subsidizing the time required for them to complete their degree requirements. Ideally, the costs would be subsidized through the organization's educational trust fund. Return of service agreements that outline the organization's expectations are a necessary part of this mutually beneficial arrangement and should include the following: a promise to conduct all degree program-required research activities locally, a promise to establish a research infrastructure that facilitates research activities within the organization, and a promise to remain with the organization for a mutually agreed upon period of time.

Step 3

All research activities that are required by the embedded researcher's post-graduate degree program should be conducted within the non-academic organization, and involve as many local programs and personnel as can be accommodated. This preliminary research work is vital for informing the embedded researcher of all the bottlenecks and barriers that exist within the organization that prevent the wider adoption of embedding research into all clinical activities. Without this organizational intelligence, the embedded researcher will struggle to create a system that supports the creation of a learning health centre.

Step 4

Operational funding of an embedded research position within the organization that realistically reflects the time commitment needed to support the aspirational research goals of the organization. In the first year, this time commitment is significant and should be at least 0.5 full-time equivalents. After the first year, depending on how much research activity exists within the organization, this time commitment may decrease but not substantially below 0.4 full-time equivalents. The organization should guarantee this operational funding for a minimum period of 5 years to provide some income security for the embedded researcher who must sacrifice part of their clinical practice to support the organization. This minimum 5-year commitment also allows the affected clinical departments

to appropriately plan for the loss of clinical services from the embedded researcher.

Step 5

The organization should attempt to create a local Research Ethics Board (REB), or if that is not feasible, partner/contract with an organization that has an REB. To facilitate the REB process, the hiring of a full-time Research Manager to help guide and manage REB submissions is critical. Many would-be community-based researchers find the REB process onerous, confusing and frustrating and having someone in the organization to assist them is invaluable. Ideally, the Research Manager should have a post-graduate degree and be familiar with the ethical and legal regulations governing human research activities. If possible, the organization should invest in a software system that supports electronic REB submissions in order to standardize, facilitate and audit the entire REB process.

Step 6

The embedded researcher should create a standardized study intake process for all research and quality improvement studies. At the Royal Victoria Regional Health Centre, the Chief Research Scientist (embedded researcher) has developed a standardized approach to the study intake process (Figure 1). This involves an informal consult with the

Chief Research Scientist to ensure that the basic requirements for study success are met;

i) Principal investigator has secured the support of ≥ 2 peers and ≥ 1 administrative leader, and

ii) Research question fulfills FINER criteria (5)

Once these requirements are met, the investigators are required to complete a standardized NEW STUDY INTAKE FORM (Figure 2). The study intake form is intended to make the investigators think critically about whether their research ideas and questions are worth committing their effort and time to study. Part of the new study intake form is the RE-AIM checklist (6) Once completed, the investigators schedule a meeting with the Chief Research Scientist to review the form.

Figure 1: Study Intake Process

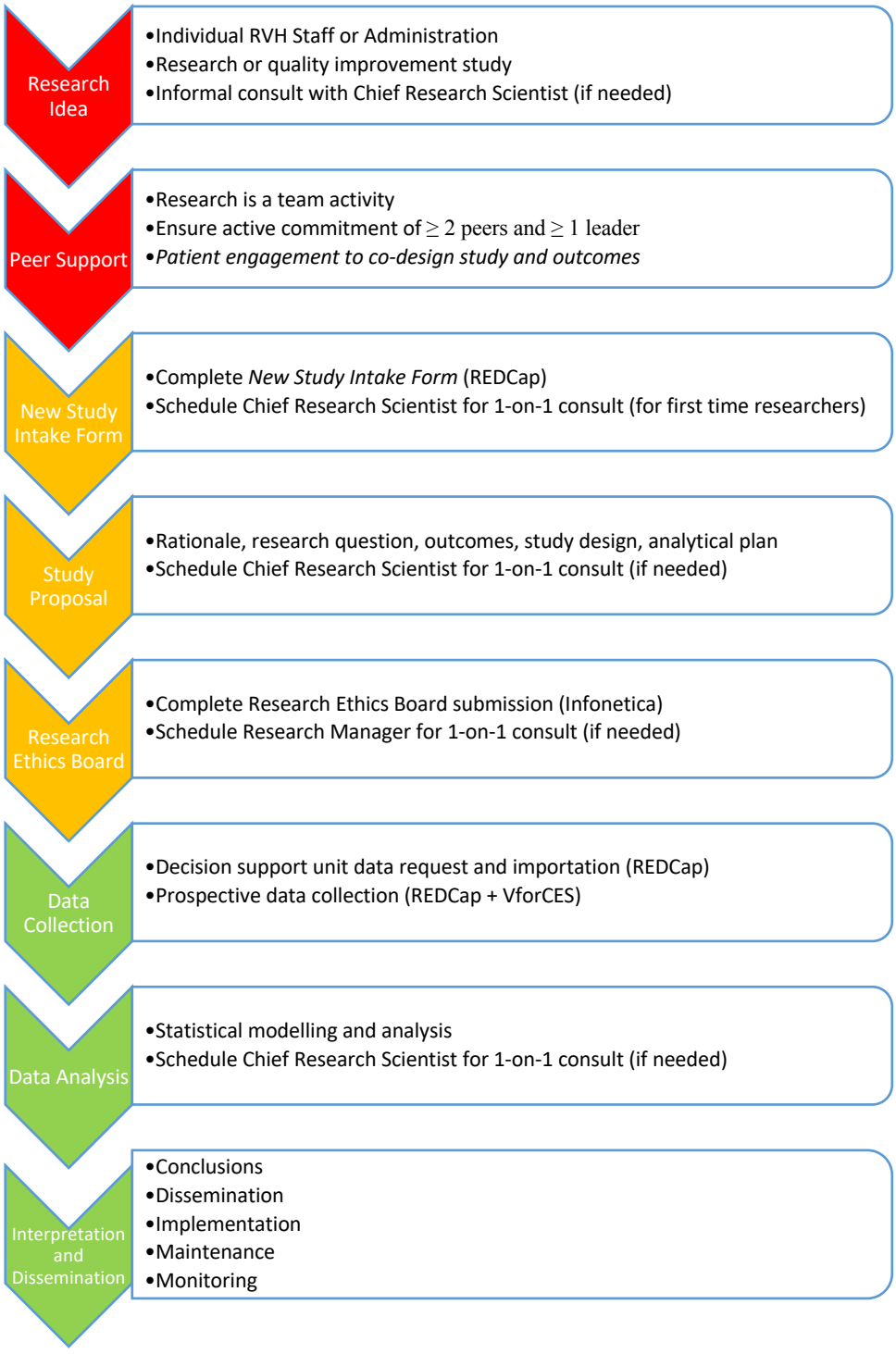


Figure 2: New Study Intake Form

Confidential

Section 1_Principal Investigator

Record ID _____

Research is a team sport, and most studies require the efforts of many collaborators to ensure their successful completion and implementation into practice. Prior to completing this form, please ensure that you have secured the support of at least 2 other collaborators and a senior administrator for whom the study is most pragmatically relevant.

Principal Investigator (First Name) _____
(Principal investigator means you are the study author and lead for your research team)

Principal Investigator (Last name) _____

Professional Grouping (eg, MD, Nurse, etc)
◯ physician
◯ nurse
◯ administrator
◯ respiratory therapist
◯ dietician
◯ social work
◯ physiotherapist
◯ occupational therapist
◯ pharmacist
◯ spiritual care
◯ volunteer
◯ librarian
◯ medical records
◯ environmental services
◯ food services
◯ decision support
◯ information technology
◯ clinical informatics
◯ SLP
◯ IPAC
◯ other

Department _____

Contact Email _____

Co-Principal Investigator
◯ Yes
◯ No
(Co-Principal Investigator means that you share the leadership responsibilities with the study Principal Investigator)

Co-Principal Investigator (First Name) _____

Co-Principal Investigator (Last name) _____

Co-Principal Investigator (Organization) _____

Senior Administrator (First name) _____

Senior Administrator (Last name) _____

Collaborator (First name) _____

Section 3_Research Question

Research Idea

(In plain language, state your research idea. EXAMPLE: Does the use of a surgical checklist reduce post-operative rates of infectious complications in general surgery patients undergoing cholecystectomy at night?)

Using the PICOT format (Population, Intervention, Control, Outcome, Time Frame), state your research question as specifically as possible. EXAMPLE: In adult patients over 65 years of age who undergo laparoscopic cholecystectomy between midnight and 7 am by any general surgeon with privileges at the Royal Victorial Regional Health Centre, does the utilization of the WHO surgical checklist by the anesthetist and general surgeon prior to surgery as determined by the random assignment of patients to either the checklist or usual practice result in decreased rate of post-surgical intra-abdominal abscess formation requiring either percutaneous drainage or re-operation within 30 days of surgery in patients undergoing the intervention from January 1, 2017 to December 31, 2017.

Population(s)

(Define in detail who you plan to recruit, observe or describe in your study.)

Intervention(s)

(Define in detail the intervention(s) you will assign, observe or describe in your study.)

Control(s)

(Define in detail the control and intervention group(s) you will directly assign, observe or describe in your study.)

Outcome(s)

(Define in detail the outcome(s) you will directly measure, observe or describe in your study.)

Time Frame

(Define in detail the duration of your study enrollment, or period of observation or description in your study.)

HYPOTHESIS.

An hypothesis is a statement that represents the testable transformation of a research question.

Hypothesis

_____
(State your null hypothesis. EXAMPLE:Eg. There will be NO difference in post-operative intra-abdominal abscess rates between ...)

Do you have more than one hypothesis?

◯ Yes
◯ No

Hypothesis

_____

Hypothesis

_____

Section 4_Study Design

What type of research study are you proposing to conduct?	◯ Primary (empirically observe a phenomenon at first hand, collecting, analyzing or presenting raw data) ◯ Secondary (interrogate primary research studies, summarizing and interrogating their data and findings) ◯ Theoretical or Conceptual (focus almost entirely on the construction of new theories rather than generating or synthesizing empirical data)
What type of data will you be collecting? (Check all that apply)	☐ Quantitative ☐ Qualitative
Why are you conducting this study (Check all that apply)	☐ Efficacy (No previous study, or equivocal results) ☐ Effectiveness (Efficacy or effectiveness demonstrated, but LOCAL relevance not yet established) ☐ Quality improvement (Program in place and local effectiveness established, but want to determine if program changes lead to improvement in outcomes) ☐ Summary (Summarize previous results) ☐ Descriptive (Summarize past and/or present disease epidemiology, outcomes, opinions, practices, etc...) ☐ Feasibility (Pilot study to determine if a larger study is feasible or study plan needs modification to ensure success) ☐ Exploratory (Hypothesis-generating, ie, exploration of associations between multiple risk factors/predictor variables with outcome(s)) ☐ Diagnostics (Assessment of test characteristics such as sensitivity and specificity, and predictive characteristics such as positive predictive or negative predictive values, likelihood ratios, area under an ROC curve, etc...)
What is your proposed study design?	◯ Experimental (Investigator has control over BOTH administration and assignment of intervention) ◯ Quasi-Experimental (Investigator has control over EITHER administration OR assignment of intervention, but NOT both) ◯ Observational (Investigator has NO CONTROL over either administration or assignment of intervention) ◯ Systematic Review (Exhaustive and systematic search for literature whose results are combined using formal quantitative or qualitative methods) ◯ Non-systematic Review (Less exhaustive search for literature and usually results are summarized in an informal (non-statistical) way) ◯ Descriptive (Qualitative or quantitative summary of an intervention, setting, illness, opinion, distribution of risk factors, etc...)

Section 5_Planning Checklist

The most important question to ask before deciding to commit the time and effort to conduct a study is "Does the study have a realistic chance to result in a clinically significant impact/improvement to patient, organizational, population or healthcare system outcomes?"

If the answer is "yes", then the best way to use this section would be to think about the issues raised, their pertinence to your study and to help you make any relevant changes before launching the study. The questions listed are generalized and meant as self-checks, so don't worry about not answering the ones that are not relevant to your unique study.

REACH

Do you hope to reach all members of your target population? If yes, provide a number or estimate for your target population. If no (due to large size of the target population or budget constraints), provide the proportion of the target population that you want to reach ideally given constraints.

_____

The demographics of my target population in terms of race/ethnicity, gender, age, and socioeconomic status are representative of the general population to whom the study results will apply?

◯ True
◯ False

How confident are you that your study will successfully attract all members of your target population regardless of age, race/ethnicity, gender, socioeconomic status and other important characteristics, such as health literacy?

Not at all confident | Somewhat confident | Completely confident

(Place a mark on the scale above)

What are the barriers you foresee that will limit your ability to successfully reach your intended target population?

_____

How do you hope to overcome these barriers?

_____

Rate how confident you are that you can overcome these barriers?

Not at all confident | Somewhat confident | Completely confident

(Place a mark on the scale above)

EFFECTIVENESS

Would you categorize your study intervention as evidence-based or a new innovation?

◯ evidence-based ◯ new innovation

Why did you choose this study intervention and its components?

_____

What are the strengths of your study intervention?

_____

Confidential

Have you come to agreement with key stakeholders about how you will define and measure "success"? ◯ Yes ◯ No

List the measurable objectives that you wish to achieve in order to accomplish your goal.

_____

What are the potential unintended consequences that may result from this study?

_____

Are you confident that your study intervention will achieve effectiveness across different subgroups, including those most at risk and having the fewest resources? If no, what can be done to increase the changes of success for these groups?

_____

Rate your confidence that this study intervention will lead to your planned outcome?

Not at all confident | Somewhat confident | Completely confident

(Place a mark on the scale above)

ADOPTION

What percent of other organizations such as yours will be willing and able to offer this study intervention after you are done testing?

_____

How confident are you that your study intervention will be adopted by those settings and staff who provide services for people in your target population who have the greatest need?

Not at all confident | Somewhat confident | Completely confident

(Place a mark on the scale above)

What do you think will be the greatest barriers to other sites or organizations adopting this study intervention?

_____

Do you have a system in place for overcoming these barriers? ◯ Yes ◯ No

What percent of your organization (e.g., departments, relevant staff, etc.) will be involved in supporting or delivering this study intervention?

_____

IMPLEMENTATION

How confident are you that the study intervention can be consistently delivered as intended?

Not at all confident | Somewhat confident | Completely confident

(Place a mark on the scale above)

How confident are you that the study intervention can be delivered by staff representing a variety of positions, levels and expertise/experience of the organization?

Not at all confident | Somewhat confident | Completely confident

(Place a mark on the scale above)

Confidential

Is your study intervention flexible (while maintaining fidelity to the original design) to changes or corrections that may be required midcourse? ◯ Yes ◯ No

Do you have a system in place to document and track the progress of the intervention and effect of changes made during the course of the study? ◯ Yes ◯ No

What is the greatest threat to consistent implementation and how will you deal with it?

_____

MAINTENANCE

What evidence is available to suggest the study intervention effects will be maintained six or more months after it is completed?

_____

How confident are you that the study intervention will produce lasting benefits for the participants?

Not at all confident — Somewhat confident — Completely confident

(Place a mark on the scale above)

What do you see as the greatest challenges to the organizations continuing their support of the study intervention?

_____

How confident are you that your study intervention will be sustained in your setting a year after the study is completed and or a year after it has been implemented?

Not at all confident — Somewhat confident — Completely confident

(Place a mark on the scale above)

Will additional funding be needed to sustain the study intervention in your organization? ◯ Yes ◯ No

Do you have key stakeholder commitment to continue the study intervention if it is successful? ◯ Yes ◯ No

How will the study intervention be integrated into the regular practice of the organization?

_____

Section 6_Patient Engagement

PATIENT ENGAGEMENT IN RESEARCH

"Engaging patients in health care research makes [investments in] research more accountable and transparent, provides new insights that could lead to innovative discoveries, and ensures that research is relevant to patients' concerns. The international experience with engaging citizens and patients in research has shown that involving them early in the design of studies, ideally as early as at the planning stage, leads to better results."

"An important goal of Canada's Strategy for Patient-Oriented Research (SPOR) is for patients (an overarching term inclusive of individuals with personal experience of a health issue and informal caregivers, including family and friends), researchers, health care providers and decision-makers to actively collaborate to build a sustainable, accessible and equitable health care system and bring about positive changes in the health of people living in Canada."

How is/was the development of the research idea/question and outcome measures informed by patients' priorities, experience, and preferences?

How are/did you involve patients in the design of this study?

Will patients be involved in helping to recruit patients for the study?
◯ Yes
◯ No

Will patients be involved in helping to conduct the study?
◯ Yes
◯ No

How will the results be disseminated to patients?

Step 7

The embedded researcher should commit to a standardized system of data collection, storage, auditing and management that is compliant with health privacy legislation. At our organization, we became a member of the Research Electronic Data Capture (REDCap™) consortium (7) This PHIPA-compliant, secure web application has been downloaded onto our hospital's server system and can be used by any healthcare provider after receiving authorization by the embedded researcher who also happens to be the system administrator. Most importantly, this database system is free to consortium members, requires minimal support from the organization's information technology department and is very simple to use and administer. The system supports all types of data collection structures needed for different study designs. It allows research team access and collaboration. In our organization, all investigators that are conducting human research that requires REB approval must use REDCap™ as their study database. This requires training through on-boarding sessions, but we have committed to training super-users who support research studies throughout the organization.

Step 8

Perhaps the most difficult bottleneck is the lack of time providers cite to identify potentially eligible patients for expressed consent (pre-screening), obtain expressed consent and informed consent and complete

the case report forms for enrolled patients, all the necessary steps for enrolling patients in prospective studies. At our organization in response to these barriers, the embedded researcher has created a unique program called ***V****olunteers* ***for*** *the* ***C****onduct of* ***E****fficacy and* ***E****ffectiveness* ***S****tudies (VforCE^{2}S)*. Essentially, this program trains the hospital's volunteers to act as delegated agents of the organization and research assistants of the investigators. Working in pairs, the delegated agents can both pre-screen and obtain expressed consent, and then inform their research assistant partners to complete the eligibility screen, obtain informed consent and continue on with data collection (Figure 3). They are all trained on REDCap™ to ensure a consistent and confidential approach to data management. Currently, there are 10 volunteers (5 teams) who have been trained to support researchers; the program is planning to expand to 20 teams by September 2018. This expansion will make available 4 teams per day, each providing support for 4 hours, 5 days a week, all at no cost to the researchers or organization.

Step 9

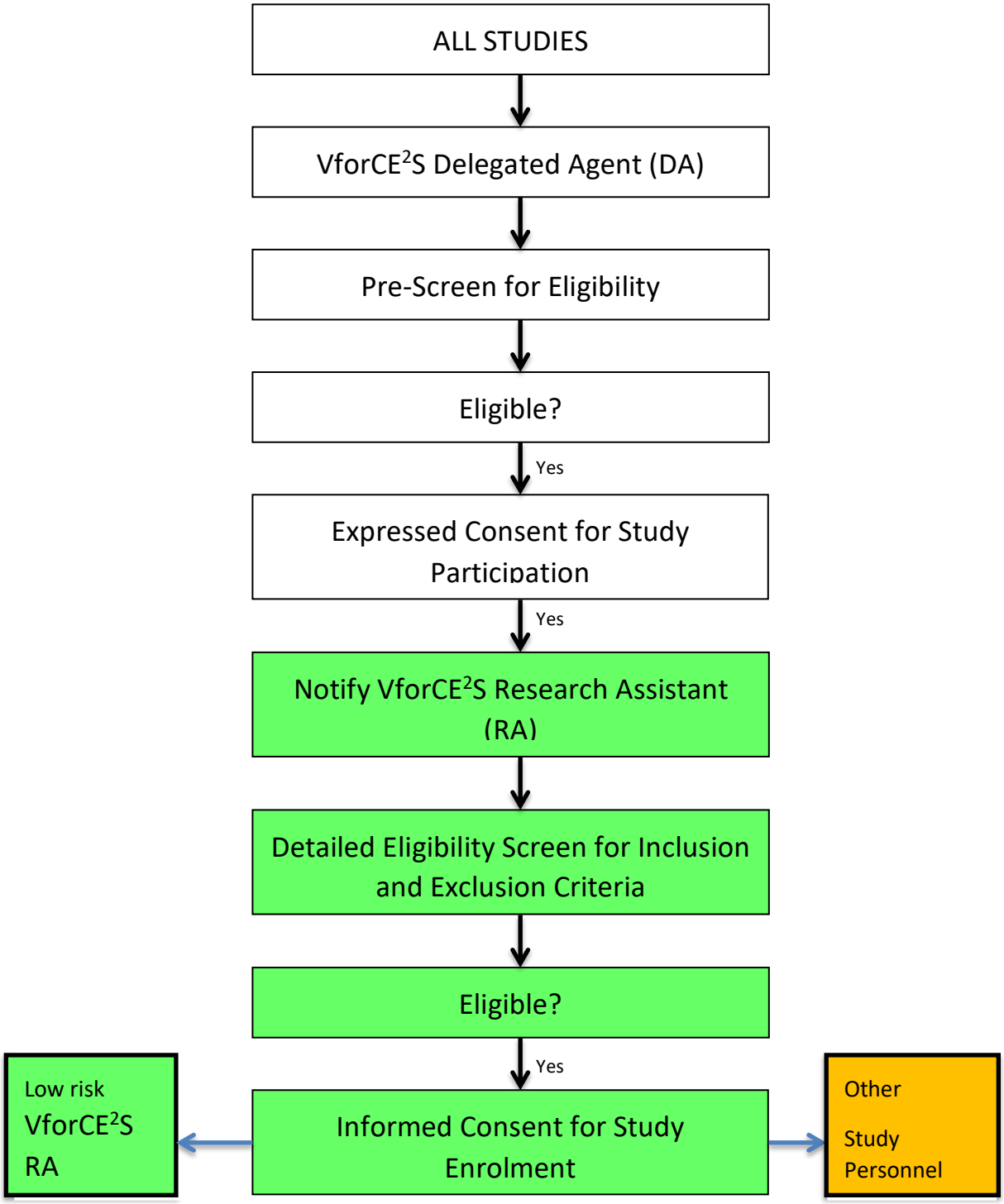
In our organization and many others, research illiteracy is a significant barrier to providers understanding research outcomes and conducting studies. It compromises our ability to implement knowledge into practice, communicate with patients and participate in research. There are a number of resources and activities that embedded

researchers can introduce to their organizations to improve research literacy. One of the most effective ways to tackle some of these barriers is to commit to a consistent approach to study design for health services research. In our organization, we endeavor to consistently use quasi-experimental designs to conduct health services research. By exposing our researchers and providers to the same study design and analysis, we not only ensure methodological rigour and strong inferential design, but also ultimately train our providers and researchers to accurately interpret the study results and increase their confidence in the validity of those results. In so doing, our providers' willingness to both conduct research and implement study results is enhanced.

Step 10

Work with the organization's foundation to raise funds to support research. As non-academic based researchers, the likelihood of submitting a successful grant to any research funding agency is infinitesimally small and not worth your time in our current research funding environment. Fortunately, there is a recognition that the research funding models need to change to support the development of learning health systems (8). These alternative funding models would not be project-based but would rather be flexible enough to support the research activities of learning health centres in a manner that was most effective for their particular context and issues (8). Until such a time that these

Figure 3: VforCE^{2}S Delegated Agent and Research Assistant Workflow



changes might occur, hospital foundations provide a much more realistic option to raise funds that can support research activities and personnel.

In my experience and in my organization, these are the foundational parts of a learning health centre that I have been instrumental in implementing and supporting. They could be used in any similar organization with a commitment to become a learning health centre. These steps are meant to provide a how-to guide for other organizations and embedded researchers. From 2013 to now, all these changes have come about as a direct result of my commitment to pursue this post-graduate degree, conduct all my degree-related research in my own organization and now become my organization's Chief Research Scientist. I cannot imagine how an iKT model could have even come close to achieving what our embedded researcher model has achieved in 4 short years. In fact we know it didn't as it has had about a decade-long head start. The CIHR would be wise to consider how much money it spends to support iKT, and for a fraction of that cost, it could instead support the operational costs of an embedded researcher in every non-academic acute care hospital in the country and potentially reap untold benefits for patients, organizations, populations and the healthcare system.

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