Prescribing Trends for Oral Vancomycin and Fidaxomicin after Guideline and Formulary Changes in Ontario, Canada: An Interrupted Time-Series Analysis

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To cite: Maximos M, Maxwell C, Gamble JM. Prescribing trends for oral vancomycin and fidaxomicin after guideline and formulary changes in Ontario, Canada: an interrupted time-series analysis. *Can J Hosp Pharm.* 2024;77(3):e3560. doi: 10.4212/cjhp.3560

ABSTRACT

Background: *Clostridioides difficile* is a pathogen causing diarrheal illness, which can be treated with vancomycin or fidaxomicin.

Objective: To evaluate changes in monthly prescription volumes for oral vancomycin and fidaxomicin in Ontario community pharmacies following implementation of the 2017 and 2021 updates to guidelines from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) and after a 2019 provincial formulary change for vancomycin.

Methods: An interrupted time-series analysis was conducted from November 2015 to October 2021 using monthly projected prescription volumes obtained from IQVIA's Compuscript database. Level and slope (trend) changes in prescribing were assessed using segmented linear regression.

Results: The volume of vancomycin prescriptions increased by 74 prescriptions per month (95% confidence interval [CI] 16 to 132) following implementation of the 2017 guideline update and by 73 prescriptions per month (95% CI 13 to 133) after the 2019 formulary change; however, no statistically significant changes were observed after implementation of the 2021 guideline update. No significant trend changes were observed for fidaxomicin.

Conclusion: Guidelines and formulary changes were correlated with increased volume of vancomycin prescriptions.

Keywords: *Clostridioides difficile*, interrupted time-series analysis, clinical practice guideline, policy, antimicrobial stewardship, vancomycin, fidaxomicin

RÉSUMÉ

Contexte : Le *Clostridioides difficile* est un agent pathogène provoquant une maladie diarrhéique pouvant être traitée avec de la vancomycine ou de la fidaxomicine.

Objectif : Évaluer les changements de volume mensuel des prescriptions de vancomycine et de fidaxomicine par voie orale dans les pharmacies communautaires de l'Ontario après la mise en œuvre des lignes directrices actualisées en 2017 et 2021 de l'Infectious Diseases Society of America (IDSA) et de la Society for Healthcare Epidemiology of America (SHEA) et à la suite d'une modification au régime d'assurance-médicaments pour la vancomycine à l'échelle provinciale en 2019.

Méthodologie : Une analyse de séries chronologiques interrompues a été réalisée de novembre 2015 à octobre 2021 à l'aide des volumes mensuels de prescriptions projetés qui ont été obtenus grâce à la base de données Compuscript d'IQVIA. Les changements du volume des prescriptions et de son évolution dans le temps (le niveau et la pente, respectivement) ont été évalués à l'aide d'une régression linéaire segmentée

Résultats : Le volume des prescriptions de vancomycine a augmenté de 74 prescriptions par mois (intervalle de confiance [IC] à 95 % 16-132) après la mise en œuvre des lignes directrices actualisées en 2017; il a augmenté de 73 prescriptions par mois (IC à 95 % 13-133) après la modification du régime d'assurance-médicaments de 2019; cependant, aucun changement statistiquement significatif n'a été observé après la mise en œuvre des lignes directrices actualisées en 2021. Aucun changement significatif de tendance n'a été observé pour la fidaxomicine.

Conclusion : Les lignes directrices et les modifications du régime d'assurance-médicaments étaient corrélées à une augmentation du volume des prescriptions de vancomycine.

Mots-clés : *Clostridioides difficile*, analyse de séries chronologiques interrompues, ligne directrice de pratique clinique, politique, gestion des antimicrobiens, vancomycine, fidaxomicine

INTRODUCTION

Clostridioides difficile, a gram-positive spore-forming bacterium found in the intestinal tract of animals and humans and in the environment,[1] poses a global public health burden, causing severe diarrheal illness, colitis, sepsis, and death.[2] Although rates of *C. difficile* infection in Canada decreased from 2009 to 2015,[3,4] infection still leads to significant health care costs and hospital admissions.[5] Historically, metronidazole has been the treatment of choice for *C. difficile* infection. For example, in the 1980s, metronidazole was considered a first-line agent for treatment of *C. difficile*–associated diarrhea because it was cheaper than vancomycin and because there was, at the time, an assumption that overuse of vancomycin would contribute to the emergence of vancomycin-resistant enterococci.[6] However, vancomycin and fidaxomicin have better outcomes than metronidazole in the treatment of mild and moderate *C. difficile* infection.[7] Vancomycin and fidaxomicin target *C. difficile* with minimal interruption of the gastrointestinal flora, thereby improving therapeutic capacity for treatment.

In their 2017 guideline update,[8] the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommended vancomycin or fidaxomicin over metronidazole for treatment of *C. difficile* infection outside of severe cases. This marked the debut of fidaxomicin in the IDSA/SHEA guidelines. In June 2021, a further update from these organizations suggested that fidaxomicin be preferred over vancomycin due to its potential to reduce recurrence of infection.[9] In the province of Ontario, vancomycin for treatment of *C. difficile* was previously available through the Exceptional Access Program (EAP), whereby funding for this drug had to be requested through an administratively time-consuming application process.[10] In September 2019, a streamlined coverage process, using a limited use (LU) code, was introduced for vancomycin. Fidaxomicin is covered by the Ontario EAP.

Coverage through the LU code and the EAP is applicable only for individuals who are eligible for Ontario's publicly funded drug plan, which is not always reflective of private drug plan coverage; however, the IQVIA Compuscript database provides an estimate of total outpatient prescription volumes irrespective of payer status. In Ontario, EAP coverage for fidaxomicin can be accessed for patients who meet the criteria for use of vancomycin but have experienced one of the following: a third or subsequent episode of *C. difficile* infection within 6 months of treatment with vancomycin for prior episodes without history of fidaxomicin trial; treatment failure with oral vancomycin for a recurrent episode of *C. difficile* infection; or severe adverse reaction or intolerance to oral vancomycin treatment that led to discontinuation of therapy.[11]

These guideline and formulary changes are considered to be "policy interventions" and offer the opportunity to study changes in prescribing behaviour following their implementation.[12] The aim of this study was to assess volumes of new vancomycin and fidaxomicin prescriptions for outpatients in Ontario between November 2015 and October 2021 following the 2017 and 2021 IDSA/SHEA guideline updates and the 2019 change in eligibility for prescribing of oral vancomycin in Ontario.

METHODS

Study Design and Data Source

An interrupted time-series analysis was conducted using data from the IQVIA Compuscript database, which contains projected monthly volumes of new prescriptions from Canadian retail pharmacies between November 2015 and October 2021. The database provides details such as molecule and product name, strength, formulation, projected numbers of new prescriptions, costs per month, province, and prescriber specialty. The projected volumes of new prescriptions are based on data from about 60% of Canadian retail pharmacies.[13] The study setting was restricted to Ontario because health care coverage in Canada is administered provincially and the change from EAP to LU code for vancomycin coverage was unique to Ontario in 2019, falling between introduction of the 2017 IDSA/SHEA guideline update and the subsequently updated guideline released in 2021.

Measures

This analysis focused on the projected monthly volumes of new prescriptions for oral vancomycin (125 mg, 250 mg) and oral fidaxomicin (200 mg) in Ontario. These oral formulations are considered most suitable for treating this infection, as *C. difficile* remains within the colonic space.[14] IV vancomycin and oral metronidazole, used for various indications, were not considered in this study. Bezlotoxumab is not approved for use in Canada and therefore was not included.

Interventions

Changes in prescription volumes were assessed after the following 3 interventions. Intervention 1, in April 2018, was the publication of the 2017 IDSA/SHEA guideline update, which indicated a preference for vancomycin or fidaxomicin over metronidazole. Intervention 2, in September 2019, was the transition in Ontario from EAP to LU access for oral vancomycin for treatment of *C. difficile* infection. Intervention 3, in June 2021, was the introduction of the IDSA/SHEA guideline update suggesting a preference for fidaxomicin over vancomycin for treatment of *C. difficile* infection.

Statistical Analyses

Descriptive statistics were calculated for projections of new prescriptions for vancomycin and fidaxomicin before and after the interventions. Changes in the level and trend

(slope) of monthly projected volumes of new prescriptions for vancomycin and fidaxomicin following the 3 interventions were estimated using a segmented linear regression model. The assumption of linearity was tested for both drugs. A significance threshold of $p < 0.05$ was applied, autocorrelation was assessed using the Durbin–Watson test,[15] and seasonality was tested. Statistical analyses were conducted using Microsoft Excel (version 16.74) and SAS version 9.4 (SAS Institute).

RESULTS

From November 2015 to March 2018, there was a mean monthly projected prescription volume of 391 for vancomycin and 15 for fidaxomicin across Ontario. From April 2018 to August 2019 (after intervention 1), projected prescriptions increased by 26% for vancomycin and 33% for fidaxomicin. From September 2019 to May 2021 (after intervention 2), the increases were 46% for vancomycin and 5% for fidaxomicin. Finally, from June 2021 to October 2021 (after intervention 3), the increases were 23% for vancomycin and 67% for fidaxomicin. Table 1 provides details regarding the projected volumes of new prescriptions for each drug after each intervention.

Figure 1 illustrates the monthly projected volumes of new prescriptions for oral vancomycin. There was an initial decrease of approximately 2 (95% CI –4 to 0) prescriptions per month until the first intervention. Following release of the 2017 IDSA/SHEA guideline (intervention 1, in April 2018), new prescriptions for vancomycin immediately increased by 74 (95% CI 16 to 132) per month and continued to rise by an average of 8 (95% CI 3 to 13) per month ($p < 0.05$). Another level increase occurred after the transition from EAP to LU coverage for vancomycin in Ontario (intervention 2), with a significant projected increase of 73 (95% CI 13 to 133) new prescriptions for vancomycin per month ($p < 0.05$). Subsequently, there was a steady but nonsignificant increase in vancomycin prescriptions. In particular, following the 2021 IDSA/SHEA guideline update (intervention 3), there was no significant change in level or trend for vancomycin prescriptions; however, the confidence intervals were wide due to few data points. Autocorrelation testing with a lag of 12 showed a nonsignificant result (Durbin–Watson statistic 2.08, $p = 0.68$).

Figure 2 illustrates the projected monthly volumes of new prescriptions for oral fidaxomicin. For fidaxomicin, none of the level or slope changes were statistically significant following any of the 3 interventions. Autocorrelation testing with a lag of 12 showed a nonsignificant result (Durbin–Watson statistic 2.08, $p = 0.68$).

DISCUSSION

This study examined the impact of multiple policy interventions on prescription volumes for oral vancomycin and fidaxomicin in Ontario. Two interventions were associated with changes in prescribing patterns. The 2017 IDSA/SHEA *C. difficile* guideline update[8] was associated with an immediate and sustained increase in projected new prescriptions for oral vancomycin among Ontario retail pharmacies. The Ontario drug benefit formulary change from EAP to LU code was associated with an immediate and significant increase in new prescriptions for oral vancomycin and a small, nonsignificant decrease in new prescriptions for fidaxomicin. The 2021 IDSA/SHEA guideline update for *C. difficile* treatment was not associated with statistically significant changes in prescribing of either vancomycin or fidaxomicin.

TABLE 1. Descriptive Statistics for Projected Monthly Prescription Volume for Oral Vancomycin and Fidaxomicin between Interventions (November 2015 to October 2021)[a]

	Projected Monthly Prescription Volume				
Period	**Mean**	**% Increase[b]**	**SD**	**Minimum**	**Maximum**
Vancomycin					
Nov 2015 to Mar 2018	391	NA	55	315	563
Apr 2018 to Aug 2019	493	26	48	416	599
Sep 2019 to May 2021	722	46	81	553	870
June 2021 to Oct 2021	886	23	51	796	921
Fidaxomicin					
Nov 2015 to Mar 2018	15	NA	6	5	28
Apr 2018 to Aug 2019	20	33	6	10	30
Sep 2019 to May 2021	21	5	7	8	35
June 2021 to Oct 2021	35	67	4	29	39

NA = not applicable, SD = standard deviation.
[a]Based on information licensed from IQVIA: CompuScript® database. All rights reserved.
[b]Relative to previous period shown in the table.

Several factors may explain why fidaxomicin prescribing did not exhibit the same extent of increase as that for vancomycin. First, fidaxomicin is much more costly. In fact, at the recommended treatment doses, it is 2.5 to 14 times more expensive than oral vancomycin (about $2200 vs $158 to $900).[16] Second, the greater administrative and time burden of the EAP process required for fidaxomicin, relative to the accessibility of vancomycin by LU code, may have deterred fidaxomicin prescribing. Third, differences in the strength and quality of evidence may have affected prescribing volumes. In the 2017 IDSA/SHEA guideline update,[8] the recommendation to use oral vancomycin or fidaxomicin rather than metronidazole was "strong" with "high quality of evidence", whereas in the 2021 IDSA/SHEA guideline update,[9] the recommendation to use fidaxomicin rather than vancomycin was "conditional" with only "moderate certainty of evidence". Finally, the evidence for fidaxomicin superiority is not related to clinical cure rate, but rather to reduction in risk of recurrence, which may affect the ability to position this medication in the therapeutic toolkit for treatment of *C. difficile*. Affordability, accessibility of medications, introduction of novel agents, and accessibility of guideline updates may shape prescribing patterns. Future research could involve a comparison of prescribing patterns across Canadian provinces and territories.

Our findings contribute to the existing literature on the impact of policies and guidelines on *C. difficile* treatment. Clancy and others[17] found that the 2017 IDSA/SHEA guideline update significantly increased the use of oral vancomycin in the United States; however, they also found a significant increase in the use of fidaxomicin. Luc and others[18] assessed concordance with the *C. difficile* treatment guidelines among medical providers in the state of Connecticut. These authors found an increase in concordance with guidelines in 2018 and 2019 relative to 2017. Khadem

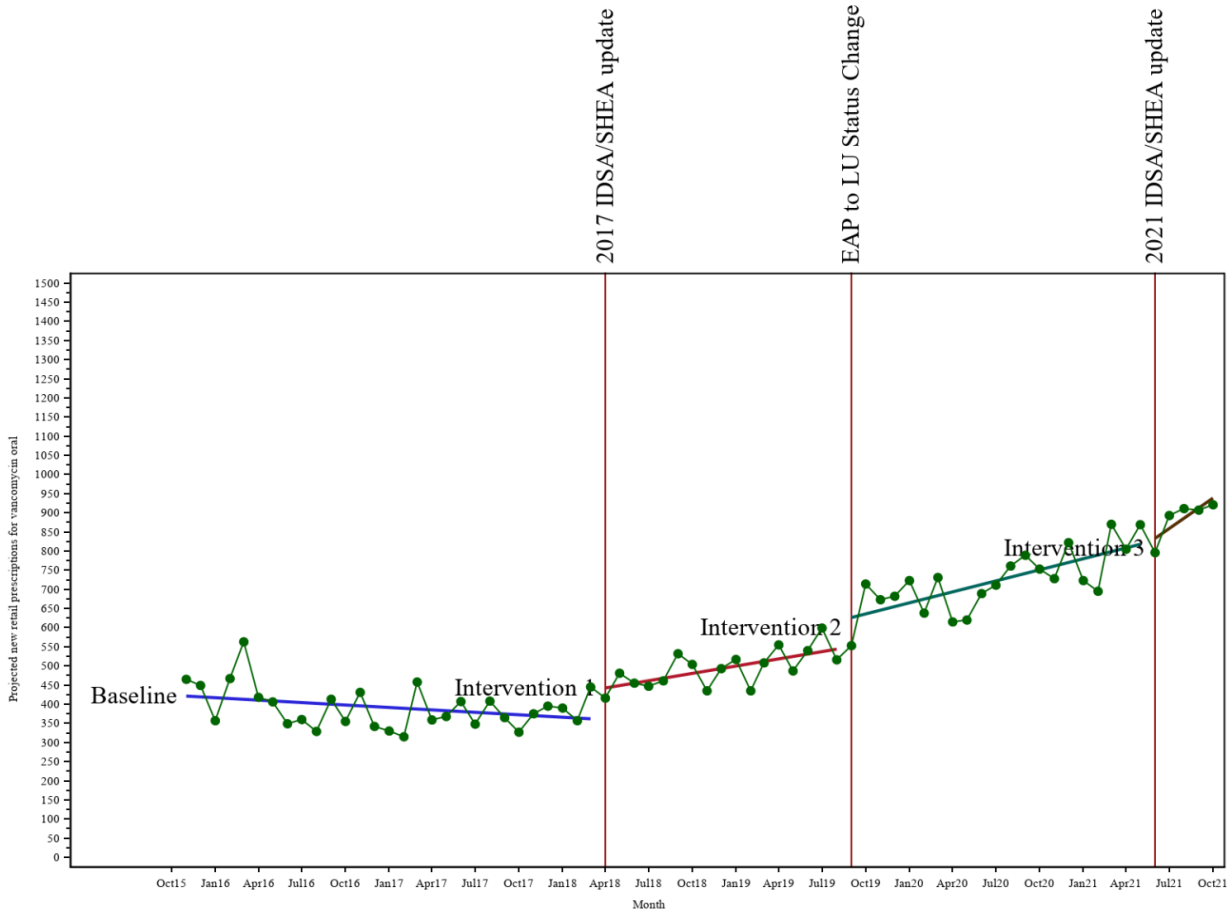

FIGURE 1. Projected volume of new monthly prescriptions for oral vancomycin in Ontario. Baseline data (October 2015 to March 2018; blue regression line) show the volume of prescriptions before any intervention. The red regression line, following "Intervention 1", shows data collected from April 2018 to August 2019, after implementation of the 2017 guideline update of the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).[8] The green regression line, following "Intervention 2", shows data collected from September 2019 to May 2021, reflecting the transition from the Exceptional Access Program (EAP) to Limited Use (LU) access for oral vancomycin in Ontario. The grey regression line, following "Intervention 3", shows data collected from June 2021 to October 2021, after introduction of the 2021 IDSA/SHEA guideline update.[9] Based on information licensed from IQVIA: CompuScript® database for October 2015 to October 2021. All rights reserved.

and others[19] reported on the use of fidaxomicin in 10 University of Pittsburgh Medical Centre community hospitals in the United States. They found that in 2018, adherence to the health system's updated treatment protocol, which was partly based on the 2017 IDSA/SHEA guideline update, was about 50%. Our findings reflect a Canadian context, with evaluation of the projected volume of new prescriptions for oral vancomycin and fidaxomicin after a drug reimbursement policy change and the IDSA/SHEA guideline updates.

This study had some limitations. We were unable to adjust for potential confounding variables that may have influenced prescribing volume, such as the patient's age, severity of illness at baseline, or sex. The lack of a control group was another limitation; however, in this context there is no suitable internal control (a treatment used for the same indication that is not expected to be affected by the interventions), and an external control group was not feasible, given low numbers of prescribing in other provinces and the fact that 2 of the 3 interventions would be expected to affect all provinces. Part of the study occurred during the COVID-19 pandemic, when there appeared to be an overall decrease in outpatient antibiotic prescriptions in Ontario[20]; this trend could in turn have affected rates of *C. difficile* infection. Trends in the incidence of *C. difficile* infections may also affect the volume of prescriptions for oral vancomycin and fidaxomicin; however, the incidence of community-associated *C. difficile* infection remained relatively stable between 2016 and 2020.[21] Another concurrent guideline publication may also have influenced prescribing rates.[22] That guideline is consistent with the IDSA/SHEA recommendations; however, it was not possible with the current study design to disentangle the impact of separate guidelines published in a similar time frame. Only 5 data points were available since introduction of the 2021 IDSA/SHEA guideline update, and prescribing patterns may have changed subsequently; as such, additional data may be

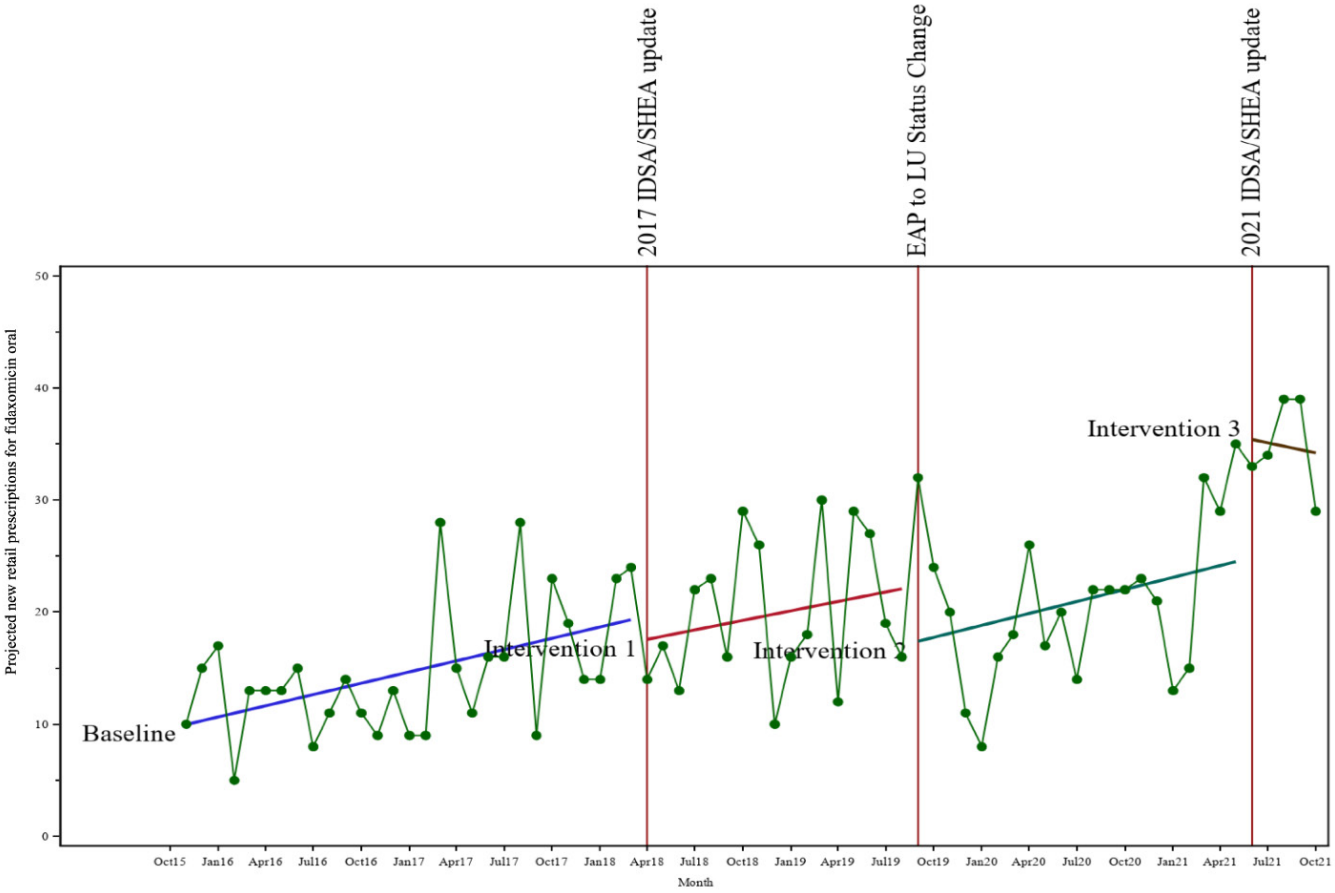

FIGURE 2. Projected volume of new monthly prescriptions for oral fidaxomicin in Ontario. Baseline data (October 2015 to March 2018; blue regression line) show the volume of prescriptions before any intervention. The red regression line, following "Intervention 1", shows data collected from April 2018 to August 2019, after implementation of the 2017 guideline update of the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).[8] The green regression line, following "Intervention 2", shows data collected from September 2019 to May 2021, reflecting the transition from the Exceptional Access Program (EAP) to Limited Use (LU) access for oral vancomycin in Ontario. The grey regression line, following "Intervention 3", shows data collected from June 2021 to October 2021, after introduction of the 2021 IDSA/SHEA guideline update.[9] Based on information licensed from IQVIA: CompuScript® database for October 2015 to October 2021. All rights reserved.

required to better assess whether a trend in prescribing is present due to the low number of time intervals following the third intervention. The number of new prescriptions for oral vancomycin was approximately 8 times that of fidaxomicin prescriptions; therefore, the fidaxomicin analyses had limited power to detect change. The indication for use of these drugs was not available from our data source; therefore, it is unclear what proportions of the population were experiencing a recurrence of infection as opposed to a first course of illness; this may have affected the total duration of therapy. Our analysis was restricted to projected new prescriptions among retail pharmacies in Ontario, with the aim of determining whether the change from EAP to LU code coverage for vancomycin played any role in prescription volume for either of the 2 agents. A new prescription in the CompuScript database represents a newly written prescription that is subsequently dispensed at a pharmacy. If the same patient received a new prescription following refills on their original prescription, it would be counted as a new prescription. This is unlikely to have had a substantial impact on the results of this study, given the acute nature of the therapies studied. Lastly, this study did not consider in-hospital use of vancomycin or fidaxomicin.

CONCLUSION

The results of this interrupted time-series analysis provide evidence that prescribing of oral vancomycin increased following a relevant clinical practice guideline update and drug coverage policy change in Ontario, but the effect was not as pronounced for fidaxomicin. These findings highlight the complexity of changes in prescribing behaviour in response to policy and guideline changes to reflect incorporation of evidence into practice.

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Competing interests: For projects unrelated to the study reported here, Mira Maximos has received grants from the Centre of Excellence for Women's Health, the London Health Sciences Foundation, and MedBuy; consulting fees from Firstline; speaker's honoraria from SPOR Evidence Alliance, the Canadian Society of Hospital Pharmacists, and Fresenius Kabi; and the Christine and David Edwards Graduate Student Travel Award. She also serves on advisory boards for SPOR Evidence Alliance and COVID-19 Resources Canada, and is a member of various academic, society, and hospital committees, including committees focused on antimicrobial stewardship. No other competing interests were declared.

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Funding: None received.

Acknowledgment: The statements, findings, conclusions, views, and opinions contained and expressed in this research article are based in part on data obtained under licence from the following IQVIA Solutions Canada Inc. information service: CompuScript® database. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IQVIA Solutions Canada Inc. or any of its affiliated or subsidiary entities.

Submitted: November 3, 2023
Accepted: March 21, 2024
Published: August 14, 2024