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The Effect of Take-Home Naloxone Kits on Opioid-related Deaths in Alberta, Canada: An Ecological Analysis

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Abstract

Objective: To estimate the association between publicly provided take-home naloxone kits and opioid-related deaths.

Method: We analyzed 2,732 opioid-related deaths and the distribution of 147,814 naloxone kits between January 2015 and June 2019 across 5 health zones in Alberta Canada.

We used a Poisson pseudo-maximum likelihood regression model with fixed effects to estimate the association between the number of kits in circulation and the number of monthly opioid-related deaths, controlling for population demographics, socio-economic indicators, other harm reduction strategies, police seizures of fentanyl and carfentanil and an estimate of awareness.

Results: Every 10,000 kits in circulation was associated with a 23.9% (95% confidence interval, 12.6% to 33.7%) reduction in opioid-related deaths. Marginal analysis suggests that if no kits had been distributed Alberta would have had 3,548 deaths (95% confidence interval, 2,264 to 4,831), 816 more deaths than were recorded during this 4-and-a-half-year period. If during this time 200,000 kits were consistently in circulation, Alberta would have had an estimated 1,587 deaths (95% confidence interval, 705 to 2,468), 1,145 fewer deaths than recorded.

Conclusion: This analysis provides evidence that the availability of naloxone kits is associated with a reduction in opioid-related deaths and suggests that a publicly funded program that allows distribution of naloxone kits to all who request them reduces mortality.

Résumé

Objectif: Estimer l’association entre la distribution publique des trousses de naloxone et les décès liés aux opioïdes.

Méthode : Nous avons analysé 2 732 décès liés aux opioïdes et la distribution de 147 814 trousses de naloxone entre janvier 2015 et juin 2019 dans 5 zones Alberta Health Services au Canada.

Nous avons utilisé un modèle de régression du pseudo-maximum de vraisemblance de Poisson à effets fixes pour estimer

l'association entre lenombre de trousses en circulation et le nombre de décès mensuels liés aux opioïdes, en contrôlant pour les facteurs démographiques de la population, les indicateurs socio-économiques, d'autres stratégies de réduction des méfaits, les saisies de fentanyl et de carfentanil par la police et une mesure pour estimer la sensibilisation publique des opioïdes.

Résultats : Chaque lot de 10 000 trousses en circulation, était associé à une réduction de 23,9 % (intervalle de confiance à 95 %, 12,6 % à 33,7 %) des décès liés aux opioïdes. Une analyse marginale suggère que si aucune trousse n'avait été distribué, l'Alberta aurait connu 3 548 décès (intervalle de confiance à 95 %, 2 264 à 4 831), soit 816 décès de plus que ce qui a été enregistré au cours de cette période de 4,5 ans. Si pendant cette période, 200 000 trousses étaient constamment en circulation, l'Alberta aurait connu environ 1 587 décès (intervalle de confiance à 95 %, 705 à 2 468), soit 1 145 décès de moins que le nombre enregistré.

Conclusion : Cette analyse suggère que la disponibilité des trousses de naloxone est associée à une réduction des décès liés aux opioïdes et qu'un programme financé par l'État qui permet la distribution de trousses de naloxone à tous ceux qui en font la demande réduit la mortalité.

Introduction

Opioids are drugs that interact with opioid receptors in the brain, have analgesic and sedative effects, and can cause euphoria.(Ghelardini et al., 2015) They are commonly prescribed to manage pain, but repeated or continuous use can increase tolerance and withdrawal symptoms and lead to opioid dependence.(Kosten & George, 2002) Opioids are the leading cause of overdose deaths in Canada; in the first half of 2024 there was an average of 21 opioid toxicity deaths per day.(Government of Canada, 2024) Most of these deaths involved illegally produced opioids which are unpredictable and often contaminated with more potent opioids like fentanyl. 79% of the opioid toxicity deaths in 2024 involved fentanyl.(Government of Canada, 2024)

The main treatment for opioid poisoning is naloxone, an antidote that blocks the effects of opioids and reverses poisoning and respiratory depression within minutes.(Chamberlain & Klein, 1994) In 2014 the WHO recommended that people likely to witness an opioid poisoning should have access to naloxone and be taught how to use it. While the WHO labelled this a strong recommendation, they found that the quality of evidence supporting the recommendation at the time was very low.(World Health Organization, 2014) Since 2014, several studies have demonstrated that distributing naloxone to those at risk of an opioid poisoning and their family and friends reduces opioid-related mortality.(Bird et al., 2016; Irvine et al., 2018; Langham et al., 2018; Parmar et al., 2017)

In December 2015, the province of Alberta, Canada initiated a naloxone distribution program that provides publicly funded kits to all who request them. The mission of the Community Based Naloxone (CBN) Program is to ensure anyone who might witness an opioid poisoning has access to naloxone through an accessible, compassionate and non-stigmatized interaction, and that they will understand how to correctly respond to an opioid poisoning; including notification of emergency services, rescue breathing, and administration of naloxone.(Alberta Health Services, 2021) From 2016 to 2019, the CBN Program had distributed more than 140,000 kits to the public via more than 1,700 provider sites. In the same time period, there have been more than 11,000 opioid poisoning reversals recorded in Alberta, according to internal data from the Community Based Naloxone program. In the year prior to the CBN program naloxone distribution was restricted to eight Alberta Community Council on HIV sites whose focus was on high risk and vulnerable populations. Prior to this only one small naloxone program existed in Alberta, and it served people who use drugs.

The aim of this analysis was to estimate the association between naloxone distribution and opioid-related deaths and assess the effectiveness of a publicly funded program that allows distribution of naloxone kits to all who request them.

Methods

Design

Given that exposure to opioids was not available at an individual level, we undertook an ecological analysis comparing naloxone distribution and death over time in the five health zones in Alberta, from January 2015 to June 2019. We controlled for population demographics, socio-economic indicators, police seizures of opioids, public awareness of opioids and naloxone and harm reduction strategies at a zone level.

Data

Opioid-related Deaths

Monthly numbers of opioid-related deaths were provided by the office of the Chief Medical Officer in Alberta and defined as drug poisoning deaths with an opioid (e.g., codeine, morphine, oxycodone, fentanyl, carfentanil, heroin, U-47700) included in the cause(s) of death listed under part 1 of the medical certificate of death. Numbers of deaths were provided by drug type (fentanyl, non-fentanyl opioid, carfentanil) and by year, month and local health zone in Alberta. The main outcome of this analysis is the total combined monthly opioid-related deaths. More information on opioid-related death data is available at the Alberta substance use surveillance system, https://www.alberta.ca/substance-use-surveillance-data.

Naloxone Kit Distribution

Monthly naloxone kit distribution for each of the five Alberta health zones (North, Edmonton, Central, Calgary, South) was provided by Alberta Health Services. The kits contained: 3 vials of injectable naloxone (each vial is 1 dose), 3 safety syringes, 3 alcohol pads, 1 pair of rubber gloves (non-latex), 1 barrier mask (for rescue breathing) and an information pamphlet explaining how to respond to an opioid poisoning and inject naloxone.(Alberta Health Services, 2019) Kits were available at no fee from hospitals, physician offices, pharmacies, post-secondary institutions, correctional facilities, and community services including community outreach programs. Data was also available on the number of kits taken out of circulation: reported as stolen, lost, confiscated, or expired. The main variable of interest was the cumulative number of kits in circulation, calculated as the sum of the number of kits distributed each month minus the number of kits out of circulation.

Population Demographics

Population demographics consisted of annual estimates of the number of people living in a municipality, including Canadian citizens, immigrants, and non-permanent residents, by age and sex. In the regression analysis we use the proportion of adults in each health zone and the proportion female in each health zone.(Alberta Government, 2021)

Socio-Economic Indicators

Previous studies have shown that socio-economic status is associated with opioid related mortality.(Altekruse et al., 2020; Carrière et al., 2021) To control for differences between health regions we used annual data on socio-economic indicators available from the Alberta Regional Dashboard.(Alberta Government, 2021). The Alberta Regional Dashboard contains data on municipal finances, labour, infrastructure, housing and real estate, energy sector, construction, business activities, transportation and education. Particular measures include provincial registry services such as the number of driver's licenses issued and the number of vehicles registered, the amount of money spent on major projects, the number of post-secondary students, the number of employment insurance recipients, property tax rates, the proportion of residential properties, residential vacancy rate, number of housing starts, the number of businesses and percent of small businesses, median internet upload and download speeds, oil and natural gas production, the value of land transfers and bankruptcies. To estimate proportion measures at the zone level population weighted proportions at the municipal level were summed.

Police Seizures

Ongoing research suggests that police seizures of opioids affects availability.(Broadhurst et al., 2021; Degenhardt et al., 2005) To control for the differences in police forces in Alberta we included data on police seizures between health zones. All seizure data was converted to weights using doses of 200 micrograms per pill and 50 micrograms per patch, as these were the doses most commonly sold on the streets in Alberta.(streetRx, 2021) Police seizure data provided an estimate of the amount and types of opioids in circulation and the police enforcement. Data on police seizures were provided by Calgary Police Services, Edmonton Police Services and the Royal Canadian Mounted Police. Monthly data was provided by the Calgary Police Service on the weight, number of pills and number of patches of fentanyl and carfentanil seizures between 2015 and June 2019. Edmonton Police Services and the Royal Canadian Mounted Police provided the same data for 2015-2018 and 2016-June 2019, respectively.

Public Awareness

It was hypothesized that as opioid-related deaths increased, the public would become more aware of the opioid epidemic and request more naloxone kits. If increased deaths caused increased naloxone distribution due to public awareness our model would have simultaneous endogeneity. This arises when one or more of the predictors (e.g., naloxone distribution) is determined by the response variable (opioid related deaths). We attempted to control for public awareness of the opioid epidemic by using data on the number of searches occurring in the province for “naloxone”, “opioid” or “fentanyl” performed in the Google search engine (date of search: 20 November 2019). This data was available from Google Trends for the province by week, but not by health zone.

Harm Reduction Strategies

Laws

The Good Samaritan Drug Overdose Act was passed by parliament as a Private Member's Bill, in May 2017. This legislation provided some legal protection for individuals who sought emergency help during a poisoning. The goal was to encourage people to make a call to help save a life by reducing the fear of police attending poisoning events.(Government of Canada, 2021) The Good Samaritan Law was included in the model as a binary variable from the date it was passed.

Supervised consumption sites

Supervised consumption services provide a place where people can use drugs in a monitored, hygienic environment to reduce harm from substance use while offering additional services such as counselling, social work, and connection to opioid-dependency treatment. There were seven supervised consumption sites in Alberta, with at least one in each zone. The first opened in November 2017. The number of supervised consumption sites by zone were included in the model from the date they opened; at the time no supervised consumption sites had closed.

Opioid Prescription and Opioid Agonist Therapy

Opioid agonist therapy has been shown to reduce opioid use(Nielsen et al., 2016; Wegman et al., 2017), criminal and other high-risk activity(Gisev et al., 2019), HIV and hepatitis transmission(Sullivan et al., 2005), and deaths from poisoning (Connery, 2015; Schwartz et al., 2013; Wegman et al., 2017). The Pharmaceutical Information Network (PIN) administrative database was used to estimate the monthly number of community-based opioid agonist therapy prescriptions and opioid-related drugs dispensed across zones between January 1, 2015 and June 30, 2019. Prescriptions were identified using the same reporting definitions adopted by the government of Alberta(Alberta Health, 2019) and further validated by clinician experts.

Missing Data

The opioid seizure data from the Royal Canadian Mounted Police was not available until 2016, given that there were very few seizures in 2016 it was assumed that seizures in 2015 would be the same as the first month of 2016. Sensitivity analysis was undertaken limiting the time from 2016.

Statistical Analysis

We used a Poisson pseudo-maximum likelihood regression model with fixed effects to estimate the effect of the number of kits in circulation on the number of monthly opioid-related deaths because the dependent variable is a count of deaths by month and health zone.(Correia et al., 2020) Fixed effects were used to account for the panel data. An interaction term between time and zone was used to capture the differences in health zones over time. All analyses were done in Stata 17.

We estimated clustered standard errors to control for heteroskedasticity and autocorrelation. We also ran a negative-binomial regression and tested for overdispersion of the dependent variable using the likelihood ratio test on the over-dispersion parameter. We tested for multicollinearity by running ordinary least square regressions and examining the variance inflation factor (VIF). The variable with the highest VIF was removed from the model until all covariates had a value of less than 10. We tested simplified models eliminating all zone level covariates to further avoid multicollinearity. We ran several sensitivity analyses: we tested lagged variables of the number of kits in circulation since the current number in circulation depends on the previous number of kits in circulation, we used fentanyl deaths as the dependent variable, we also tested the inclusion of a non-linear time trend to understand the effects of imposing less structure on the data.

We hypothesized that opioid-related deaths and the number of kits in circulation may be simultaneously endogenous. This means that the number of kits in circulation may affect the number of opioid-related deaths, but also the number of deaths may affect the number of kits distributed, as individuals who hear about opioid-related deaths in the news may be more likely to request a kit. We tried to control for this in our main model by including a measure of public awareness. Additionally, we identified three variables that might be used as instrumental variables: the number of pharmacies dispensing naloxone kits, the number of kits ordered and the number of kits in stock. We hypothesized that each would be correlated with the number of kits in circulation but were less correlated with the number of deaths. Since the pharmacies were paid a distribution fee they were incentivized to distribute kits regardless of the number of deaths, and since ordering was centralized, it was assumed that the number of kits

ordered and the number in stock would be less influenced by deaths in each zone. A two-stage model was used to account for endogenous covariates.

Average marginal effects were estimated for different levels of naloxone kits in circulation over 4.5 years. We estimated opioid-related deaths if there had been no naloxone kits in circulation during this time and opioid-related deaths if there had been 40,000 kits in distribution in each zone throughout the time.

Access to the study protocol and programming code may be obtained by contacting the corresponding author. The raw data must be accessed through the Government of Alberta.

Results

From January 2015 to June 2019 147,814 naloxone kits were distributed across Alberta (Figure 1) at no cost to the recipients from a variety of pharmacies, community programs and AHS centers. The highest proportion of kits were distributed through community programs with 35.7% being supplied by the Alberta Community Council on HIV outreach programs; 17.5% were distributed by pharmacies and 11.9% were distributed through the emergency department or urgent care centers.

During the study period Alberta experienced 2,732 opioid-related deaths. Of these deaths 74.5% were caused by fentanyl and 13.7% were caused by carfentanil. The Calgary and South zones had the highest rates of opioid-related deaths with 70.7 and 64.9 per 100,000, respectively.

In our main analysis we found that every 10,000 kits in circulation was associated with a 23.9% (95% confidence interval, 12.6% to 33.7%) decrease in opioid-related mortality, all else equal (Table 1). All sensitivity analyses supported the main findings, although including a non-linear time trend did have a 95% confidence interval ranging from 0.465 to 1.004 (Table 2).

Figure 2 reports the average marginal effects per zone at two different levels of distribution. If no kits had been distributed, our model estimates that Alberta would have had 3,839 deaths (95% confidence interval, 3,356 to 4,323), 1,107 more deaths than were recorded during this 4-and-a-half-year period. These results suggest the Community Based Naloxone Program in Alberta averted 1,107 deaths, with one death averted for every 134 kits distributed or 54 kits were distributed for every opioid-related death. If during this time 200,000 kits were consistently in circulation (40,000 kits per zone) Alberta would have had 1,290 deaths (95% confidence interval, 1,128 to 1,453), 1,442 fewer deaths than were recorded.

Discussion

We estimated the association of naloxone kit distribution with opioid-related deaths in Alberta between January 2015 and June 2019. During this period 147,814 kits were distributed, and 2,732 opioid-related deaths were recorded. Naloxone kit distribution started slowly with fewer than 800 kits distributed before 2016 when the CBN program officially began.(Alberta Community Council on HIV, 2020) The most kits distributed in a month was in March 2018. Deaths peaked in December of 2017 but by early 2019 death rates were similar to monthly deaths in 2015 (Figure 1). During this time the opioid epidemic affected each of the 5 health zones in Alberta differently; this analysis takes advantage of the between zone variation to estimate the average effect of having 10,000 naloxone kits in circulation. Our analyses suggest that every 10,000 kits in circulation was associated with a 23.9% reduction in opioid-related

mortality. This was supported by numerous sensitivity analyses which explored simplified and instrumental variable models.

This was a retrospective study based on a program that was implemented broadly at the time of a public health crisis. It was not possible to do a clinical trial because the program was already operationalized. One of the main limitations of this study is the lack of data on individuals. No data is available on who had a naloxone kit or who had used a naloxone kit. Additionally, no data is available on individuals' use of opioids. One challenge to not knowing when the naloxone kits are used is that we may overestimate the number of kits in circulation. This will underestimate the association between naloxone kits and opioid related deaths. Two concerns of ecological studies are uniformity of ascertainment and time trends.(Coggon et al., 2002) Ascertainment of naloxone kits by health zone is known and was used as the exposure in this analysis. We attempted to control for the differences in effects of the opioid crisis on zones by including socio-economic variables, police seizures and other demographic variables that change over time. We recognize that this is not a perfect solution and that if zones that increased naloxone kit distribution also had a decreased use of opioids this would cause an overestimation of the association. One of the main concerns of ecological studies is when inferences about the nature of individuals are deduced from inferences about the group to which those individuals belong. We avoid this by making no claims about the effects of naloxone distribution on individuals but focus on the group effect.

Previous analyses support the finding that naloxone kit distribution is associated with a reduction in opioid-related mortality, however this is the first study to explore a program that is publicly available and not limited to those at risk of an opioid poisoning and their family or friends. An analysis of the Take Home Naloxone Program in British Columbia estimated that the program averted 298 deaths over 5 years, and that they had distributed 64.7 kits per death averted.(Irvine et al., 2018) This model based estimation required a number of assumptions: the effect of fentanyl; the effectiveness of the take-home naloxone program; the change in risk behaviors; the rate of non-fentanyl related deaths and the compliance of opioid substitution therapy. An assessment in Scotland recommended that the national take home naloxone programs should issue 9-20 times as many naloxone kits as there are opioid-related deaths per annum.(Bird et al., 2016) This study was undertaken in a very risky population over a short period estimating the change in the percent of opioid-related deaths in people released from prison within 4 weeks of death. The Alberta CBN Program distributed 134 kits per death averted or 54 kits per opioid-related death, these ratios are higher than those previously reported since the population eligible for a naloxone kit in Alberta was broader. The advantage of the CBN program's population health approach versus the more targeted approach is that it is less stigmatizing and is a simpler process to operationalize.

Conclusion

This analysis provides evidence that the availability of naloxone kits is associated with a reduction in opioid-related deaths and suggests that a publicly funded program that allows distribution of naloxone kits to all who request them is effective.

Contributions to knowledge

What does this study add to existing knowledge?

- The take-home naloxone program in Alberta is associated with an estimated 816 lives saved in 4.5 years.
- For each 10,000 naloxone kits distributed opioid-related deaths are associated with a decrease of 23.9%.
- This is the first analysis of administrative health data that reports that take-home naloxone is life-saving.

What are the key implications for public health interventions, practice or policy?

- The broad distribution of naloxone kits is associated with reduced opioid-related mortality.
- More naloxone kits distributed to more people is associated with saving lives.

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Table 1: Regression Results of the Main Model

	IRR	[95% Confidence Interval]	
Cumulative kits in circulation (per 10,000)	0.76	0.66	0.87
Time	1.03	1.02	1.05
Zone			
Calgary		Reference	
Central	6150674	394	9.61E+10
Edmonton	143	0.01	1921245
North	8.32E+11	2.93E+07	2.36E+16
South	1594	0.06	4.43E+07
Zone-Time Interaction			
Calgary		Reference	
Central	0.98	0.96	0.99
Edmonton	0.99	0.98	1.01
North	0.96	0.95	0.97
South	0.99	0.97	1.00
Good Samaritan Law	1.06	0.92	1.23
Number of Supervised Consumption Sites	1.00	0.89	1.12
Google Searches (per 1,000)	0.55	0.36	0.85
Seized Fentanyl (per 100 grams)	0.99	0.98	0.99
Seized Carfentanil (per 100 grams)	1.00	1.00	1.01
Bankruptcies (per 1000)	1.00	1.00	1.00
EI Recipients	1.00	1.00	1.00
Value of Land Transfers ($)	1.00	1.00	1.00
Air Quality	1.97	0.24	16.25
Property Tax Rate	1.06	0.97	1.17
Constant	8.65E-16	1.17E-20	6.41E-11
Ln(population)	1 (exposure)		

*The main model excludes variables that were found to cause multicollinearity. These include age, sex, opioid prescription and opioid agonist therapy.

Table 2. Sensitivity Analyses

	IRR Cumulative kits in circulation (per 10,0000)	[95% Conf.	Interval]
Main Model	0.76	0.66	0.87
Simplified model*	0.76	0.70	0.83
Including 1 year lag on cumulative kits in circulation	0.76	0.66	0.88
Non-linear time trend #	0.68	0.47	1.00
Non-linear time trend and 1 year lag^	0.68	0.47	1.00
Dependent variable Fentanyl-related deaths	0.70	0.60	0.83
Limited Analysis Using Data Between 2016-2019	0.72	0.57	0.92
Instrumental variable main model α	0.61	0.43	0.88
Instrumental variable of simplified model	0.67	0.59	0.76

*The simplified model excluded the socio-economic indicators, the police seizure, public awareness, and harm reduction covariates. It included the zone and time covariates and interaction.

Although the upper 95% confidence interval rounds to 1.00 the p-value is 0.047.

^When we impose less structure on the data by including a non-linear time trend and a 1 year lag on the cumulative kits in circulation the results are not statistically significant at p-value=0.05 with a p-value of 0.053.

α The instrumental variable analysis on the main model did not meet the Durban-Wu-Hausman test suggesting there was no evidence of endogeneity.

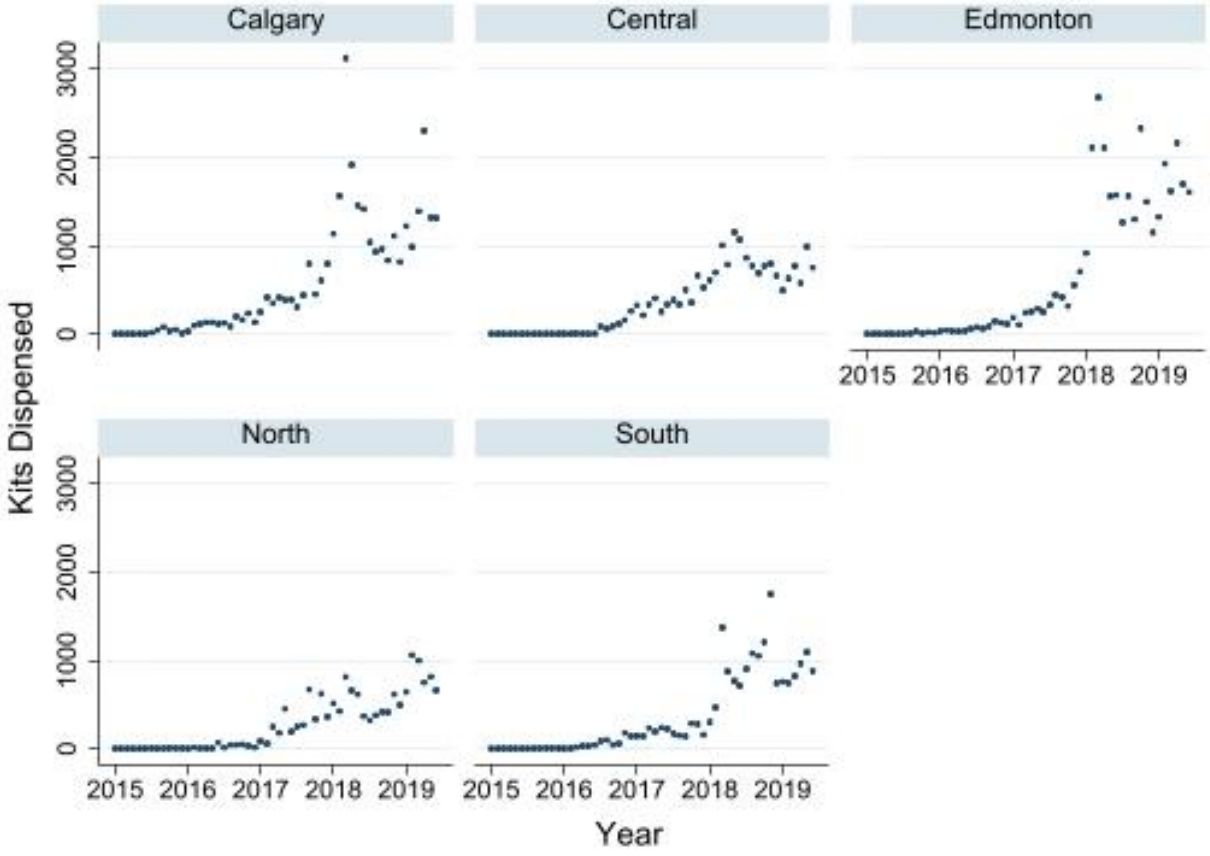

Figure 1: Kit distribution per zone January 2015 to June 2019

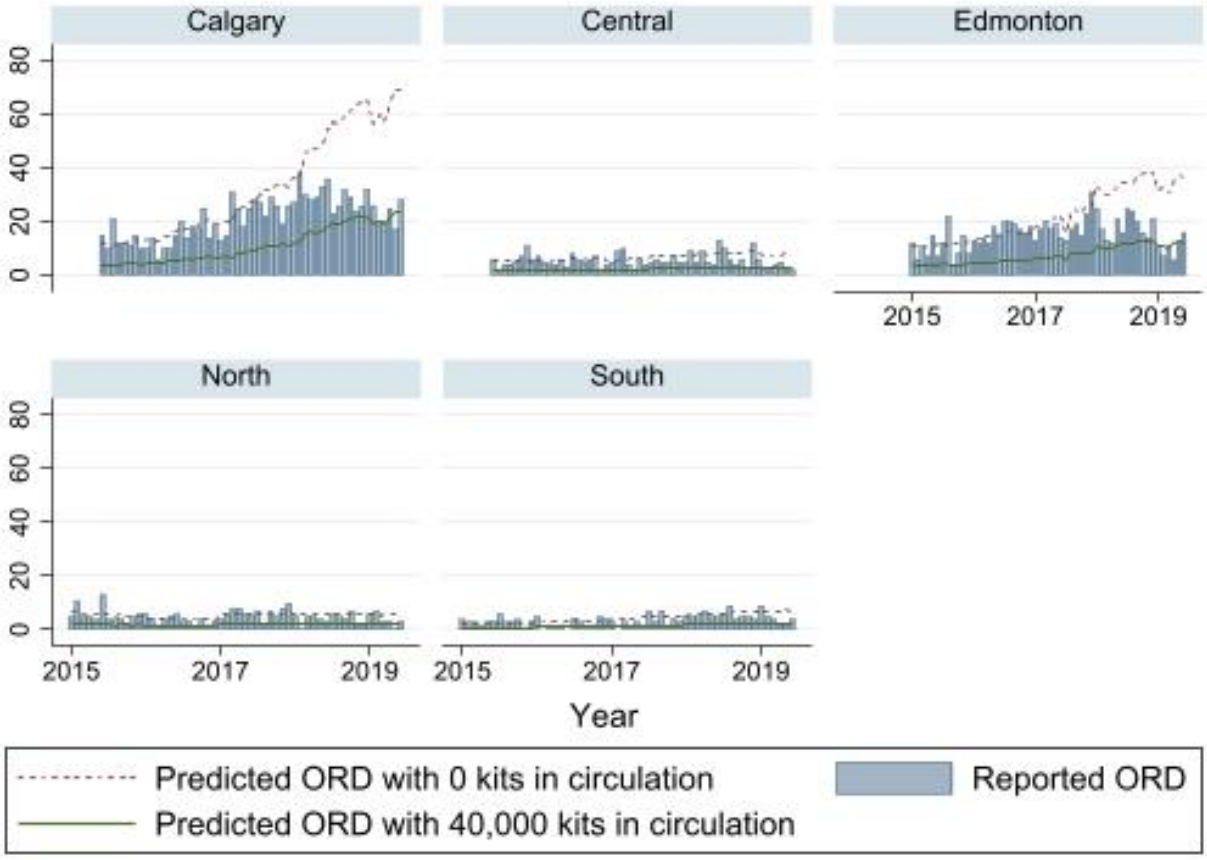

Figure 2: Average number of opioid-related deaths per zone January 2015 to June 2019 and predictions by the number of kits in circulation

Appendix 1

To control for differences between health regions we used annual data on socio-economic indicators available from the Alberta Regional Dashboard. The Alberta Regional Dashboard contains data on municipal finances, labour, infrastructure, housing and real estate, energy sector, construction, business activities, transportation and education. Particular measures include provincial registry services such as the number of driver's licenses issued and the number of vehicles registered, the amount of money spent on major projects, the number of post-secondary students, the number of employment insurance recipients, property tax rates, the proportion of residential properties, residential vacancy rate, number of housing starts, the number of businesses and percent of small businesses, median internet upload and download speeds, oil and natural gas production, the value of land transfers and bankruptcies. To estimate proportion measures at the zone level population weighted proportions at the municipal level were summed.

Data on police seizures were provided by Calgary Police Services, Edmonton Police Services and the Royal Canadian Mounted Police. Monthly data was provided by the Calgary Police Service on the weight, number of pills and number of patches of fentanyl and carfentanil seizures between 2015 and June 2019. Edmonton Police Services and the Royal Canadian Mounted Police provided the same data for 2015-2018 and 2016-June 2019, respectively.

Appendix 2

We used a Poisson pseudo-maximum likelihood regression model with fixed effects because the dependent variable is a count of deaths by month and health zone. Fixed effects were used to account for the panel data. An interaction term between time and zone was used to capture the differences in health zones over time. We estimated clustered standard errors to control for heteroskedasticity and autocorrelation. We also ran a negative-binomial regression and tested for overdispersion of the dependent variable using the likelihood ratio test on the over-dispersion parameter. We tested for multicollinearity by running ordinary least square regressions and examining the variance inflation factor (VIF). The variable with the highest VIF was removed from the model until all covariates had a value of less than 10. We tested simplified models eliminating all zone level covariates to further avoid multicollinearity. We ran several sensitivity analyses: we tested lagged variables of the number of kits in circulation since the current number in circulation depends on the previous number of kits in circulation, we used fentanyl deaths as the dependent variable, we also tested the inclusion of a non-linear time trend to understand the effects of imposing less structure on the data.

We hypothesized that opioid-related deaths and the number of kits in circulation may be simultaneously endogenous. This means that the number of kits in circulation may affect the number of opioid-related deaths, but also the number of deaths may affect the number of kits distributed, as individuals who hear about opioid-related deaths in the news may be more likely to request a kit. We tried to control for this in our main model by including a measure of public awareness. Additionally, we identified three variables that might be used as instrumental variables: the number of pharmacies dispensing naloxone kits, the number of kits ordered and the number of kits in stock. We hypothesized that each would be correlated with the number of kits in circulation but were less correlated with the number of deaths. Since the pharmacies were paid a distribution fee they were incentivized to distribute kits regardless of the number of deaths, and since ordering was centralized, it was assumed that the number of kits

ordered and the number in stock would be less influenced by deaths in each zone. A two-stage model was used to account for endogenous covariates.