

Impact of policy changes on the provision of naloxone by pharmacies in Ontario, Canada: a population-based time-series analysis

Tony Antoniou^{1,2,3,4}, Diana Martins¹, Tonya Campbell², Mina Tadrous^{2,5,6}, Charlotte Munro⁷, Pamela Leece⁸, Muhammad Mamdani^{1,2,6,9,10}, David N. Juurlink^{2,4,6,10,11} & Tara Gomes^{1,2,6,9} 

Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada,¹ ICES, Toronto, Ontario, Canada,² Department of Family and Community Medicine, Unity Health, Toronto, Ontario, Canada,³ Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada,⁴ Women's College Hospital, Toronto, Ontario, Canada,⁵ Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada,⁶ Ontario Drug Policy Research Network Lived Experience Advisory Group, Toronto, Ontario, Canada,⁷ Public Health Ontario, Toronto, Ontario, Canada,⁸ Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada,⁹ Department of Medicine, University of Toronto, Toronto, Ontario, Canada,¹⁰ and The Sunnybrook Research Institute, Toronto, Canada¹¹

ABSTRACT

Background and aims In June 2016, the Ontario, Canada government implemented the Ontario Naloxone Program for Pharmacies (ONPP), authorizing pharmacists to provide injectable naloxone kits at no charge to all Ontario residents. In March 2018, the program was amended to include intranasal naloxone and remove the requirement to present a government health card to the dispensing pharmacist. We examined whether these changes increased naloxone dispensing through the ONPP. **Design** Population-based time-series analysis using interventional autoregressive integrated moving average models. **Setting** Ontario, Canada. **Participants** All Ontario residents between 1 July 2016 and 31 March 2020. **Measurements** Monthly rates of pharmacy naloxone dispensing. **Findings** Overall, 199 484 individuals were dispensed a naloxone kit during the study period. In the main analysis, the rate of pharmacy naloxone dispensing increased by 65.1% following program changes (55.6–91.8 kits per 100 000 population between February 2018 and May 2018; $P = 0.01$). In subgroup analyses, naloxone dispensing increased among individuals receiving opioid agonist therapy (OAT) (3374.9–7264.2 kits per 100 000 OAT recipients; $P = 0.04$) among individuals receiving other prescription opioids (192.8–381.8 kits per 100 000 population prescribed opioids; $P < 0.01$), among individuals with past opioid exposure (134.7–205.6 kits per 100 000 population with past opioid exposure; $P < 0.01$) and in urban centers (56.2–91.4 kits per 100 000 population; $P < 0.01$). We did not observe a clear impact on pharmacy-dispensed naloxone to individuals with no or unknown opioid exposure (34.4–39.3 kits per 100 000 population with no/unknown opioid exposure; $P = 0.42$) and in rural regions (50.4–97.2 kits per 100 000 population; $P = 0.09$). **Conclusions** Changes to the Ontario Naloxone Program for Pharmacies to add intranasal naloxone and remove the requirement to present a government health card appeared to increase pharmacy-based naloxone dispensing uptake in Ontario, Canada, particularly among individuals at high risk of inadvertent opioid overdose.

Keywords Drug policy, harm reduction, health services research, naloxone, opioid, policy evaluation.

Correspondence to: Tara Gomes, Li Ka Shing Knowledge Institute of St Michael's Hospital, ICES, 30 Bond St., Toronto, Ontario M5B 1W8, Canada.

E-mail: tara.gomes@unityhealth.to

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INTRODUCTION

Overdoses and deaths involving opioids are a public health crisis in North America, with approximately 72 600 opioid-related deaths occurring in Canada and the United States in 2018 alone [1,2]. In Ontario, Canada's largest province, opioid-related deaths increased by more than 400% between 2000 and 2018, from 1.9 to 10.2

deaths per 100 000 population [3,4]. Importantly, in 2018, more than 90% of opioid-related deaths in Canada were accidental and potentially preventable [5]. Although illicitly derived, non-prescribed fentanyl analogues have contributed to most opioid-related deaths since 2017 [1,2], prescription opioids remain important drivers of opioid-related harm in Ontario [5]. Because the majority of opioid overdoses are accidental and reversible

with the prompt administration of the opioid antagonist naloxone [6–14], expanding access to take-home naloxone kits has become a widely accepted harm-reduction measure [15], with an estimated effectiveness of 96% for reversing opioid overdoses when administered by laypeople [16].

Pharmacist-dispensed naloxone is a relatively novel strategy for optimizing the distribution of take-home naloxone [17]. A 2016 scoping review of 16 international studies found that pharmacy-dispensed naloxone research encompassed five domains, including pharmacist perceptions of naloxone, legal issues, pharmacist training, supply systems and costs and identification and recruitment of patients [18]. Evidence supporting the effectiveness of such programs is increasing, with findings from a recent US study showing that jurisdictions granting pharmacists direct authority to dispense naloxone had greater declines in opioid-related deaths than jurisdictions implementing alternative naloxone strategies [19]. In 2016, the Ontario Ministry of Health and Long-Term Care (MOHLTC) granted pharmacists the authority to provide injectable naloxone kits at no charge to all Ontario residents through the Ontario Naloxone Program for Pharmacies (ONPP) initiative [20]. Recent evaluations of the ONPP found that uptake was not uniform among Ontario residents between July 2016 and March 2018, with limited engagement by individuals prescribed high-doses of opioids and those with a prior history of opioid-related harm, and lower dispensing rates in rural relative to urban regions [21,22]. In an effort to remove potential barriers to naloxone uptake through the ONPP, the program was amended in March 2018 to include intranasal naloxone and remove the requirement for residents to produce a valid health insurance card to the dispensing pharmacist as a condition of obtaining a naloxone kit [23]. We examined whether these changes increased the distribution of pharmacy-based naloxone through the ONPP.

METHODS

Setting

We conducted a population-based time series analysis of all residents in Ontario between 1 July 1 and 31 March 2020.

Data sources

Data sources are summarized in Supporting information, Appendix S1. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require Research Ethics Board review.

Study population and outcomes

For each month of the study period, we determined rates of naloxone dispensing by Ontario pharmacies per 100 000 Ontario residents, defined as the number of naloxone kits dispensed in a given month divided by the population of Ontario for that period. To determine if naloxone dispensing rates varied among individuals at differential risk of opioid-related harm, we stratified the population of Ontario residents dispensed naloxone into four mutually exclusive, pre-defined groups, using a pre-defined hierarchical stratification approach that we applied in our previous work [21,22]. First, we identified recipients of opioid agonist therapy (OAT) as individuals with any prescription for methadone or buprenorphine/naloxone dispensed on the naloxone claim date or in the 14 days preceding it. Secondly, we defined individuals taking other prescription opioids at the time they were dispensed a naloxone kit, defined by any non-OAT opioid prescription with a supply overlapping the naloxone claim date. Thirdly, we defined individuals with a prior history of chronic prescription opioid exposure as those with either a prescription for a long-acting non-OAT opioid in the prior 4 years, five or more prescriptions for an immediate release non-OAT opioid in the prior 4 years or any health service use for opioid-use disorder or opioid-related harm in the 5 years preceding the receipt of naloxone. We developed this definition to exclude individuals who were unlikely to have had chronic opioid exposure in the past. The remaining population was defined as those individuals with no or unknown opioid exposure history. We similarly applied the mutually exclusive stratification method for all Ontario residents to define population denominators in each month during the study period, and computed rates of naloxone dispensing per 100 000 population for each exposure group. Because we could not identify patients obtaining a naloxone kit without an Ontario health card in our administrative databases, we excluded these individuals from the stratified analysis. To explore regional variation in the impact of the March 2018 policy changes, we also stratified our analyses according to rural and urban regions of Ontario.

Statistical analysis

We used interventional autoregressive integrated moving average (ARIMA) models to examine the impact of including intranasal naloxone and removing the requirement to produce a health card on naloxone dispensing rates overall, and stratified by pre-defined opioid exposure group and urban and rural regions, between July 2016 and March 2020 [24]. This study period encompasses all months for which data regarding the ONPP were available for analysis. Because we speculated

that these changes would lead to immediate increases in the uptake of naloxone through community pharmacies, we tested for an immediate change in the rate of naloxone dispensing using a step function following implementation of these program changes (i.e. March 2018). We also included ramp intervention functions in all models to account for slope trends in rates of naloxone dispensing before and after the program changes and changes in naloxone dispensing associated with the May 2017 publication of Canadian guidelines for the use of opioids in chronic non-cancer pain, which supported the provision of naloxone to patients at risk of overdose [25]. We used differencing to achieve a stationary time-series, and stationarity was confirmed using the augmented Dickey–Fuller test [26]. We examined autocorrelation function (ACF), partial autocorrelation function (PACF) and inverse correlation function (IACF) plots to guide appropriate moving average or autoregressive terms for the models. We assessed model fit using the ACF, PACF and IACF plots, white noise probability plots (Supporting information, Appendix S2) and Ljung–Box χ^2 test for white noise [24,27]. The analysis was not pre-registered. All analyses were completed at ICES and St Michael's Hospital using SAS Enterprise Guide, version 6.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Overall, 199 484 individuals were dispensed a naloxone kit through the ONPP during the study period, 35 909 of

whom (18.0%) were OAT recipients, 38 294 (19.2%) were prescription opioid recipients, 16 835 (8.4%) had past opioid exposure and 113 808 (57.1%) had no or unknown opioid exposure. The majority [$n = 150 885$ (75.6%)] of individuals accessed the ONPP after March 2018. During the 45-month study period, 446 690 naloxone kits were dispensed (56.9% intranasal), and the monthly rate of pharmacy naloxone dispensing increased from 1.9 to 111.5 kits per 100 000 population. Prior to the March 2018 program changes, only the injectable formulation of naloxone was dispensed through Ontario pharmacies. The inclusion of intranasal naloxone in the pharmacy program in March 2018 shifted the pattern of naloxone dispensing, with the intranasal formulation representing 72.8% of all kits dispensed in March 2020. Similarly, the proportion of all naloxone kits dispensed without presentation of a personal health card increased from 0.0% to 37.3% between July 2016 and March 2020 (Fig. 1).

In our main analysis, the overall rate of naloxone dispensing increased immediately after the implementation of program changes in March 2018. Specifically, between February 2018 (the month preceding the policy change) and May 2018 (2 months following the policy change), the rate of pharmacy naloxone dispensing increased 65.1% (from 55.6 to 91.8 kits per 100 000 population; $P = 0.01$) (Fig. 2). In stratified analyses, we found immediate increases in rates of pharmacy naloxone dispensing between February 2018 and May 2018 among individuals receiving OAT (115.2% increase; 3374.9–7264.2 kits per 100 000; $P = 0.04$), prescription

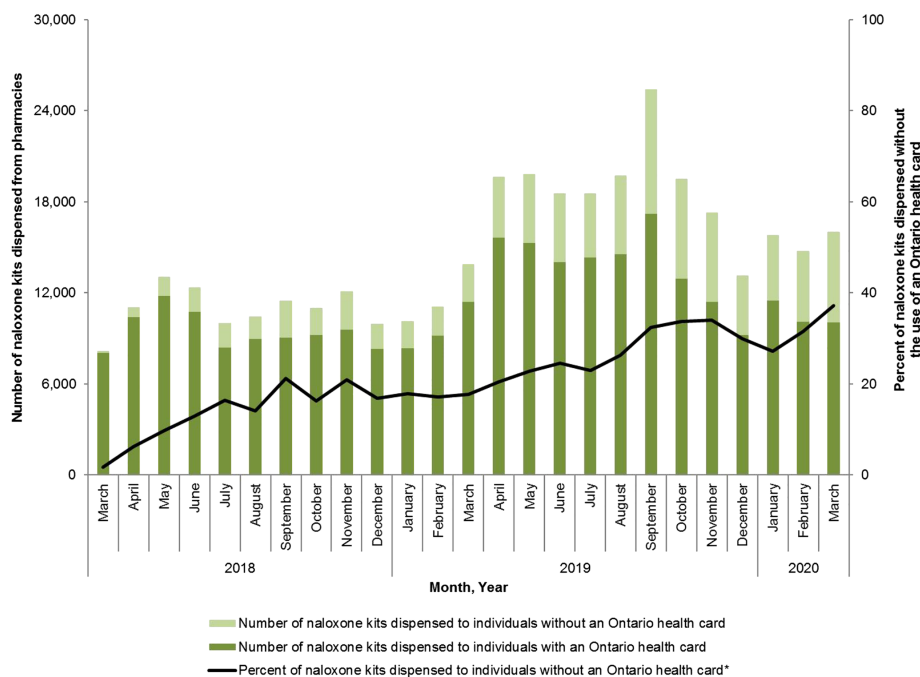


Figure 1 Number and percentage of pharmacy-dispensed naloxone kits in Ontario, stratified according to whether provincial health card provided at time of dispensing. [Colour figure can be viewed at wileyonlinelibrary.com]

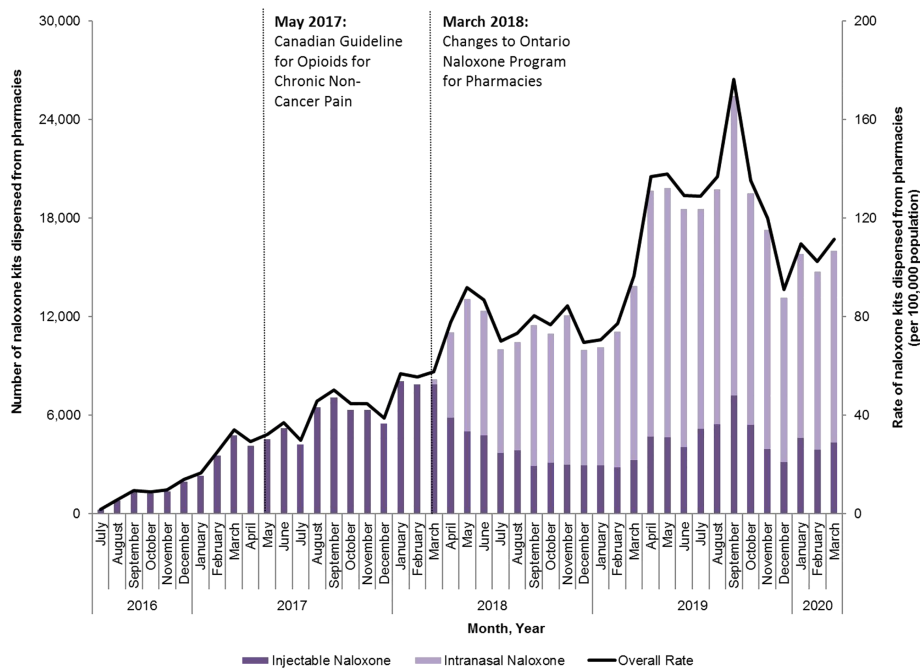


Figure 2 Number and rate (per 100 000 population) of pharmacy naloxone distribution in Ontario, July 2016–March 2020. [Colour figure can be viewed at wileyonlinelibrary.com]

opioid recipients (98.0% increase; 192.8–381.8 kits per 100 000 population; $P < 0.01$), individuals with prior opioid exposure (52.6% increase; 134.7–205.6 kits per 100 000 population; $P < 0.01$) and in urban regions of Ontario (62.6% increase; 56.2–91.4 kits per 100 000 population;

$P < 0.01$) (Figs 3 and 4). Conversely, we found no impact on pharmacy naloxone dispensing between February 2018 and May 2018 among individuals with no or unknown opioid exposure history 2018 (34.4 versus 39.3 kits per 100 000 population; $P = 0.42$) and in rural

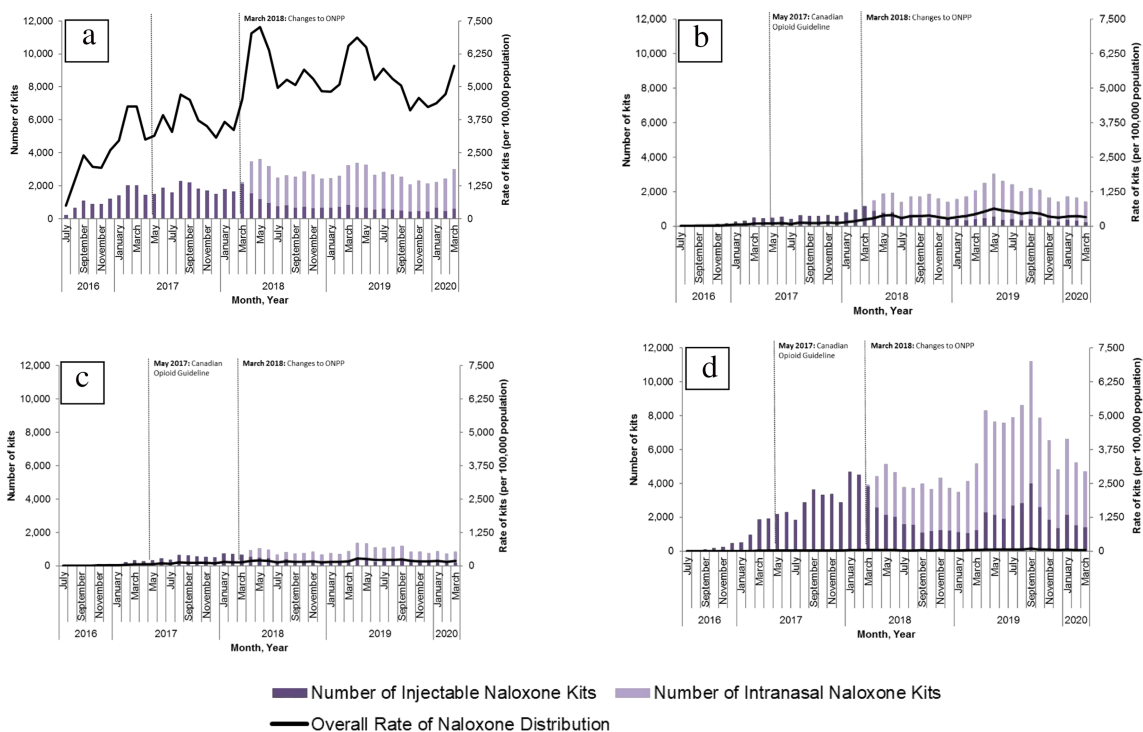


Figure 3 Number and rate (per 100 000 population) of pharmacy-dispensed naloxone distribution in Ontario, stratified by opioid exposure group, July 2016–March 2020. (a) Prescription opioid agonist therapy recipients; (b) prescription opioid recipients; (c) people with past opioid exposure; (d) people with no/unknown opioid exposure. [Colour figure can be viewed at wileyonlinelibrary.com]

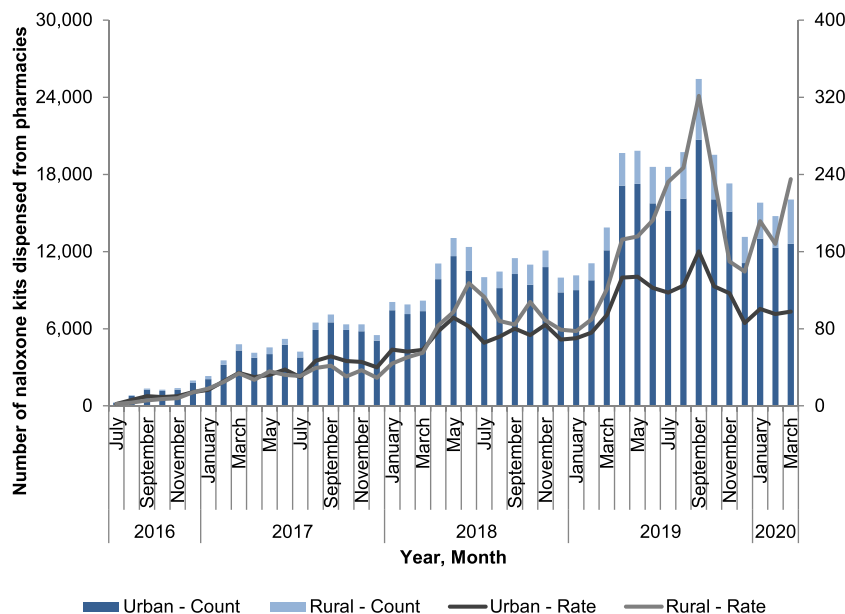


Figure 4 Number and rate (per 100 000 population) of pharmacy naloxone distribution in Ontario, by urban and rural region. [Colour figure can be viewed at wileyonlinelibrary.com]

Ontario (92.9% increase; 50.4–97.2 kits per 100 000 population; $P = 0.09$).

DISCUSSION

In this population-based study, we found that introduction of intranasal naloxone and the removal of the requirement to present a provincial health card were associated with an immediate increase in rates of pharmacy naloxone dispensing. This finding was consistent among OAT recipients, past and present opioid recipients and in urban regions of Ontario, with no immediate impact observed among individuals with no or unknown opioid exposure and rural regions of Ontario. Our findings highlight the importance of a policy intervention aimed at expanding naloxone formulation options and removing potentially stigmatizing requirements for identification in increasing access to naloxone through community pharmacies.

Our findings add to earlier research. Although several US studies have found that the passage of naloxone access laws significantly increased naloxone dispensing rates [17,28,29], ours is the first, to our knowledge, to quantify the effect of policy changes in an existing program targeting specific barriers to naloxone access. Moreover, our findings demonstrate that the program changes were associated with a 98.0% increase in naloxone dispensing among current recipients of prescribed opioids. This finding is important, because several US studies have found that individuals prescribed opioids may not feel comfortable availing themselves of naloxone through other distribution channels, such as harm reduction sites, and may be at low self-perceived risk of inadvertent opioid overdose [30–33]. However, changes to the ONPP did not appreciably

increase naloxone dispensing rates to individuals with no or unknown opioid exposure history, a heterogeneous group that includes family and friends of individuals at risk of opioid overdose. Further research exploring barriers of naloxone access in this population is warranted, as prior international research has demonstrated that bystanders who have received naloxone training are more likely to recognize overdose scenarios and identify when naloxone administration is indicated compared to those with no such training [34–36].

Our study has some limitations. First, our study does not include naloxone distributed through other channels such as harm reduction sites and physicians' offices, and therefore underestimates total naloxone access by Ontario residents during the study period. However, we were specifically interested in quantifying the impact of changes to the ONPP on pharmacy-based naloxone dispensing, which now represents the majority of naloxone distribution in Ontario [37]. Secondly, we cannot quantify separately the impact of including intranasal naloxone and removing the requirement to present an Ontario health card because both program changes were implemented in March 2018. However, we speculate that the availability of intranasal naloxone was the more impactful of the two changes, given that nearly two-thirds of individuals continued to present a health card at the time of naloxone dispensing in March 2020, at which point intranasal naloxone represented 72.8% of all kits dispensed. A preference for the intranasal formulation probably reflects a greater sense of comfort and ease of use relative to injectable naloxone, and has been confirmed in a recent study of opioid recipients to be the preferred formulation of the drug [38]. Thirdly, some individuals may have been misclassified when deriving

our exposure group definitions. However, our previous work summarizing the demographics of each exposure group suggests that any misclassification is probably minimal [21]. Finally, we did not have sufficient data to identify and account for seasonality in our models, or pharmacy characteristics that may influence pharmacy-dispensed naloxone rates.

In summary, our study suggests that the addition of intranasal naloxone and removal of the requirement to present a government health card were associated with an increased rate of pharmacy-based naloxone dispensing, including to individuals at risk of inadvertent opioid overdose. These findings can inform the development of pharmacy-based naloxone programs in other jurisdictions by highlighting program components that were associated with a marked uptake in naloxone access through community pharmacies.

Declaration of interests

P.L. reports non-financial support from Adapt Pharma through in-kind donation of naloxone on an unrelated study. Adapt Pharma is not involved in the design or conduct of the project. M.M. reports receiving honoraria for serving as member on *ad-hoc* advisory boards for Allergan and Novo Nordisk and receiving an honorarium from Celgene. No other authors report any conflicts of interest.

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Author contributions

Tony Antoniou: Conceptualization; funding acquisition; writing-original draft. **Diana Martins:** Formal analysis; project administration; writing-review & editing. **Tonya Campbell:** Data curation; formal analysis; writing-review & editing. **Mina Tadrous:** Conceptualization; funding acquisition; writing-review & editing. **Charlotte Munro:** Conceptualization; funding acquisition; writing-review & editing. **Pamela Leece:** Conceptualization; funding

acquisition; writing-review & editing. **Muhammad Mamdani:** Conceptualization; funding acquisition; writing-review & editing. **David N. Juurlink:** Conceptualization; funding acquisition; writing-review & editing. **Tara Gomes:** Conceptualization; funding acquisition; methodology; writing-review & editing.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information

Data S2. Supporting information