EVALUATING BC PROVINCIAL ACADEMIC DETAILING SERVICE'S INTERVENTION ON ANTIBIOTIC PRESCRIBING FOR SUSPECTED URINARY TRACT INFECTIONS IN BRITISH COLUMBIA'S NURSING HOMES

by

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Abstract

Background: From June 2016, an academic detailing (AD) intervention took place in 115 nursing homes (NHs) in British Columbia. Physicians, nurses, and NH staff received AD to reduce unnecessary antibiotic treatment. We hypothesized that local health areas (LHAs) with NHs visited by academic detailers experienced a decreasing trend in UTI-linked and overall antibiotic prescribing.

Methods: We used population-based administrative datasets of services provided to NH residents from June 2015 till March 2017, aggregated by month for LHA intervention and control groups. Ecologic change in the UTI-linked and overall prescribing trend was evaluated with linear segmented regression. Sensitivity analysis to evaluate potential bias from linking antibiotic use to the occurrence of UTI-related diagnoses by fee-for-service provider's billings was undertaken.

Results: In the study period, there were 93,327 antibiotic prescriptions and 24,081 prescriptions linked to UTI diagnostic codes. For the UTI-linked analysis, the control's antibiotic prescribing pre-intervention trend was a monthly decrease of -0.15 DDD/1,000 residents/day per month versus -0.09 after start of the intervention – a slope change of 0.06 (95% CI: -0.16 to 0.29) DDD/1,000 residents/day per month. The intervention group's pre-intervention trend was almost identical to the controls', a monthly decrease of -0.14 DDD/1,000 residents/day vs -0.27 after start of the intervention – a slope change of -0.13 (95% CI: -0.32 to -0.07) DDD/1,000 residents/day per month. The difference in slope changes was -0.19 (95% CI: -0.29 to 0.80) DDD/1,000 residents/day per month. The sensitivity analysis indicated that linkage bias was unlikely to bias the UTI-linked analysis' trends.

Conclusions: This ecologic study found that a population-level AD intervention was associated with decreases in UTI-linked prescribing trends but not overall prescribing trends.

Lay Summary

In British Columbia (BC), the Provincial Academic Detailing (PAD) Service visited doctors, nurses and other staff in 115 nursing homes (NHs). This was done to reduce unnecessary antibiotic prescribing for suspected urinary tract infections (sUTI) among the elderly. From June 2016, PAD's staff provided education to doctors and NH staff on reducing unnecessary treatment of sUTIs. This study evaluated how PAD could have changed doctor's prescribing behaviour by looking at whether prescribing rates for UTIs in local health areas (LHAs) changed from June 2015 to March 2017. In the post-intervention period, prescribing trends continued to decrease in both areas that were and were not visited by BC PAD. In the post-intervention period, it would take the control group a year to achieve the same reduction in UTI-linked prescribing that would take the intervention group only four months. These aggregated findings showed that the intervention was associated with a reduction in UTI-linked prescribing trends but not overall prescribing trends.

Preface

This thesis is representative of the graduate student's work as a co-investigator and lead author. The analysis described in Chapters 2 - 4 was approved by UBC Behavioural Research Ethics Board (Project H17-01391).

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List of Abbreviations

Phrase	Abbreviation
Asymptomatic bacteriuria	ASB
Antimicrobial stewardship program	ASP
Antimicrobial stewardship	AMS
British Columbia	BC
Defined daily dose	DDD
Local health area	LHA
Nursing home	NH
Provincial Academic Detailing	PAD
Urinary tract infection	UTI

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Chapter 1: Introduction

1.1 Purpose

From June to December 2016, the British Columbia Provincial Academic Detailing (PAD) Service initiated an academic detailing intervention in British Columbia's nursing homes (NHs). The intervention's objective was to educate providers on optimal diagnosis and antibiotic treatment of urinary tract infections in NHs. To support an evaluation of this academic detailing intervention, the literature on measuring antibiotic utilization, antibiotic prescribing in Canadian NHs, resident and systemic factors that affect prescribing patterns, academic detailing for antibiotic stewardship and the context of long-term care in British Columbia has been reviewed.

1.2 Summary of literature

- Urinary tract infections (UTIs) are a common infection in NHs; they were the most commonly linked indication for an antibiotic prescription in British Columbia's (BC) NHs in 2014
- Resident (e.g. case-mix and infection rate) and facility level (e.g. size and country) factors influence antibiotic prescribing in NHs. Prescriber treatment preferences are key determinants of UTI diagnosis, antibiotic treatment initiation, duration, and antibiotic agent.
- Academic detailing is an educational strategy to create behaviour change. It can influence drug prescribing but has not been rigorously evaluated for NH antibiotic prescribing at a population level.
- From June to December 2016, in an academic detailing intervention, the BC Provincial Academic Detailing Service met with staff at 114 NHs to discuss the prevalence and

overtreatment of asymptomatic bacteriuria (ASB) and recommended management of suspected UTIs.

1.3 Literature review

1.3.1 The long-term care facility setting and antibiotic resistance

In the coming years, the proportion of seniors (older than 65 years of age) in Canada will grow from 17% in 2017 to around 24% in 2037 (1). This demographic change will require additional resources to care for seniors with chronic conditions and medically complex conditions (2). Because of declining health and other factors, some individuals are placed in post-acute care settings. Post-acute care ranges from retirement homes, assisted living facilities and nursing homes. Residential care facilities, personal care homes, special care homes, nursing homes and skilled nursing facilities are synonyms of NHs. For consistency, this thesis will use the term nursing homes (NHs) to refer to this level of post-acute care. (3)

Antibiotic use in NHs is ubiquitous. In a year, 47-79% of NH residents are exposed to at least one antibiotic course (4–6). Factors that affect antibiotic use are geopolitical (American NHs prescribe at greater rates than Canadian NHs), differences in case-mix (burden of comorbidities), differences in infection rate and physician preference (5,7–10). A consistent association between antibiotic use and the emergence of antibiotic resistance is evident from ecological, quasi-experimental studies, randomized control trials, and meta-analyses (11,12). Antibiotic use increases the selection pressure for resistant organisms. The structure of NH care and characteristics of the resident population potentiate the intense use of antibiotics in NHs. Specific resident characteristics and structural factors are described in Section 3.2 “Urinary tract infection and asymptomatic bacteriuria in NHs” and Section 3.5 “Systemic and human factors

that influence antibiotic prescribing in NHs", respectively. A nationally representative study of NHs in the United States and a study of participating NHs in 19 European countries found that urinary tract infections (UTIs) are the most common infection (13,14). With their high incidence, UTIs contribute to intense NH antibiotic use.

1.3.2 Urinary tract infection and asymptomatic bacteriuria in NHs

For a NH resident without an indwelling catheter, Stone's surveillance definition defines a UTI as: site-localizing genitourinary signs and symptoms in addition to a positive urine culture (the cut-off for a positive result depends on the urine collection method) (15). However, severe cognitive impairment, dementia and other communication barriers impede efforts to identify UTI-specific symptoms (16,17). Due to these difficulties, signs that are not specific to UTIs, such as fever, delirium and malodourous urine often lead to diagnostic testing for UTIs (18–20). Furthermore, the genitourinary system of NH residents can be asymptomatically colonized by bacteria, referred to as, asymptomatic bacteriuria (ASB). Several factors promote the development of ASB in the elderly: diminished cell-mediated immunity, increased receptivity of bacteria for epithelial cells of the elderly genitourinary system, presence of neurogenic bladder dysfunction, altered bladder defences (e.g. mucin production), changes to hormone levels and the urinary and vaginal pH, presence of urinary and faecal incontinence and long-term catheter use (21–26). These factors contribute to a high prevalence of ASB in NHs, 25-50% of female and 15-40% of male residents have ASB (27). In the institutional elderly, ASB is not associated with reduced survival; thus, it is considered a benign condition (27). Treatment guidelines from the Infectious Disease Society of America do not recommend antibiotic treatment of ASB in NH populations (27). Nonetheless, positive urine culture results with nonspecific signs or without localizing symptoms–ASB–are treated as UTIs. 30-66% of ASB patients are treated with

antibiotics (28–31). Difficulties in diagnosing UTIs in NH residents and a high prevalence of ASB contribute to the overtreatment of ASB.

1.3.3 Measuring antibiotic use in NHs

The simplest metric for measuring antibiotic use is the number of antibiotic prescriptions. However, this measure gives no information regarding treatment length (4 or 7-day course) or treatment intensity (low or high dose). These additional factors are incorporated in the World Health Organization's Defined Daily Dose (DDD) methodology. A common method that converts the physical quantities of a drug (pills, vials, inhalers, etc.) into the defined daily dose (32). The DDD assumes and uses for calculations an average maintenance dose per day for a specific drug and its primary indication in adults. For acute drug use like antibiotics, the WHO suggests constructing the metric as the number of DDDs per inhabitant per year (32). In this form, the DDDs per inhabitant per year estimates the average number of days each inhabitant is treated annually. For example, an estimate of seven DDDs per inhabitant per year indicates that utilization is equivalent to treating every inhabitant with a seven-day course in a given year. This interpretation makes it easy to see the relation to another measure of antibiotic use, the average days of therapy (DOT).

The DOT is the number of individual antibiotic agents given to a patient on each calendar day. For example, if a patient receives two antibiotics in one day, the corresponding DOT measure would be two–this measure is less sensitive to variations in dosing across healthcare facilities. In the elderly, antibiotic doses can be decreased in the case of renal insufficiency (decreasing the administered daily dose relative to DDD dose) or have an increased dose for severe infections. Polk and collaborators retrospectively analysed administrative claims data from 130 American hospitals to evaluate discrepancies between DOT and DDD rates for

antibiotics. DOT and DDD rates generally correspond when the administered daily dosage are nearly equivalent to the DDD (33). However, when the DDD was greater than the administered dose, antibiotic utilization measurements based on DDD rates were lower than DOT rates (33). Zagorski et al. compared the DDD and DOT in a single hospital setting for patients with and without renal insufficiency. Renal insufficiency was arbitrarily defined as having a mean serum creatinine in the cohort's upper quartile of serum creatinine. This study analysed parenteral courses of vancomycin, levofloxacin and ceftriaxone. Patients with renal insufficiency had decreased antibiotic utilization as measured by both DDD and DOT rates relative to patients without renal insufficiency (34). While parenteral use of antibiotic agents in NHs is not widespread (1% of prescriptions in a yearlong study of NHs in Canada and the United States), the finding that renal adjustment alters a facilities' antibiotic volume measures would likely hold true to oral antibiotics (6).

The DOT method is also sensitive to course adjustment due to renal insufficiency. For example, if an antibiotic with a long half-life is administered every two days to account for renal function, the days in between the actual drug dosing days would not be counted with the DOT. The concept of exposure days (ExD) accounts for this. Kubin et al. compared standard DOTs to 1) ExD where days in between administered doses were counted if the antibiotic was stopped and restarted within 2 days and 2) an ExD that had different cut points for individual antibiotic agents (e.g. levofloxacin's cut point was 3 days, tobramycin and vancomycin's cut points were 4 days) (35). There were no significant differences between the various measures of DOT, however, the single-centre hospital study population limits the applicability of these results to the NH setting. Additionally, a Canadian Delphi panel came to a consensus that when DOT is feasible, it is the preferred metric of antibiotic consumption relative to the DDD methodology

(36).

1.3.4 Antibiotic prescribing in Canadian NHs

In 2012, 30.5% of NH residents covered through public drug programs in Canada had a claim for a fluoroquinolone antibiotic; contrastingly, 13.5% of community-dwelling seniors had a fluoroquinolone claim (37). In 2014, 86% of community-dwelling Canadian seniors (60 years and older) that visited a nationally-representative cohort of physicians received an antibiotic prescription (38). Unfortunately, NHs represent a gap in Canadian antibiotic use surveillance (38). Considering this, the population-based studies from NHs in the Canadian province of Ontario can provide insight into antibiotic prescribing in the Canadian NH setting.

Loeb and colleagues studied 22 NHs from November 1996 to October 1997 (9). The incidence of antibiotic prescriptions for any indication ranged from 2.9 to 13.9 antibiotic courses per 1,000 patient-days. Additionally, 66% percent of residents received an antibiotic in the study period. These results are concordant with Mylotte's observation that operationalizing prescribing volume as an incidence density can give a diminished perception of prescribing relative to the incidence proportion of treated residents (39). While both measures provide an important characterization of antibiotic prescribing volume, the rate is necessary for inter-facility comparisons. Furthermore, 33% of antibiotics prescribed were for UTIs (30% of which were ASB). 87% of the variation in the UTI antibiotic prescribing rate can be explained by a surrogate and potentially collinear measure of the UTI infection rate (the UTI prescribing rate multiplied by the proportion of treated UTIs identified by McGeer's surveillance definition).

Results from this analysis of variance are like studies conducted by Mylotte in the state of New York. In Mylotte's studies, 48% and 65% (adjusted for case-mix) of the general antibiotic use incidence were explained by variation in the overall infection rate (8,40). However, it must

be recognized that Loeb's and Mylotte's studies used the monthly prescribing rates and monthly infection rates in their regression analysis and do not report a measure of residual autocorrelation. Monthly rates often correlate to their preceding and subsequent monthly rates, in other words, monthly rates are serially dependent. Regressing two non-independent monthly rates can lead to spurious regression (41). While recognizing that UTI hospitalization (and by proxy UTI infection rate) may be less seasonal in the elderly relative to the young, if these rates are autocorrelated, the reported influence of infection rates may be potentially overestimated (42).

Daneman *et al.* conducted a point-prevalence study of antibiotics prescribed in 363 NHs in Ontario (43). On the study date, 2,190 of 37,371 residents (6%) were receiving antibiotic therapy. Antibiotic prescribing prevalence varied across NHs (2% to 11%) even after adjusting for resident and facility characteristics. Nursing homes were divided into quintiles according to the antibiotic prescribing point-prevalence. Facilities in the fifth quintile had a greater prevalence of long duration antibiotic treatment. In the lowest and highest facility quintiles, 60% and 68% of patients received antibiotic courses longer than ten days, respectively. Additionally, nitrofurantoin was associated with chronic therapy (longer than 90 days). While this study does not present information on prescribing indication, nitrofurantoin is used solely for UTI treatment. This finding highlights that for a UTI indication, antibiotic use can be acute or prophylactic in the NH setting.

Building on the results of the point-prevalence study where variation in treatment duration was observed. Daneman and colleagues conducted a retrospective cohort study of residents of 630 NHs in the 2010 calendar year (5). The proportion of antibiotic courses longer than seven days per prescriber was the main measure of interest. The key finding is that prescribers above

the third quartile had 4 times the odds of prescribing prolonged antibiotic treatments than the lowest quartile prescribers, independent of resident factors. Highly suggestive of the role of prescribers in determining antibiotic duration.

Following up on these results, a cohort study of residents in 607 NHs facilities in Ontario further demonstrated the variability in antibiotic prescribing at the facility level, 20.4 –192.9 DOT per 1000 resident-days (44). Smaller facilities, private ownership and rural location were associated with high antibiotic use. Resident characteristics were similar across levels of antibiotic use, though notably, there was a greater proportion of residents with do-not-hospitalize (DNH) orders in high-use facilities relative to low-use facilities. A low DNH prevalence can potentially shift an NH's antibiotic prescribing volume from the NH to the hospital setting. Higher health instability and increased cognitive impairment are associated with DNH designation (Peter Tanuseputro, pers. commun.). For NH-level antibiotic surveillance, antibiotic prescribing for hospital transferees can be considered differentially lost to follow-up.

1.3.5 Systemic and human factors that influence antibiotic prescribing in NHs

In NHs, care is provided by care aides, nurses and physicians; with care aides providing 75 to 80 per cent of direct care to nursing home residents in Canada (45,46). Care aides in NHs have a high turnover rate (47). This high frequency may limit the durability of educational antibiotic stewardship interventions in the NH setting, as intervention-trained participants leave to work elsewhere. Additionally, unless NHs are adjacent to or within a hospital, results of urine culture may not be timely–thus contributing to empiric choice of antibiotic agents (48). In a cohort of six community NHs, over a three-year period, 21% of antibiotics were prescribed empirically (20).

NH physicians are frequently off-site, thus antibiotic prescribing is often done over the telephone (49). The initial rationale for the urinalysis/culture is not always documented making it difficult to communicate relevant clinical information. In the absence of this information, antibiotics are often prescribed in response to bacteriuria. Additionally, due to the physical separation, physicians depend on the assessment by nurses at the facility and their request for antibiotics when making decisions to prescribe antibiotics (49). This also creates a social pressure to agree and prescribe an antibiotic, even if it is not judicious (50,51). Factors exogenous to NH staff can also influence the prescribing of antibiotics. Pressure from families and managers/medical directors (to reduce liability) can influence the decision to order urine cultures and antibiotics (52). Additionally, some patients may have advance care plans that can indicate patient preference's with respect to life prolonging antibiotic treatment (53).

Care for NH residents is unevenly distributed among physicians. In 2005, 53% of physicians provided care for 90% of NH residents in a 30-day window (54). Antibiotic prescribing in NHs is similarly skewed in Ontario. In the 2010 calendar year, 22% of prescribers were responsible for 80% of antibiotic prescriptions (5). In 2014, with a study sample of Ontario physicians of all specialties, 70.7% of NH prescribing physicians were male and the median number of years in practice was 30 years (late-career stage) (10). In the outpatient setting, elderly patients with acute upper respiratory infections are more commonly prescribed antibiotics by clinicians in their mid- and late-career stage prescribe than early-career physicians (55).

Physician prescribing preference influences the duration of antibiotic treatment, independent of resident factors (5). Additionally, preference also influences the tendency to start antibiotic treatment and choice of antibiotic class (10). While increasing prescriber age is associated with

longer antibiotic duration, there is not a consistent relationship between demographic factors and prescribing preferences. Importantly, these prescribing preferences are stable over time (10).

1.3.6 Risks of antibiotic prescribing in NHs

Antibiotics were the second most common cause of drug-related adverse events in a yearlong study of 18 community-based NHs in Massachusetts (56). Rashes and *Clostridium difficile* diarrhea were the most prevalent adverse events. In a large population-based study of the risks of antibiotics in NH residents, the primary complications were *Clostridium difficile* diarrhea and antibiotic-resistant infections (44). Living in facilities with intense antibiotic use has indirect risks for residents. For residents not receiving antibiotics, the antibiotic-related adverse event rate is 1.2% larger in high antibiotic use NHs relative to a low antibiotic use NHs (9.9% and 8.7%, respectively) (44). Furthermore, receiving quinolone or third- or fourth- generation cephalosporins can increase the odds of colonization by a multidrug resistant organism (odds ratio of 1.89 and 1.16, respectively) (57). Over 35% of residents are colonized by multidrug resistant organisms (58). As such, NHs can act as reservoirs of resistant organisms that can later spread to hospitals and other settings (59–61). Antibiotic-resistant infections are associated with increased mortality and increased healthcare expenditure (approximately 6,000–30,000 USD) stemming from more costly second-line antibiotic use and increased hospital stay (62,63).

1.3.7 Persuasive interventions addressing antibiotic treatment of UTIs in NHs

Fleming and colleagues designate three general categories for antimicrobial stewardship activities: “persuasive (e.g. audit and feedback; educational interventions), restrictive (e.g. formulary restriction) and structural (e.g. computer decision support systems) (64).” Interventions to address antibiotic overtreatment of UTIs using these various strategies have been conducted (65–72). This section will focus on persuasive antimicrobial stewardship activities in

NHs.

Audit and feedback involves a summary of clinical performance that is given to health professionals to give insight into their practice and change behaviour. In general, audit and feedback in NHs have been implemented at small scales and evaluation methods do not provide strong evidence that observed changes can be attributed to the intervention. Pate *et al.* conducted audit and feedback, where once weekly, antibiotic prescribing would be reviewed and if necessary non-binding recommendations made. In the 15-month intervention period, 251 recommendations were made. The before-after analysis indicated a 21% decrease in antimicrobial use from 914 to 712 DDD per 1000 patient-days. However, this result does not exclude the effect of pre-existing trends. Doernberg *et al.*'s interrupted time series analysis accounts for this common threat to internal validity. The investigators implemented an audit and feedback intervention in 3 NHs for 6 months. There was an immediate change in prescribing (26% reduction) and an average reduction of 6% per post-intervention month. While their analysis reduces the concerns of certain threats to internal validity, this study highlights the issue of intervention durability, an issue common in the antibiotic stewardship literature. For instance, with only six post-intervention observations, it is hard to determine if the intervention's effects are durable. Zimmerman and colleagues implemented audit and monthly feedback in NHs in North Carolina (73). The multifaceted audit and monthly feedback intervention also provided education on a several clinical issues. The results were consistent with an effect on overall prescribing (IRR 95% CI: 0.79–0.95) and UTI-related prescribing (IRR 95% CI: 0.66–1.05).

Antimicrobial stewardship programs frequently include educational components (74,75). A type of educational intervention, "academic detailing/educational outreach" has been modeled after the pharmaceutical industry's approach of sending representatives to meet with physicians

for marketing purposes (76). The first step of academic detailing is a systematic review and critical evaluation of the existing literature (76). Next, the results of this review are drafted into accessible formats for end users. Trained academic detailers then meet with practicing healthcare professionals and engage them in interactive educational discussions. Academic detailers are usually healthcare professionals (e.g. pharmacists, nurses and physicians) unaffiliated with the pharmaceutical industry that have been trained in adult learning theory and communication methods (76). Systematic reviews of randomized control trials employing academic detailing indicate that it is an effective means for influencing prescribing behaviour (77,78). The findings of a Cochrane meta-analysis of academic detailing interventions on changes to prescribing are small (median 4.8%, interquartile range 3.0% to 6.5%) (78).

There have been three studies evaluating academic detailing as it pertains to antibiotic prescribing in NHs. Linnebur *et al.* implemented an academic detailing intervention to improve guideline-concordant prescribing for nursing home-acquired pneumonia in 8 intervention nursing homes and 8 control nursing homes (79). Hutt *et al.* similarly implemented an academic detailing intervention in two nursing homes and assessed differences with a pre-post design (80). Pasay and colleagues performed the largest published AD intervention (21 intervention NHs and 21 control NHs) with academic detailing and a checklist (decision-making tool) in rural NHs (81). In this evaluation, their data were consistent with a decrease of 2.5 to 1.7 per 1,000 resident-days in urine culture testing in the intervention group. Similarly, a decrease of 1.0 to 0.4 per 1,000 resident-days of UTI-associated antibiotics was observed. In all these studies, academic detailing was employed alongside cointerventions (e.g. financial incentives). This obfuscates the specific change that is attributable to academic detailing. The study by Pasay was the only AD study that quantified changes in antibiotic prescribing rates.

1.3.8 British Columbia's Provincial Academic Detailing service

The British Columbia Provincial Academic Detailing (PAD) service implemented an academic detailing program ("UTIs in Primary and Long Term Care") to reduce inappropriate antibiotic prescribing of suspected urinary tract infections. Twelve pharmacist academic detailers conducted meetings (the intervention) from June 1 to December 31, 2016 (82). This academic detailing program targeted both nurses and physicians in addition to care aides. Facilities were not visited at random, NHs with greater than 70 beds and whose residents were covered under BC's public drug program for NH residents (Pharmacare Plan B) were preferred. Several facilities were visited on more than one occasion. In the sessions, there were four key messages conveyed to attendees:

1. Do not assume that non-specific symptoms are a urinary tract infection.
2. Dipstick urinalysis and urine cultures should not be ordered unless there are urinary tract infection-specific symptoms present.
3. Most residents with asymptomatic bacteriuria should not be treated with antibiotics.
4. Preferred antibiotics for empiric treatment of UTIs.

This educational intervention thus leveraged human factors to influence antibiotic prescribing while not changing administrative factors.

1.3.8.1 British Columbia's NH context

In BC, in September 2016, there were approximately 27,760 publicly funded residential care beds in 335 regulated facilities (83). 4.4% of BC's seniors (older than 65 years of age) were NH residents (83). Chronic or progressive conditions are requisites for publicly subsidized residential care in British Columbia (84). The Canadian Institute for Health Information collects

administrative and demographic information on Canadian NH residents in the Continuing Care Reporting System (CCRS) using the RAI–Minimum Data Set (MDS) 2.0 instrument. The MDS assessment is done upon NH admission, every quarter, or if there is a significant change in the residents' clinical status. From 2015 to 2016, BC's NH residents were on average 85 years old and 64.5% of residents were female (85). The three most common conditions were some level of bladder incontinence, dementia and some indication of health instability (67.4%, 63.1%, 53.2%, respectively) (85).

In British Columbia's NHs, from 2007 to 2014, antibiotic use ranged from 31.4 to 29.4 DDDs per 1000 residents per day (86). In 2014, UTIs were the most commonly-linked indication for antibiotic prescription–accounting for 18.5% of antibiotic prescriptions. Nitrofurantoin, ciprofloxacin and trimethoprim/sulfamethoxazole were the most commonly prescribed antibiotics linked to a UTI indication. Furthermore, the decrease in the antibiotic prescribing rate was differential across health authorities–potentially indicative of antimicrobial stewardship at the health authority level.

Starting July 26, 2016, nurse practitioners in British Columbia could prescribe federally controlled drugs and substances–including antibiotics (87). Prior to 2013, nurses accounted for less than 1% of outpatient antibiotic prescriptions (88). It is unlikely that this change in the scope of practice will increase the proportion of antibiotics prescribed by nurse practitioners. In 2016, there were seven nurse practitioners working in BC's NH sector (89). Therefore, the change in scope of practice may affect antibiotic prescribing at a few facilities, but it is unlikely to significantly alter overall prescribing. Nurse practitioners' attitudes towards antibiotic stewardship is currently uncharacterized in BC. However, local antibiotic stewardship programs have engaged these healthcare professionals. For example, Bugs & Drug, an

antimicrobial/infectious diseases reference book, has been systematically distributed to nurse practitioners in addition to other healthcare professionals (90).

1.4 Research Question

1.4.1 Ecologic interrupted time series

In BC, the BC Ministry of Health defines 80 geographic areas as local health areas (LHA). The specific research question asks at an ecologic level, whether intervention status (LHAs with a NH visited by BC PAD) was associated with changes in UTI-related and overall antibiotic prescribing rates from June 01, 2015 to March 31, 2017.

1.4.2 Hypothesis

Relative to their pre-intervention trends, intervention LHAs will have a greater reduction in UTI-related and overall antibiotic prescribing in the post-intervention trend than non-intervention control LHAs.

Chapter 2: Methods

This ecological interrupted time series study used a retrospective cohort of residents and prescribers from the BC Pharmanet dataset and fee-for-service prescribers in the Medical Services Plan dataset. This was to determine whether BC PAD's intervention was related to changes in UTI-linked and overall antibiotic prescribing in BC's nursing home population. Local health areas (LHAs) were grouped by whether a nursing home in the LHA was visited by BC PAD. The unit of analysis was LHAs aggregated by intervention status.

2.1 Data sources

2.1.1 Outcome data: Pharmanet and Medical Services Plan

In BC, pharmacists record all prescription drug dispensing into BC Pharmanet, a population-based administrative database, regardless of residents' insurance status. Information within this database is anonymized and captures prescription drug dispensations in the community and hospital outpatient setting. From PharmaNet, Pharmacare Plan B (nursing home insurance) marked data was extracted. On the basis of de-identified public health numbers and service dates, Pharmanet data was linked to the BC Medical Services Plan (MSP) payment dataset for services by fee-for-service providers. The prescription indication was determined by the International Classification of Disease – 9th revision code associated with a MSP service billing that occurred 5 day before a patient's prescription was dispensed. The linkage algorithm has been described previously (86). In Pharmanet, antibiotics were classified by the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD) measurement unit developed by the WHO Collaborating Centre for Drug Statistics and Methodology (91).

2.1.2 Demographic and denominator data: Home and community care

The home and community care database captures transactions for publicly-funded residents of nursing homes, assisted living facilities, family care homes and group homes, clients in adult daycare programs, and clients receiving home care and home support services. This dataset contains demographic data, such as age and sex for nursing home residents and denominator data for monthly rate calculations was aggregated by intervention status of the LHA. The data was not available at the resident-level, thus, it was not possible to estimate resident's person-time in a LHA.

2.1.3 Process data

The facility visit date was extracted from the detailer's logs. The number of publicly subsidized nursing homes operating by January 2018 was extracted from the 2018 Residential Care Quick Facts Directory (Nora Huber, pers. Comm.). The ggmap package with the Google Maps API was used to assign an LHA to each nursing home based on the address, city, and postal code from this data to calculate the total number of nursing operating in the LHA.

2.2 Measures

2.2.1 Explanatory measure

Intervention status was a dichotmous variable. In this ecologic study, the intervention group was defined as LHAs with any NH visited by a BC PAD detailer from 1 July 2016 to 31 March 2017.

2.2.2 Outcome measure

Antibiotic prescribing volume was operationalized as defined daily doses (DDDs) per 1000 residents per day. An antibiotic's DDD corresponds to an assumed average maintenance dose for adults used in a day (92). Monthly DDDs per 1,000 residents were standardized by the number of

days in a month primarily for comparability to previous work by "Do Bugs Need Drugs?" in BC (86). Accounting for month length reduces calendar effects on the monthly observations (93). Antibiotic multi-therapy (not including fixed-dose combinations with assigned DDDs) contributed separately to the total when aggregated. If a resident's actual prescribed daily dose is similar to the DDD, then the number of DDDs on any particular day can be a proxy for the number of residents taking antibiotics. For this reason, DDDs/100 residents/day approximates the average percent (daily point prevalence) of residents taking antibiotic treatment.

2.2.3 Descriptive demographic and geographic measures

Size of nursing homes was arbitrarily categorized based on the maximum number of publicly-subsidized residents as small (1 to 29 residents), medium (30 to 99 residents), large (≥ 100 residents). To describe the LHA contexts, the BC Ministry of Health's geographic service area definitions were adapted to define LHA geographic characteristics using BC Statistics' 2016 sub-provincial population estimates (P.E.O.P.L.E. 2017) (94,95). Geographic characteristics were: 1) remote LHA (less than 10,000 population) 2) rural LHA (10,001-40,000 population) 3) urban/rural LHA (40,001-190,000 population) and 4) metro LHA (≥ 190,001 population).

2.3 Inclusion and exclusion criteria

To estimate UTI-related use in the UTI-linked analysis, the analytic sample included antibiotics that had one of the following indications from the MSP dataset: pyelonephritis, cystitis, prostatistis, and other disorders of urethra and urinary tract. Pharmanet Plan B antibiotic prescriptions were excluded from LHAs with no publicly-subsidized residents during the study period according to the HCC data.

2.4 Statistical analyses

2.4.1 Primary analysis

Monthly UTI-linked and overall antibiotic prescribing rates from June 1, 2015 to March 31, 2017 were regressed with 13 pre-intervention observations before July 2016. The interruption began July 2016 and there were 9 post-intervention observations. The linear model included six terms: 1) an intercept term for the control's baseline rate 2) a variable that started at observations from June 2015 and incremented by 1 every month that described the control's pre-intervention trend 3) an incrementing variable for the months following the intervention that described the control's post-intervention trend 4) an indicator variable for the intervention group, 5) an interaction term of intervention status and pre-intervention trend that describes the trend difference relative to the control group's pre-intervention trend and 6) an interaction term of intervention status with post-intervention trend that describes the trend difference of the intervention group's pre-intervention trend with the control's post-intervention trend relative to the intervention group's actual post-intervention trend. Estimating the difference between the control and intervention groups' change of slopes was the primary interest of the analysis, as it reflects the intervention group's differences from pre-existing trends and potential co-intervention effects. In accordance with our proposed impact model/hypothesis, level change parameters were not included in the model.

Analysis of UTI linked antibiotic prescribing trends from 2009 to 2014 did not indicate a strong seasonal effect (data not shown). Accordingly, UTI-linked data is not deseasonalized. For the overall prescribing analysis, seasonality was removed by seasonal and trend decomposition using Loess. Autocorrelations were assessed through autocorrelation and partial-autocorrelation plots of the model residuals. R Statistics (v. 3.4.1) was used for analysis. While the analytic data

are not a sample, 95% confidence intervals are presented to incorporate broader event-based uncertainty (e.g. outbreaks) and to aid in external generalizability (96,97). When estimates of interest were not directly parametrized by the regression model, data-resampling bootstrapping was undertaken with 100,000 resamples to create 95% confidence intervals. The confidence interval's lower and upper values were the 2.5% and 97.5% quantiles of the bootstrapped estimates, respectively. The analysis plan was reviewed and approved by the UBC Behavioural Research Ethics Board (Project H17-01391) and the BC Ministry of Health. Analytic code is available through http://doi.org/10.5281/zenodo.2573337.

2.4.2 Sensitivity analysis of linkage bias

The process of linking BC Pharmanet prescribing data to the MSP dataset excludes prescribing by non fee-for-service providers. In BC, medical services provided by salaried and sessional physicians and service organizations funded through the Alternative Payments Program would not be captured by the MSP dataset. In 2015-2016, fee-for-service composed 70% of overall physician compensation (98). However, alternative payments are not uncommon in geriatric care (99). Certain demographics are more likely to participate in alternative payment programs in NHs (e.g. younger physicians and female physicians) (100,101). Thus, excluding prescriptions without a fee-for-service billing has the potential to bias results. This sensitivity analysis was undertaken to assess the potential strength of this bias and its effect on the primary analysis. The outcome rate was defined as (Total UTI-linked DDDs monthly prescriptions in group + Total DDDs of any unlinked or non-UTI coded nitrofurantoin in group)/(Monthly population of group)/Days in the month. The analytic method was identical to the linear regression described in the primary analysis.

Chapter 3: Results

3.1 Study cohort

In this ecologic study using administrative data, there were an average of 27,583 publicly subsidized nursing home residents per month from May 1, 2015 to March 31, 2017 in 320 nursing homes (Table 1). In BC, residents older than 80 years of age constituted over 70% of the nursing home cohort (n = 20,003/27,583). Overall, 65% of residents were women and this was the same in both intervention and control (n = 18,076/27,583). UTI-linked prescriptions were common, 32% of residents received an antibiotic linked to a UTI indication (n = 8,746//27,583). Throughout the province, there were 2,787 unique prescribers with an antibiotic linked to a UTI-indication. Physicians accounted for 96.4% of linked prescribers (n = 2,688/2,787) and this high proportion of physicians was consistent in both intervention and control groups.

Table 1. Characteristics of publicly subsidized nursing homes, nursing home residents and Pharmanet Plan B prescribers with UTI-linked prescriptions in British Columbia, June 2015 – March 2017

Characteristics	Control	Intervention	P-value	Overall
Nursing home administrative factors				
Number of nursing homes	46 (14.4)	274 (85.6)		320 (100.0)
Small	43 (93.5)	165 (60.2)	< 0.01	208 (65.0)
Medium	3 (6.5)	107 (39.1)	< 0.01	110 (34.4)
Large	0 (0.0)	2 (0.7)	NA	2 (0.6)
Geographic				
Total LHAs	26 (100.0)	48 (100.0)		74 (100.0)
Remote	12 (46.2)	3 (6.2)	< 0.01	15 (20.3)
Rural	12 (46.2)	14 (29.2)	0.23	26 (35.1)
Urban/rural	2 (7.7)	25 (52.1)	<0.01	27 (36.5)
Metro	0 (0.0)	6 (12.5)	NA	6 (8.1)
Residents				
Average number of residents in a month in the study period	2,241 (8.1)	25,341 (91.9)		27,583 (100.0)
Average number of female residents*	1,452 (64.8)	16,623 (65.6)	0.46	18,076 (65.5)
Unique residents with a UTI-linked prescription*	706 (31.5)	7,687 (30.3)	0.26	8,393 (30.4)
*Age**				
15-64	122 (5.5)	1,510 (6.0)	0.35	1,633 (5.9)
65-80	503 (22.5)	5,442 (21.5)	0.30	5,946 (21.6)
80+	1,615 (72.1)	18,388 (72.6)	0.63	20,003 (72.5)
Prescribers				
Unique prescribers with a UTI-linked prescription	388 (100.0)	2,073 (100.0)		2,461 (100.0)
Nurse practitioner	9 (2.3)	28 (1.4)	0.23	37 (1.5)
Other	0 (0.0)	13 (0.6)	0.24	13 (0.5)
Pharmacist	5 (1.3)	33 (1.6)	0.83	38 (1.5)
Physician	374 (96.4)	1,999 (96.4)	1.00	2,373 (96.4)

*Percentage of average number of residents in study period

3.2 Program reach

From July 2016, the academic detailing intervention occurred in 66.2% (n = 49/74) of LHAs with a NH (Table 1). The control LHAs were largely rural or remote, 92.4% (n = 24/26). Whereas, in the intervention groups, rural or remote LHAs only accounted for 35.4% (n = 17/48) of LHAs. In both the control and intervention groups, NHs were predominantly small (< 29 publicly-subsidized residents), 93.5% (n = 43/46) and 60.2% (n = 165/274), respectively. The intervention group had a greater proportion of medium and large NHs, 39.1% (n = 107/274) 0.7% (n = 2/274) than the control group.

3.3 Overall and UTI-linked antibiotic prescribing in Pharmanet Plan B

During the study period, there were 93,327 antibiotic prescriptions (Table 2). Nitrofurantoin alone constituted 34.6% of prescribed antibiotics (n = 32,304). As an indicator of linkage-validity, approximately one third of nitrofurantoin was linked to a UTI-related indication (n = 10,872/32,304) and 52.7% of nitrofurantoin was unlinked (n= 13,622/32,304). 25.8% of antibiotic prescriptions in British Columbia were linked to a UTI-indication (n = 24,081/93,324). In both intervention and control groups, cystitis was the most commonly linked indication, and overall accounted for 50.1% of UTI-linked prescriptions (n = 12,058/24,081).

Table 2. Characteristics of all and UTI-linked antibiotic prescribing in Pharmanet Plan B, June 2015 to March 2017

Prescription characteristics (n%)	Control	Intervention	Overall
Antibiotics			
Number of antibiotic prescriptions	8,203 (100.0)	85,121 (100.0)	93,324 (100.0)
UTI-linked prescriptions	1,971 (24.0)	22,110 (26.0)	24,081 (25.8)
All nitrofurantoin	3,334 (40.6)	28,970 (34.0)	32,304 (34.6)
UTI-linked nitrofurantoin*	894 (26.8)	9,978 (34.4)	10,872 (33.7)
Unlinked nitrofurantoin*	1,758 (52.7)	11,864 (41.0)	13,622 (42.2)
Nitrofurantoin linked to other indications, including multiple	682 (20.4%)	7,128 (24.6%)	7,810 (24.2%)
Indications of linked prescriptions			
Cystitis†	922 (46.8)	11,136 (50.4)	12,058 (50.1)
Other disorders of urethra and urinary tract†	391 (19.8)	5,960 (27.0)	6,351 (26.4)
Prostatitis†	0 (0.0)	19 (0.1)	19 (0.1)
Pyelonephritis†	220 (11.2)	340 (1.5)	560 (2.3)
Symptoms involving urinary system†	438 (22.2)	4,655 (21.1)	5,093 (21.1)

*Percentage of all nitrofurantoin
†Percentage of UTI-linked prescriptions in the group

3.4 Trends for all antibiotics in Pharmanet Plan B

Both control and intervention had similar prescribing rates at baseline, 33.25 and 33.32 DDD/1,000 residents/day, respectively (Table 3). In the pre-intervention period, the control's antibiotic prescribing trend was a monthly decrease of -0.09 DDD/1,000 residents/day per month versus -0.35 after start of the intervention – a slope change of 0.26 (95% CI: -0.81 to 0.29) DDD/1,000 residents/day per month. The intervention group's pre-intervention trend was a monthly decrease of -0.31 DDD/1,000 residents/day per month vs -0.04 from the start of the

intervention – a slope change of 0.35 (95% CI: -0.09 to 0.68). The difference in slope changes was 0.61 (95% CI: -0.27 to 1.22) DDD/1,000 residents/day per month.

Table 3. Baseline prescribing rate and trend estimates from segmented regression of overall and UTI-linked antibiotic prescribing rates

	All antibiotics	UTI-linked
Variable	**Estimate (95% CI)**	**Estimate (95% CI)**
Baseline DDD prescribing, June 2015 (DDD/1,000 residents/day)		
Control	33.25	9.46
Intervention group	33.32	9.07
Difference	0.07 (-2.79 — 2.93)	-0.39 (-2.16 — 1.39)
Pre-intervention trend (DDD/1,000 residents/day per month)		
Control	-0.09	-0.15
Intervention group	-0.31	-0.14
Difference	-0.22 (-0.58 — 0.14)	0.02 (-0.33 — 0.36)
Post-intervention trend (DDD/1,000 residents/day per month)		
Control	-0.35	-0.09
Intervention group	0.04	-0.27
Difference	0.40 (-0.28 — 0.80)	-0.18 (-0.58 — 0.15)
Change in pre- and post-slopes (DDD/1,000 residents/day per month)		
Control	-0.26 (-0.81 — 0.29)	0.06 (-0.16 — 0.29)
Intervention group	0.35 (-0.08 — 0.67)	-0.13 (-0.32 — -0.07)
Impact: Difference in slope changes	0.61 (-0.25 — 1.23)	-0.19 (-0.77 — 0.25)

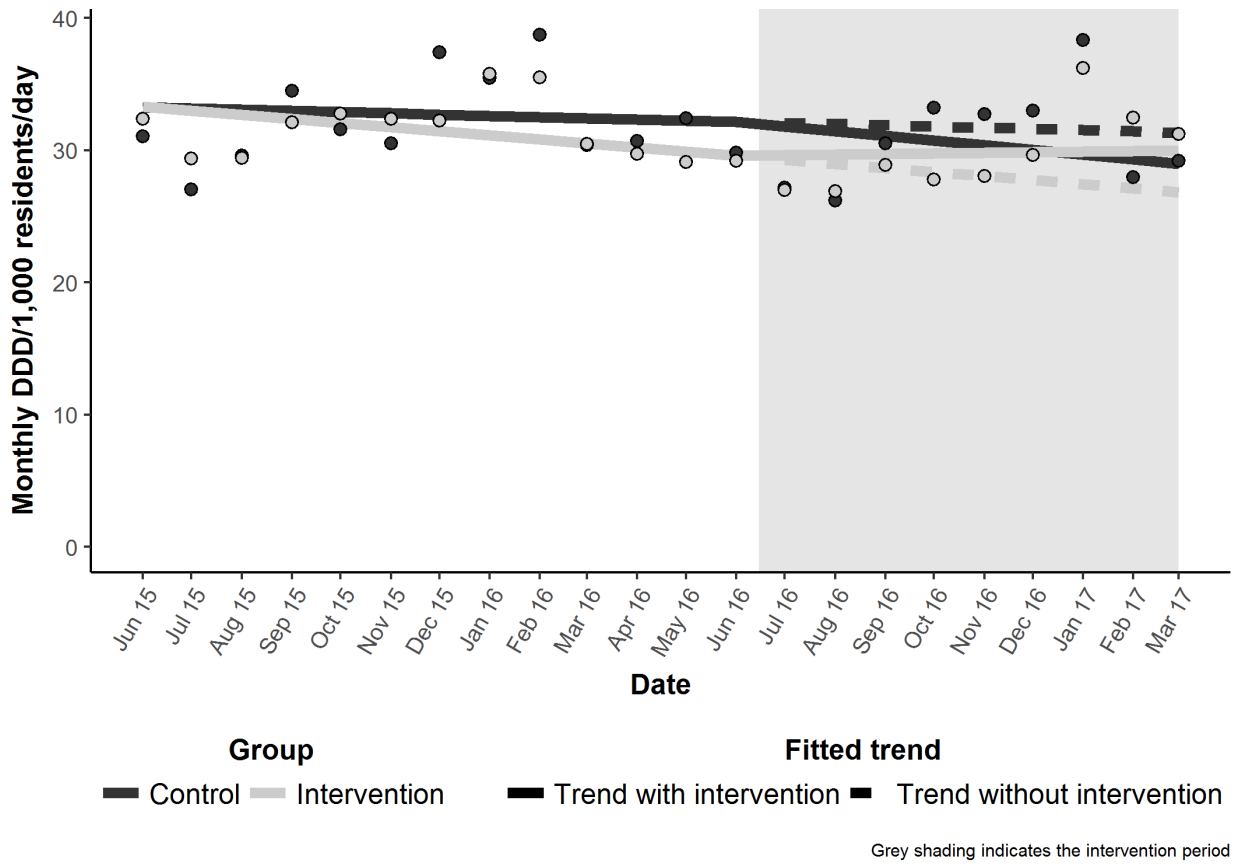

Figure 1. Prescribing trends of all antibiotics in Pharmanet Plan B from June 2015-March 2017 stratified by LHA intervention status

Points are the observed deasonalized DDD rates for overall prescribing

3.5 Intervention's impact on UTI-linked prescribing

The groups had comparable pre-intervention UTI-linked prescribing rates (Figure 2). At baseline, in June 2015, the intervention group had a -0.39 (95% CI: -2.16 to 1.39) DDD/1,000 residents/day lower prescribing rate relative to the control (Table 3). The control's antibiotic prescribing pre-intervention trend was a monthly decrease of -0.15 DDD/1,000 residents/day per month versus -0.09 after start of the intervention – a slope change of 0.06 (95% CI: -0.16 —

0.29) DDD/1,000 residents/day per month. The intervention group's pre-intervention trend was almost identical to the controls', a monthly decrease of -0.14 DDD/1,000 residents/day per month vs -0.27 after start of the intervention – a slope change of -0.13 DDD/1,000 residents/day per month. The difference in slope changes was -0.20 (95% CI: -0.68 to 0.29) DDD/1,000 residents/day per month. By taking the reciprocal of the trend, we can express how many months it would take to make a 1 unit reduction in the DDD/1,000 residents/day. In the post-intervention period, it would take the intervention group 4 months to create the same reduction that would take the control group a year.

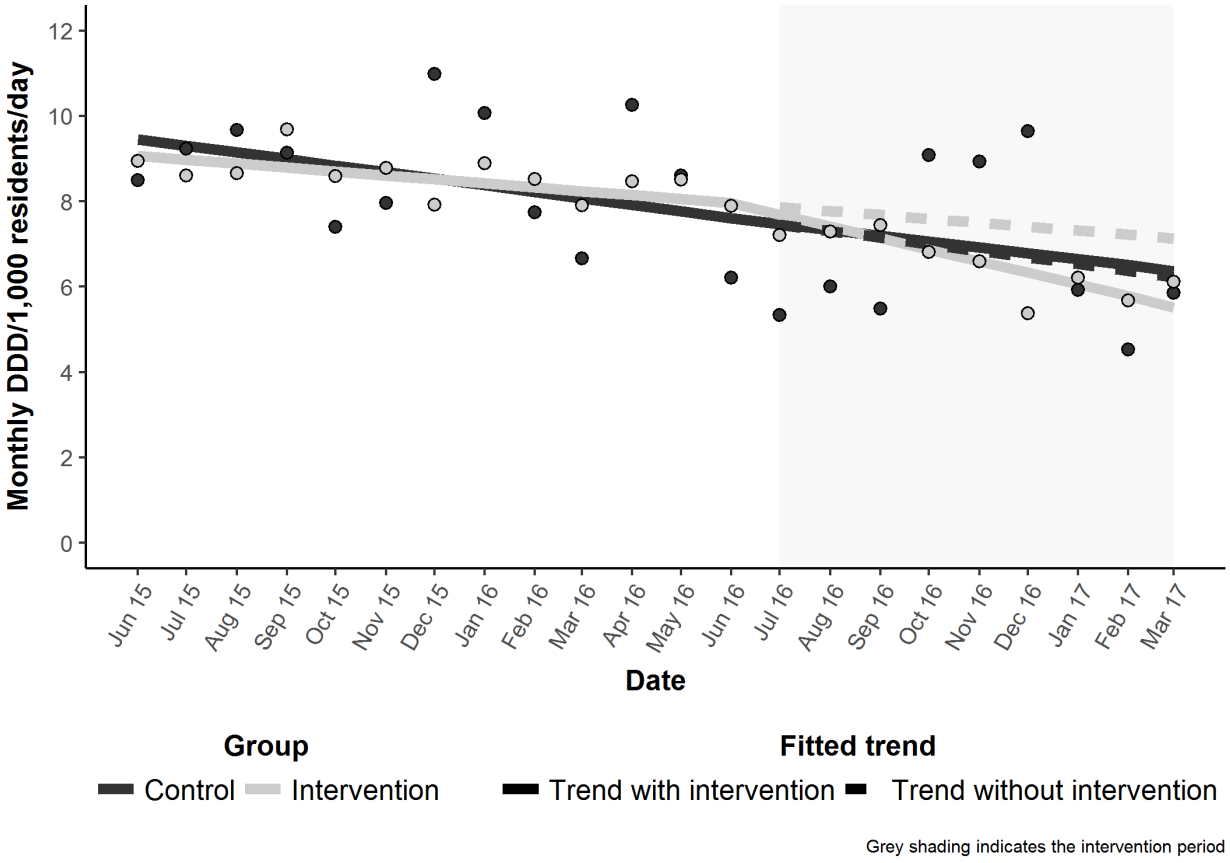

Figure 2. NH UTI-linked prescribing rates and trends from June 2015-March 2017, stratified by LHA intervention status

Points are observed UTI-linked DDD rates.

3.6 Linkage sensitivity analysis

Relative to primary UTI-linked antibiotic analysis (X mark), the sensitivity analysis with nitrofurantoin prescriptions with unlinked and non-UTI related ICD-9 codes (triangle) highlighted the potential impact of misclassified/missing prescriptions (Figure 2). Relative to the primary analysis, the control's and intervention's baseline prescribing rate increased by 5.98 and 4.79 DDD/1,000 residents/day, respectively (Supplementary Table A1). Despite this level change, the trend parameters in the sensitivity analysis were like those in the primary analysis. For both control and intervention groups, nitrofurantoin as a proportion of UTI-linked prescribing remained unchanged during the study period (results not shown).

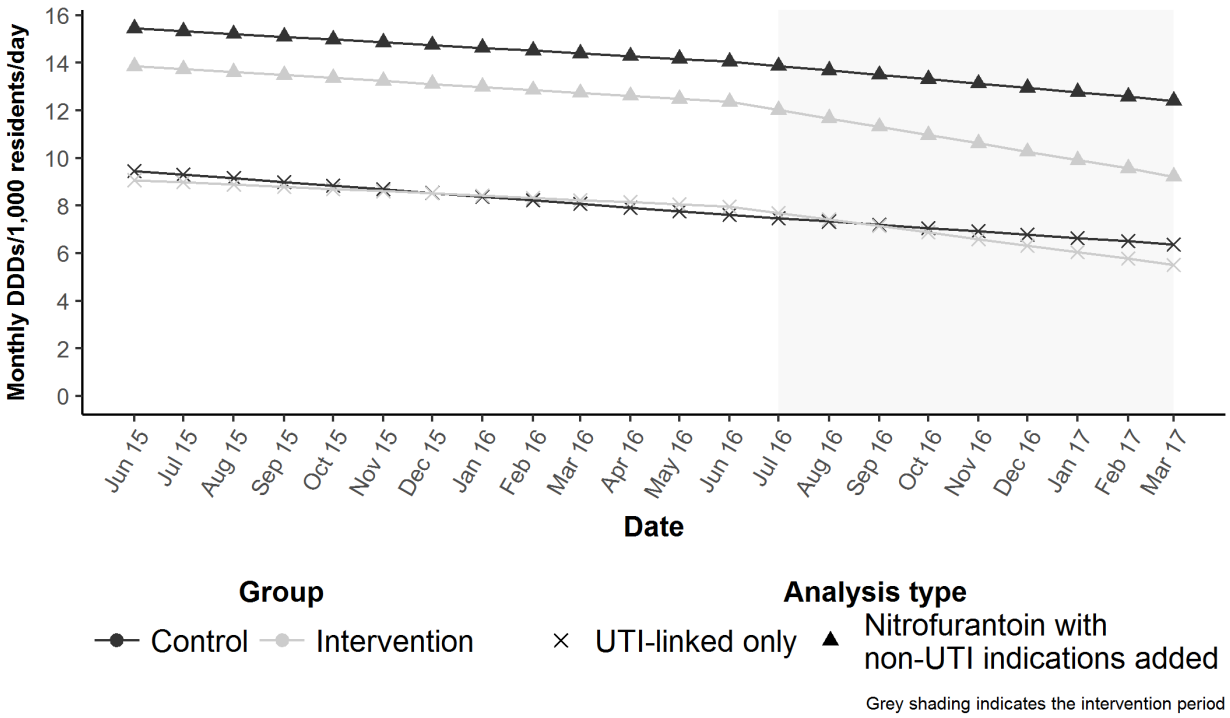

Figure 3. Trends in DDD prescribing rates in Pharmanet Plan B stratified by LHA intervention status of UTI-linked and nitrofurantoin-added analytic datasets, June 2015-March 2017

Chapter 4: Discussion

4.1 Summary of results

In this ecologic quasi-experimental study, in the UTI-linked analysis, the control's antibiotic prescribing pre-intervention trend was a monthly decrease of -0.15 DDD/1,000 residents/day per month versus -0.09 after start of the intervention – a slope change of 0.06 (95% CI: -0.16 to 0.29) DDD/1,000 residents/day per month. The intervention group's pre-intervention trend was almost identical to the controls', a monthly decrease of -0.14 DDD/1,000 residents/day vs -0.27 after start of the intervention. A slope change of -0.13 (95% CI: -0.32 to -0.07) DDD/1,000 residents/day per month. The difference in slope changes was -0.19 (95% CI: -0.29 to 0.80) DDD/1,000 residents/day per month. UTIs have previously been the most commonly linked indication for prescriptions to BC's NH population, however, the intervention was not related to a reduction in the intervention group's overall antibiotic prescribing trends. From the intervention's start, the intervention group's overall prescribing rate was increasing by 0.04 DDD/1,000 residents/day per month.

4.2 Discussion

Our study adds to prior evidence on educational interventions for antibiotic stewardship purposes in the nursing home setting. This study is unique in that it ecologically surveys the changes due to a large-scale intervention on antibiotic prescribing in 320 nursing homes. A 2018 systematic review of nursing home antibiotic stewardship identified fourteen interventions that were classified as good or fair quality (72). Most interventions had an educational component. However, only three had explicit academic detailing components. Linnebur and colleagues

implemented a multi-faceted intervention on nursing home–acquired pneumonia in 16 NHs (79). There was no difference in the improvement in the mean adherence for optimal antibiotic use in both control and intervention groups. In a study from Colorado, USA, Hutt *et al.* used academic detailing to complement guidelines for NH-acquired pneumonia in two NHs (80). In the intervention facilities, there was a 20% absolute increase in guideline-concordant prescribing; whereas, guideline-concordant prescribing decreased 13% in the control arm. Pettersson and colleagues conducted a cluster randomized controlled trial in fifty-eight NHs that included feedback, guidelines and educational outreach (i.e. academic detailing) (70). Their intervention similarly focused on UTIs, however, direct comparisons are not possible as the antibiotic-related outcomes were proportions rather than prescribing rates. In both arms, there was no difference in the reduction of UTI incidence and the proportion of quinolones. Recently, Pasay and colleagues conducted academic detailing and a checklist (decision-making tool) intervention in rural NHs (21 intervention NHs and 21 control NHs) (81). Their data were compatible with a decrease of 2.5 to 1.7 per 1,000 resident-days in urine culture testing in the intervention group. Similarly, a decrease of 1.0 to 0.4 per 1,000 resident-days of UTI-associated antibiotics was observed. Pasay *et al.*'s and the present study's results are suggestive of a small intervention effect for academic detailing to change antibiotic prescribing patterns for ASB in nursing homes; consistent with the findings of a Cochrane meta-analysis on academic detailing (78).

A systematic review of educational outreach visits found that there was no statistically significant difference between single component academic detailing or multifaceted interventions (78). Additionally, in the present study, there was no observed change in the overall prescribing level. This finding of a condition-specific intervention not impacting overall antibiotic is not unique. Loeb *et al.*'s cluster randomized trial of educational antibiotic

stewardship for UTIs found an equivocal difference in control and intervention group's total prescribing rates (95% CI: 1.17 to 0.44 antimicrobial use per 1000 resident days) (65). NH antibiotic prescribing is a multi-step pathway (53). Both, the inefficacy of a potential multifaceted intervention and no changes in overall prescribing may relate to an intervention's inability to address several different determinants of prescribing behavior (102). For instance, Feldstein's systematic review identified that only ID consultation and a multi-stakeholder intervention (family, residents, and healthcare workers) reported decreases in overall antibiotic prescribing. Those methods have an ability to address different determinants of prescribing behavior. Programs might be more likely to influence overall antibiotic practice if they target different barriers to change (e.g. organizational policies, administrative and staff buy-in and families). Multifaceted interventions in NHs may need to differentiate themselves from stewardship approaches conceived in the hospital setting, as a population-level intervention in the Canadian province of Ontario did (102). Their identified implementation strategies work on several elements of the Theoretical Domains Framework.

While BC PAD's intervention was planned as a single component academic detailing intervention. The decreases in the intervention group's all antibiotic prescribing and UTI-linked prescribing rates in the pre-intervention period suggest: pre-existing sensitivity to antibiotic stewardship concordant practices, improving infection control practices or contemporaneous initiatives (e.g. continuing medical education from the Do Bugs Need Drugs? program). In this large population of 320 nursing homes, these possible co-interventions would have worked like components of a multifaceted intervention.

In the present study, the sensitivity analysis assessed the potential influence of linkage bias. Including any nitrofurantoin prescribed highlighted the extent of missing data from

focusing on fee-for-service billing. The greater change in the control's baseline rate compared to the intervention group's rate highlighted the potential for bias. Nonetheless, the trend parameters in the primary and sensitivity analysis were similar. This suggests that the exclusion of non-FFS prescribers is unlikely to bias the study's primary analysis.

4.3 Limitations

There are two core limitations of the study. Firstly, this was a non-randomized quasi-experimental study. While, interrupted time series are considered one of the strongest quasi-experimental designs; this rests on the control group's validity (103). For the UTI-linked analysis, both intervention and control had similar pre-intervention trends and baseline rates. However, the control group had a large proportion of rural and remote LHAs. Thus, it is potentially unable to detect cointerventions in urban and metropolitan LHAs. To avoid this issue, future interventions in the province would benefit from prospective randomization of interventions that allows for a more comparable control group. Secondarily, the ecologic fallacy must be considered in interpreting the study's results (104). The present study's changes at an aggregate level may not occur at the individual nursing home level. While, there are several reasons for the ecologic fallacy, as an example, the detailers preferred visiting large NHs (situated in urban areas) (105). An LHA was categorized in the intervention group if a single NH within it was visited by BC PAD. Thus, even if the intervention was not effective, if an intervention LHA had other NHs implementing related co-interventions, it might make the intervention appear more effective. Our access to only aggregated data necessitated the present study's ecologic design. Additionally, a longer follow-up would assist in better assessing both intervention durability and whether changes in overall prescribing rates were influenced by seasonality.

4.4 Conclusion

In this ecologic interrupted time series analysis, academic detailing was associated with greater change in the UTI-linked prescribing trend relative to the control, a difference of -0.19 DDD/1,000 residents/day per month that accounts for co-interventions and pre-existing trends. It would take the intervention group four months, while it would take a year for the control group to achieve an identical reduction in the UTI-linked prescribing rate. The control series suggest that this change was not attributable to co-interventions. However, the intervention was not associated with changes to the level of overall prescribing in Pharmanet Plan B**.** The study demonstrated that it was possible for a small academic detailing team to visit a large number of NHs in population-based ASP intervention in British Columbia. Future research with longer follow-up periods and population-level studies at the prescriber that considers nursing-home level factors is needed. For instance, to assess how institutional factors affect prescriber's stewardship-concordant practices in multiple nursing homes. Additionally, identifying which elements of a multifaceted intervention work well together will be an important avenue of future research in population-level AMS interventions in NHs.

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Appendices

Appendix A

A.1 Supplementary table: Baseline prescribing rate and trend estimates in the primary and sensitivity analysis, June 2015 – March 2017

	Estimate (95% confidence interval)	
Baseline DDD prescribing, June 2015 (DDDs/1,000 residents/day)	**UTI-linked antibiotics (primary)**	**Nitrofurantoin added* (sensitivity)**
Control group (reference)	9.46	15.44
Intervention group	9.07	13.86
Difference	-0.39 (-2.16 — 1.39)	-1.58 (-3.52 — 0.35)
Pre-intervention trend (DDDs/1,000 residents/day per month)		
Control group (reference)	-0.15	-0.12
Intervention group	-0.14	-0.12
Difference	0.02 (-0.33 — 0.36)	-0.01 (-0.25 — 0.24)
Post-intervention trend (DDDs/1,000 residents/day per month)		
Control group	-0.09	-0.18
Intervention	-0.27	-0.35
Difference	-0.18 (-0.58 — 0.16)	(-0.83 — 0.11)
Change in pre-and post-slope (DDDs/1,000 residents/day per month)		
Control	0.06 (-0.16 — 0.29)	-0.07 (-0.44 — 0.31)
Intervention	-0.13 (-0.32 — -0.07)	-0.23 (-0.41 — -0.07)
Difference	-0.20 (-0.68 — 0.29)	-0.16 (-0.94 — 0.27)

*Nitrofurantoin prescriptions for non-UTI ICD-9 codes and those without an ICD-9 codes were added to analytic dataset