Distribution of take-home opioid antagonist kits during a synthetic opioid epidemic in British Columbia, Canada: a modelling study

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Summary

Background Illicit use of high-potency synthetic opioids has become a global issue over the past decade. This misuse is particularly pronounced in British Columbia, Canada, where a rapid increase in availability of fentanyl and other synthetic opioids in the local illicit drug supply during 2016 led to a substantial increase in overdoses and deaths. In response, distribution of take-home naloxone (THN) overdose prevention kits was scaled up (6·4-fold increase) throughout the province. The aim of this study was to estimate the impact of the THN programme in terms of the number of deaths averted over the study period.

Methods We estimated the impact of THN kits on the ongoing epidemic among people who use illicit opioids in British Columbia and explored counterfactual scenarios for the provincial response. A Markov chain model was constructed explicitly including opioid-related deaths, fentanyl-related deaths, ambulance-attended overdoses, and uses of THN kits. The model was calibrated in a Bayesian framework incorporating population data between Jan 1, 2012, and Oct 31, 2016.

Findings 22 499 ambulance-attended overdoses and 2121 illicit drug-related deaths (677 [32%] deaths related to fentanyl) were recorded in the study period, mostly since January, 2016. In the same period, 19 074 THN kits were distributed. We estimate that 298 deaths (95% credible interval [CrI] 91–474) were averted by the THN programme. Of these deaths, 226 (95% CrI 125–340) were averted in 2016, following a rapid scale-up in distribution of kits. We infer a rapid increase in fentanyl adulterant at the beginning of 2016, with an estimated 2·3 times (95% CrI 2·0–2·9) increase from 2015 to 2016. Counterfactual modelling indicated that an earlier scale-up of the programme would have averted an additional 118 deaths (95% CrI 64–207). Our model also indicated that the increase in deaths could parsimoniously be explained through a change in the fentanyl-related overdose rate alone.

Interpretation The THN programme substantially reduced the number of overdose deaths during a period of rapid increase in the number of illicit drug overdoses due to fentanyl in British Columbia. However, earlier adoption and distribution of the THN intervention might have had an even greater impact on overdose deaths. Our findings show the value of a fast and effective response at the start of a synthetic opioid epidemic. We also believe that multiple interventions are needed to achieve an optimal impact.

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See Comment page e205

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Introduction

Illicit synthetic opioid use has increased rapidly over recent years in North America,[1,2] in part due to the large consumption of prescription opioids compared with other resource-rich countries.[3,4] In British Columbia (a province in western Canada with a population of 4·6 million), since late 2015, we have experienced a large increase in overdose and death events among people who use drugs with a particular emphasis on the synthetic opioid fentanyl,[5] which is estimated to be between 50 and 100 times more potent than heroin.[6]

Misuse of any opioid can result in overdose leading to death or other health complications. However, due to its high potency relative to other opioids and drugs of abuse, illicit fentanyl poses a substantially higher threat to health. Illicit fentanyl is not regulated, which means the amount and type of fentanyl or other adulterants in an ingested dose is unknown to the user and can be highly variable. The range between effective and lethal dose can be much narrower in fentanyl analogues than in prescription-grade heroin.[6] Individuals might also mistakenly take fentanyl products believing they are heroin, oxycodone, or another non-opioid substance, placing them at increased risk of an accidental overdose.[7]

Since 2015, British Columbia has seen a substantial increase in the number of fentanyl-detected illicit drug deaths compared with the rest of North America, with non-fentanyl-detected deaths remaining relatively static.[5]

Research in context

Evidence before this study

Naloxone is an opiate antagonist that has been shown to be highly effective at reversing overdoses and averting deaths due to opioid overdose. From late 2015 to early 2016 there was an unprecedented increase in the availability of high potency synthetic opioids (especially fentanyl) in British Columbia. In the context of a large-scale fentanyl-driven epidemic it was not clear what impact could be expected for the take-home naloxone (THN) kit programme. We searched PubMed on May 27, 2017, with the search terms "naloxone" AND "fentanyl" AND "overdose" for publications from Jan 1, 2011, to May 27, 2017, restricted to English language, but with no restriction on geographical location. Of the four studies identified, none directly tried to estimate the effectiveness of a naloxone programme in the context of a sudden epidemic of overdose events.

Added value of this study

This is the first study to estimate the impact of a THN programme on the number of overdose deaths during an epidemic of fentanyl use. We use a simple mathematical model, calibrated to multiple sources of data on opioid overdoses and overdose deaths, to estimate the number of deaths averted through the British Columbia THN programme. These results will have important implications for other regions in Canada and the rest of the world that are seeing an increase in fentanyl in their illicit drug supply.

Implications of all available evidence

Our findings suggest that the British Columbia THN programme was effective at reducing the number of overdose-related deaths during a large and rapidly developing synthetic opioid epidemic. Counterfactual modelling to project the impact of different interventions to the crisis showed that earlier distribution of THN kits could have had greater impact despite escalating fentanyl use. We find that multiple interventions will probably have the most impact in reducing the overall burden of such an epidemic.

This increase has taken place over a general background of increases in both licit and illicit opioid use, overdoses, and deaths. However, beginning in 2015 and more pronouncedly in 2016, the rates of fentanyl-linked deaths in the province increased by three times and 8·9 times, respectively, compared with average pre-2015 rates.[5,6] This increase is believed to be due to a shift in procurement patterns of illicit opioids to online and overseas manufacturers, leading to a greater amount of fentanyl in the supply. Additionally, in many contexts neither buyer nor seller is aware of the addition of fentanyl. Indeed, a 2016 study indicated fentanyl was present in 82% (sample size 922) of selected heroin samples at a Vancouver supervised injection site, where clients were offered the opportunity to test their drugs.[8–10]

In response to the escalating crisis, the provincial government and local health authorities proposed a number of strategies including the rapid expansion of a take-home naloxone (THN) kit programme.[9] The programme began in 2012. Between Jan 1, 2012, and Oct 31, 2013, there were 85 documented cases of kits being used to reverse overdoses, with no deaths in these cases.[11] THN kits have proven efficacy in reversing overdoses and have similarly been used in other settings as a first-line measure. They are estimated to be 94% effective when administered by laypersons and have been shown to be cost-effective in certain jurisdictions.[12–15] As of Sept 30, 2017, 55 112 kits had been distributed to people who use drugs and their close personal contacts in British Columbia. The THN programme expanded in the context of ongoing provincial-wide treatment and a supervised consumption site in Vancouver. Overdose prevention sites have also been introduced around the province since Dec 8, 2016.

There are no estimates of how many deaths the THN programme has averted, including during the fentanyl-misuse epidemic. Here, we apply a simple Markov chain model of overdoses and deaths linked to opioids, explicitly accounting for a variable proportion of fentanyl in the illicit drug circulation. The model was designed so that it could incorporate provincial overdose and death data from Jan 1, 2012, to Oct 31, 2016, where the main changing intervention was the expansion of the THN programme, and thus can be used to estimate the impact of the programme on mortality. We also estimate the impact of three alternative interventions through counterfactual modelling: earlier distribution of THN kits, reduction of the population potentially exposed to fentanyl (eg, as would be seen through other interventions such as increased addictions treatment or implementation of a prescription heroin programme), and prevention of the increase in fentanyl supply to the illicit market.

Methods

Data sources

Monthly data for fentanyl-linked illicit drug overdose deaths and total illicit drug overdose deaths (including fentanyl-related deaths) were obtained from Jan 1, 2012, to Oct 31, 2016, for the whole of the province from the Coroners Service of British Columbia.[5,16] Fentanyl-linked deaths included cases where fentanyl was identified alone or in combination with other drugs, when drug overdose was the confirmed cause of death. Deaths were excluded if fentanyl had been prescribed or there was suspected self-harm. Post-mortem testing for fentanyl remained consistent throughout the entire study period and was tested for in every overdose death.

Data for ambulance-attended overdoses were provided by the British Columbia Emergency Health Service as an extract from their Patient Care Report database. In these data, we defined an overdose following the definition used by the British Columbia Centre for Disease Control for illegal drug overdose surveillance:[17] any ambulance-attended event indicating the patient experienced an overdose of illegal substances, excluding alcohol or the patient's own prescription drugs, and including those where naloxone was administered. These data do not distinguish between fentanyl-related and other opioid overdoses. Monthly numbers of ambulance-attended illicit drug overdoses were tabulated for the period Jan 1, 2012, to Oct 31, 2016.

THN kit programme data were gathered in two categories: the monthly number of kits distributed, and the number of kits replaced due to an overdose event. Details of how each of these different datasets were incorporated into our model are given in the next section.

Weather data were extracted from a publicly available data source for Vancouver, British Columbia.[18] A mean of the average daily feels-like temperature and precipitation were extracted and converted into monthly temperatures and precipitation. The feels-like temperature was used since this is more indicative of how an individual would experience the weather.

Model design

We designed a model of the population of people who use drugs in the form of a Markov chain model (figure 1).[19] People who use drugs are modelled as being in one of three states: individuals at risk of overdose (state F; ie, they are using opioids from a drug supply that can potentially contain fentanyl or other opioids at unknown concentrations); individuals not at risk of overdose (state R; ie, they are compliant with opioid substitution therapy or are otherwise not in contact with the general supply); and individuals who have recently relapsed into illicit drug use and are hence at increased risk from both fentanyl and non-fentanyl overdose (state H).[20] Since we had no evidence of substantial changes in the population of at-risk individuals over the study period, we simplified the model by fixing the proportion of individuals in each category. Numbers were informed from population estimates of people who use drugs and the number of individuals enrolled in the provincial methadone programme.[21]

A major challenge in this work is that the proportion of opioid users who will be exposed to a clinically significant concentration of fentanyl in the illicit drug supply (fentanyl-related overdose risk) each month is unknown. We addressed this by modelling the proportion as a latent (unobserved) time series, describing an increase in the rate of overdoses occurring among people in states F and H of the model. This time series was modelled as a random walk with drift. This model assumes that month-to-month changes in the proportion of fentanyl in the supply were due to a constant drift along with a monthly variability. This latent series incorporates all effects that would lead to a change in overdose risk, such as behaviour changes in response to the previous month's overdose deaths. The model is therefore agnostic to reasons why people who use drugs might have taken fentanyl.

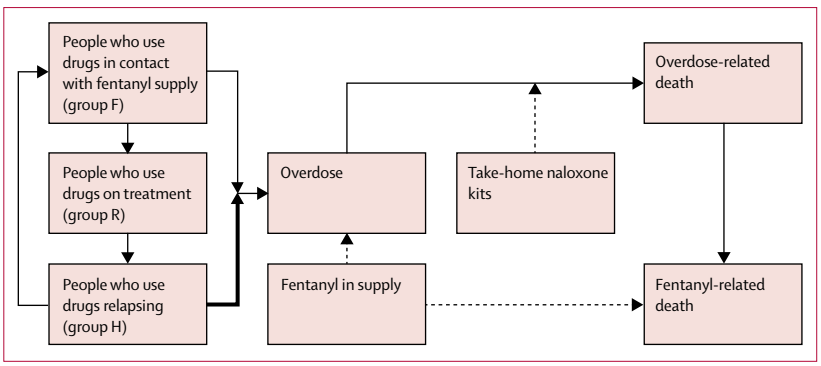

Figure 1: **Model overview**
Flow of people who use drugs through different states (left). A certain proportion of people who use drugs relapsing or in contact with fentanyl supply will overdose, which is influenced by the fentanyl in supply. A certain percentage of overdoses will turn into overdose-related deaths, which is influenced (represented by a dashed line) by the take-home naloxone kits and the weather. Of those overdose-related deaths, a proportion will be fentanyl-related deaths, which are also influenced by the fentanyl in supply.

The monthly numbers of overdoses in the population can be modelled by multiplying the numbers of people in each state (F and H) by the monthly risk of overdose due to the regular drug supply and the fentanyl-including supply, with each risk weighted by the proportion of contact with the fentanyl supply. We also applied an increased risk of overdose to individuals in the relapse group H.

The impact of the entire THN programme was incorporated into our model in two ways. First, we included the known cumulative number of kits in circulation each month and converted this number into a probability that a THN kit was used during an overdose event. This calculation was achieved by dividing the number of kits in circulation by the at-risk population size and multiplying by an effectiveness parameter. The effectiveness parameter includes all aspects of kit effectiveness in the field: kit loss, availability for use, proper application, and success in reversing an overdose. Second, the model included the number of used THN kits returned for replacement; these were kits that had been used due to an overdose.

We also included the effect of weather on the probability of mortality following an overdose event. The hypothesis is that, due to British Columbia's temperate oceanic climate in the densely populated parts of the province where most overdoses take place, cold or precipitation, or both, could lead to people using opioids in more isolated settings, reducing the possibility of assistance in the event of an overdose. A logistic impact on the mortality was considered for both temperature and precipitation.

See Online for appendix

All parameters for the model were given prior probability distributions based either on literature estimates or expert opinion (see appendix for a full description). These distributions thus allowed us to incorporate prior information available from previous work, either as a point estimate with a measure of its SE or as a range of plausible values. The model fitting also incorporated comprehensive data on ambulance-linked overdoses, coroner-confirmed deaths due to fentanyl, coroner-confirmed deaths due to non-fentanyl drug-overdose, and on the supply of THN kits in the population.

Calibration and validation of the model

This analysis used a Bayesian inference approach, which allows expert opinion and previous estimates of the parameters to inform the model calibration and produces a final model fit with error that includes both parameter and model uncertainty and is therefore of greater fidelity than using single point estimates.[22–24] The fitted model was then validated through a cross-validation scheme, where each of the four data sources were left out of the model-fitting process in turn, and the various predicted values were then compared with the original data source that had been removed. Validation accuracy was assessed through the percentage overlap of the datapoints with the 95% predictive interval for each of the data sources.

Counterfactual scenarios

After full model calibration we did several counterfactual studies, focusing on the period Jan 1 to Oct 31, 2016. We examined what would have happened if there had been different numbers of THN kits distributed, fewer at-risk people in the population, or changes to the supply of fentanyl over that period. We were thus able to assess the entire impact of the THN programme up to Oct 31, 2016, by comparing with a scenario where the programme did not exist. We also considered scenarios where the population of at-risk people who use drugs was halved; where all the kits distributed in 2016 were instead distributed at the start of 2016; where the kits were distributed at the start of 2016 and the at-risk population was reduced by a half; and where the proportion of fentanyl in the supply was the same as in 2015. All scenarios were compared with the scenario where no THN kits were distributed.

The statistic used to compare between scenarios was the estimated number of deaths averted. This number was calculated by firstly drawing a sample set of parameters from the posterior. For each parameter sample, a model simulation was done with the intervention and without the intervention or THN kits distributed (baseline). The cumulative difference between each scenario and the baseline (no THN programme) was then summed from Jan 1 to Oct 31, 2016, to determine the number of deaths averted. This calculation was repeated 10 000 times and the median and 95 percentiles were taken to produce the estimated deaths averted with credible intervals (CrIs) in each scenario.

Role of the funding source

The funders (British Columbia Centre for Disease Control and the Canadian Institutes of Health Research) had no role in the study design, collection, analysis, or interpretation of the data, writing of the report, and no responsibility in the decision to publish. MAI, MG, and DC had full access to all data used in this study and the corresponding author had final responsibility to submit for publication.

Results

22 499 ambulance-attended overdoses and 2121 illicit drug-related deaths (677 [32%] deaths related to fentanyl) were recorded in the study period between Jan 1, 2012, and Oct 31, 2016. The number of fentanyl-related overdose deaths in British Columbia steadily increased from 2012 until 2015, reaching 11–16 deaths per month by the end of 2015 (figure 2). This increase was followed by a large spike in cases in the first months of 2016, reaching a peak of 47 deaths in March, followed by a general decline, although with high month-to-month variation (range 37–47 per month; figure 2A).

By comparison, all drug-related overdose deaths (including fentanyl) also increased until 2016, reaching a maximum in January with 84 deaths per month (4·7 times the pre-2012 median; figure 2A). There was a steady increase from 20 deaths in January, 2012, to 67 deaths in December, 2015, with a higher rate in 2016 (with overdose deaths attributable to fentanyl rising from 0% in January, 2012, to a maximum of 77% in May, 2016). Ambulance-related overdoses also followed the general pattern of drug-related and fentanyl-related deaths, climbing from 256 overdose reports in January, 2012, to 484 reports in November, 2015, with a large increase in 2016 (range 597–720, January, 2016, to October 2016; figure 2B). The THN programme underwent massive scale-up in 2016, with 13 757 (80·3%) kits being distributed from Jan 1 to Oct 31, 2016 (figure 2C); in total, 19 074 THN kits were distributed during the study period.

When overdose data were removed from the fit, the accuracy of the fit dropped from 94·8% to 55·2%, with much of the error occurring during 2016 when overdose and death rates jumped substantially (appendix p 12). When drug-related death data were removed from the fit, we found a validation accuracy of 69·0%. Although the drug-related deaths were underestimated in the validation step where illicit drug deaths were removed from model fitting, throughout the course of the epidemic, there was overlap between the validation fit and the actual fit (appendix p 12). Because the proportion of fentanyl in the opioid supply drove the overdose and related deaths, removing the fentanyl-related deaths decreased accuracy from 94·8% to 15·5% (appendix p 12).

Removing the number of THN kits returned changed accuracy from 82·8% test accuracy to 48·3% validation accuracy. This change was due to the large uncertainty in the effectiveness of THN, which was strongly informed by the number of kits returned in the full fits. Overall, our model behaved rationally in this leave-one-out validation process, giving us good confidence in our full-fit results.

After fitting and validatioFn (appendix pp 5–13), our model estimated that the prevalence of individuals coming into contact with a high proportion of fentanyl essentially doubled from 2015 to early 2016 (an increase of 2·3 times [95% CrI 2·0–2·9]). We compared the marginal posterior estimates of model parameters with the prior estimates. Those that showed a significant difference between the posterior and the prior were the overall THN kit probability of effective use (posterior estimate 85% [95% CrI 73–97] *vs* prior estimate 50% [3–98]) and the fentanyl-related overdose rate (0·09 overdoses per person-month [95% CrI 0·09–0·10] *vs* 0·62 overdoses per person-month [0·37–1·04]). The model fitted parameters indicate an approximately ten-fold increase (10·0 [95% CrI 9·7–10·7]) in the rate of fentanyl overdose compared with the background opioid level (0·0091 overdoses per person-month [95% CrI 0·0089–0·0093]). Other parameters, including the size of the population at risk, showed some degree of change in the posterior estimates; however, these were not significant when compared with the prior estimates. The log-baseline death rate also showed a large degree of change, but this overlapped with the prior estimates, due to the uncertainty in this parameter in the prior estimates.

Overdoses, fentanyl-related deaths, and drug-related deaths were all well fitted by the model, with 94·8%, 94·8%, and 98·3% of the dataset falling within the 95% predictive interval for each observable, respectively (appendix p 14). The number of kits returned did slightly worse, with only 82·8% falling within the predictive interval. This result might be due to secondary effects of the THN programme such as greater awareness in the population meaning more kits would be used than expected. The goodness of fit indicated the rise in overdose deaths was explainable due to the increase in risk of contact with fentanyl.

The impact of weather on the rate of mortality following overdose was marginally significant. The mortality rate varied between 10·4% and 9·1% between winter and summer, with a proportional increase of 14%. Temperature was the dominant impact on weather-dependent mortality, with an effect size 4·2 (95% CrI 1·7–10·5) times greater than the effect of precipitation (appendix p 15).

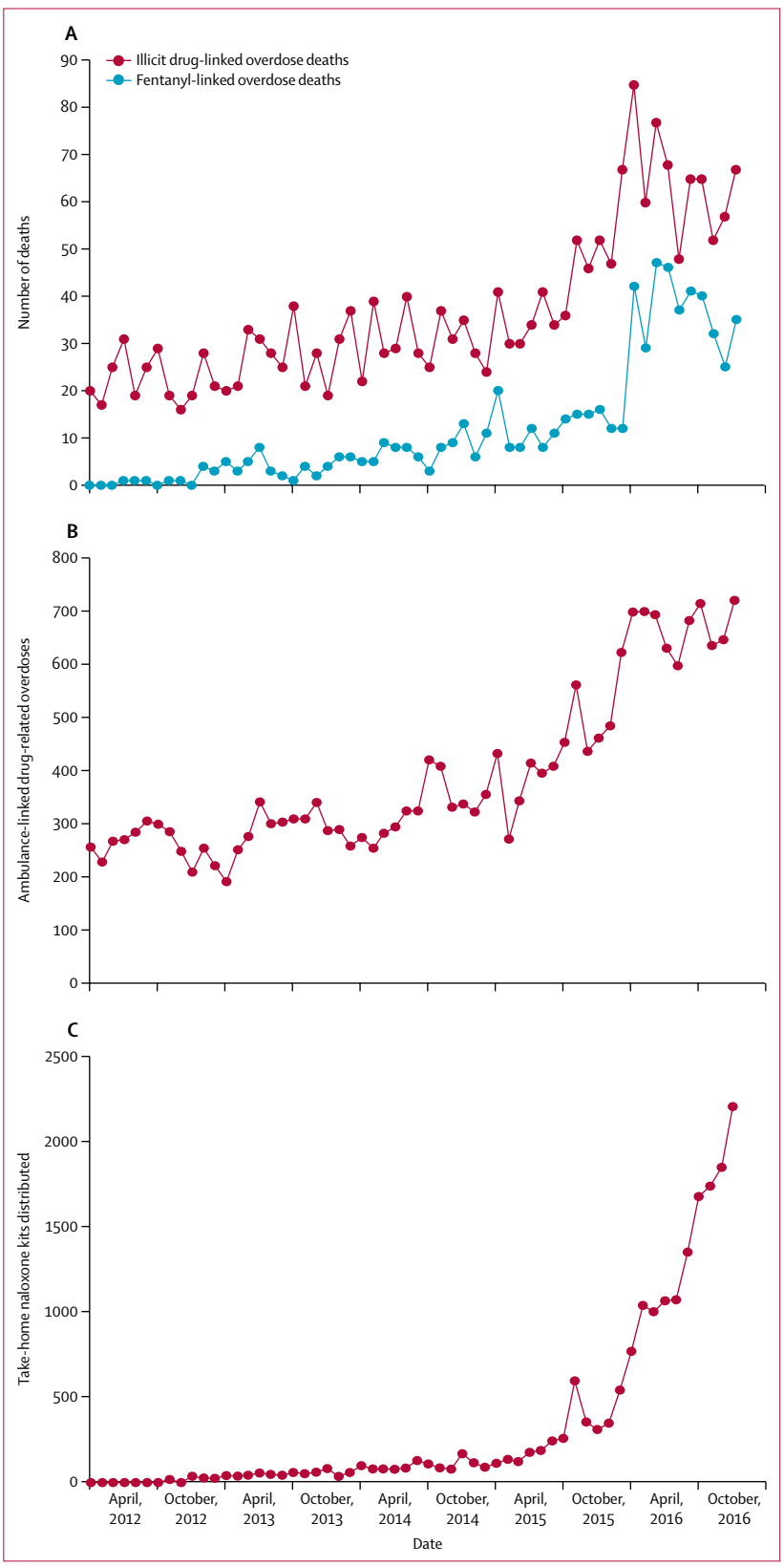

Figure 2: **Overview of the fentanyl epidemic and response data**
(A) Fentanyl-linked overdose deaths and illicit drug-linked overdose deaths. (B) Ambulance-linked overdoses. (C) Number of take-home naloxone kits distributed. See appendix (pp 6, 7) for tabulated data.

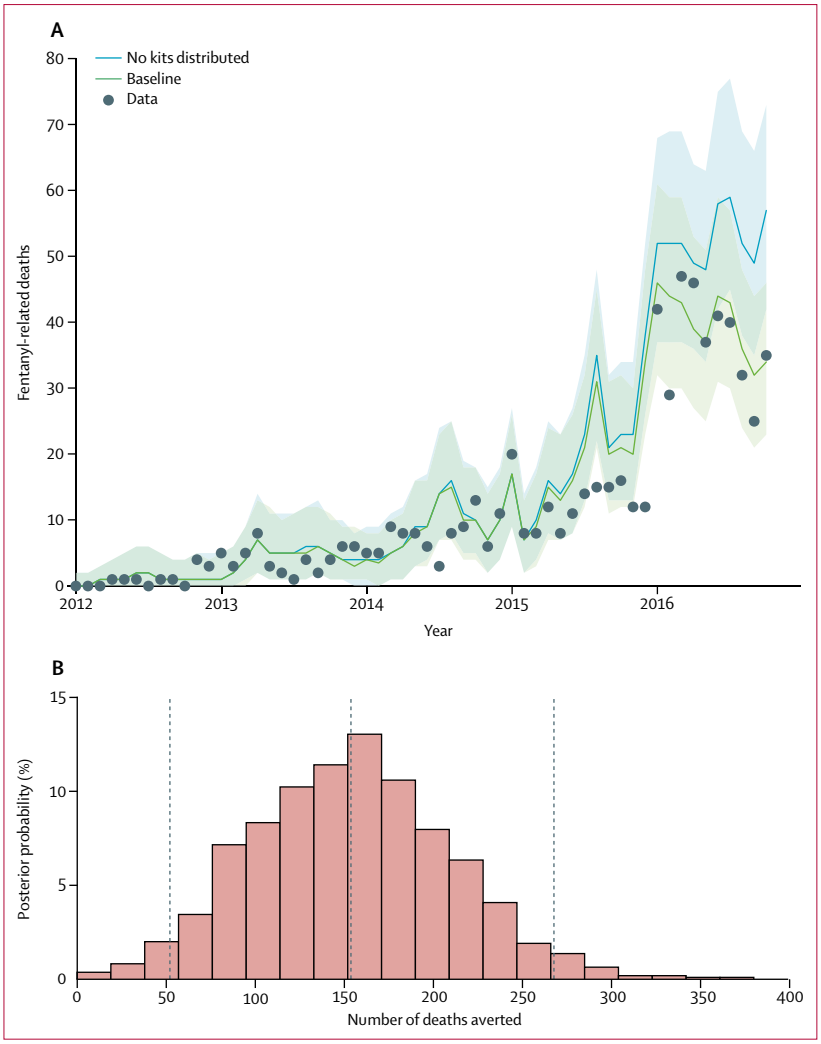

Figure 3: **Total naloxone impact on fentanyl-related deaths**
(A) Comparison in the number of fentanyl-related deaths between the actual distribution of take-home naloxone kits (baseline) with a counterfactual scenario in which no kits were distributed. Shaded area shows the respective 95% credible interval. (B) Estimated number of fentanyl-related deaths averted during the study period due to distribution of take-home naloxone kits. Dashed lines are median and 95% credible intervals.

Model fitting was also done without the inclusion of the THN programme data. Although the observed deaths and overdoses could be explained by a monthly change in overdose rate alone, the number of THN kits administered was only explained with the inclusion of THN kits distributed into the model (appendix p 19).

Comparing the scenario where no kits were distributed with the full model fit, we estimated the total number of deaths averted due to the THN programme since 2012 to be 298 (95% CrI 91–474). Of those deaths averted, 155 (95% CrI 54–268) were linked to fentanyl (figure 3B). The estimated number of deaths averted per month was relatively small (around two) for each year before 2016. However, this number increased to 11 in January, 2016, and from February to October, 2016, we estimated a mean number of deaths averted of 22 per month (range 14–35).

The number of kits used per death averted between Jan 1, 2012, and Oct 31, 2016, was 10·1 (95% CrI 5·6–34·6) and the number of kits distributed per death averted was 64·7 (36·3–222·3).

The estimated number of deaths averted were compared for a number of retrospective scenarios from Jan 1 to Oct 31, 2016 (figure 4). We estimated that THN kits as distributed by the programme averted 226 deaths (95% CrI 125–340), with 85·2 kits (95% CrI 61·1–132·5) distributed per death averted. This estimate represents 33% (95% CrI 19–45) of all deaths in that period. If the proportion of fentanyl in the drug supply was the same as in 2015, we estimated the number of deaths prevented would have been 310 (95% CrI 195–420; figure 4). Similar impacts were estimated in scenarios where the number of individuals at risk of a fentanyl-linked overdose was halved, and where all THN kits were distributed at the start of 2016 (ie, Jan 1, 2016), with 344 deaths averted (95% CrI 267–425), representing an additional 118 deaths (95% CrI 64–207) averted and 51·4 kits (95% CrI 42·2–64·4) distributed per death averted. This estimate represents 53% (95% CrI 41–66) of all deaths in that period. Unsurprisingly, the scenario with the greatest impact was where both the at-risk population was halved and the THN kits were distributed at the start of 2016, with 720 deaths (95% CrI 650–790) averted between Jan 1 and Oct 31, 2016 (figure 4). Reducing the at-risk population also had an impact on the rate of overdoses (total overdoses including those leading to death). Halving the at-risk population averted 3500 overdoses (95% CrI 3200–3900) between Jan 1 and Oct 31, 2016 (data not shown).

Discussion

Distribution of naloxone has been shown to be effective at reversing opioid overdoses.[12,19] Until now, however, there has not been an estimate of deaths averted due to a mass naloxone distribution campaign during an opioid overdose epidemic. We fitted and analysed a Markov chain state model of overdoses and deaths occurring in the presence of a dynamically varying proportion of fentanyl in the general illicit drug supply.

We estimate that the British Columbia THN programme averted 226 deaths (95% CrI 125–340) from Jan 1 to Oct 31, 2016. This estimate represents 33% (95% CrI 19–45) of the deaths that occurred over that time period. In comparison, if the programme had achieved scale-up earlier and all kits that were distributed in 2016 had been distributed by the beginning of the year, we estimate that 344 deaths (95% CrI 267–425) would have been averted. This estimate represents 53% (95% CrI 41–66) of all deaths over that time period. This is comparable to our estimates for scenarios where the fentanyl supply was at the same level each month as in 2015, or where the at-risk population is halved. We also find an additive effect of combining interventions on the number of deaths averted.

The model fit indicates a 10·0 times (95% CrI 9·7–10·7) increase in the rate of an overdose due to fentanyl

compared with the background overdose rate. The spike in overdoses and overdose-related death during 2016 is reflected in a doubling of the modelled probability of a person who uses drugs coming into contact with fentanyl in the general supply. Although weather and in particular temperature was also considered a factor in the increase in cases in late 2015 to early 2016, our analysis does not support a significant impact from this factor alone.[25]

Our findings suggest that an earlier scale-up of THN before the rapid increase in fentanyl would have had a pronounced impact on both deaths averted and the cost-effectiveness of the THN programme. 85·2 kits (95% CrI 61·1–132·5) distributed per death averted (ie, if kits were distributed between Jan 1 and Oct 31, 2016) compared with 51·4 kits (42·2–64·4) if they were distributed earlier (ie, refers to the counterfactual scenario where all kits distributed in 2016 were instead distributed on Jan 1, 2016). These figures show the need for a rapid response by authorities to avert more severe outcomes and might help inform decisions in other jurisdictions.

There is an urgent need for a multifaceted approach to the global opioid epidemic.[2] To this end we studied the impact of reducing the overall at-risk population in combination with the distribution of naloxone. Reducing the population has the added benefit of also averting the number of overdoses by 3500 (95% CrI 3200–3900), whereas there might be a limited impact on the number of overdoses reduced with THN since a kit is only administered once an overdose has occurred. Multiple interventions can contribute towards the reduction of the at-risk population, including the use of opioid substitution therapy.[26] As shown, these would likely have a large impact on the number of overdoses. In future work we intend to more explicitly model multiple interventions in the ongoing fentanyl epidemic and their associated costs, to better understand the long-term impacts in the ongoing crisis.

Our study had limitations. Fentanyl is assumed to affect the rate of overdoses alone and not the probability of death following an overdose. Fentanyl contact rate was modelled as a latent time series. If more regular sampling of the general illicit drug supply occurred then this could be included in the estimation. A linear relationship is assumed between the THN effectiveness and the number of kits that are distributed. Although certain risk behaviours might have changed over time this was not explicitly modelled, but instead incorporated into the overdose rate as a latent time series (see appendix pp 17–21 for exploratory and sensitivity anlyses of these limitations). The model was constructed in the context of an increasing concentration of fentanyl adulterant in the general drug supply, so other factors might need to be considered in other jurisdictions where the population of people who use drugs is also changing. Non-fentanyl-related deaths were assumed to occur at a constant rate. This assumption was justified as non-fentanyl-related deaths did not change substantially in the study period. We assumed that the number of people compliant with opioid substitution therapy was constant and that this group was not at risk of overdose; however, the actual number of patients increased modestly during this period and this group certainly has a risk of overdose (see appendix p 17 for a sensitivity analysis of the at-risk population).[27]

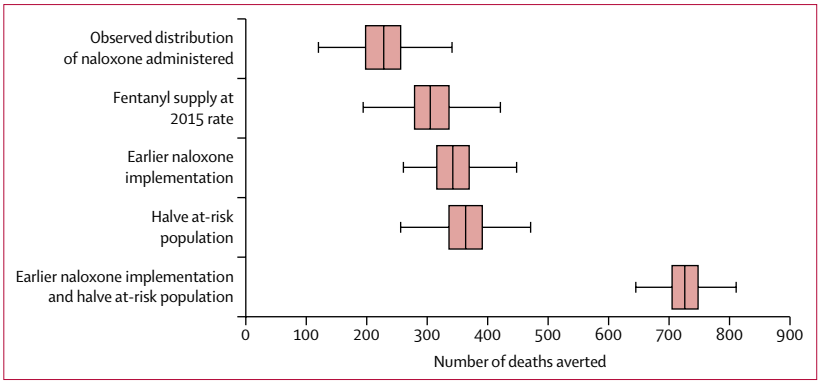

Figure 4: **Estimated number of deaths averted from Jan 1 to Oct 31, 2016, for the retrospective scenarios**
The scenarios were: the actual number of take-home naloxone kits that were distributed (baseline); the rate of fentanyl in the supply was the same as in 2015; all the kits distributed in 2016 were instead distributed on Jan 1, 2016; the population of people who use drugs was halved; and the kits were distributed on Jan 1, 2016, and the at-risk population was reduced by a half. Middle line is the median, shaded area is the 50% credible interval, whiskers show the 95% credible interval, and diamonds show the 5% outliers.

Our findings suggest that THN was effective at mitigating the number of overdose-linked deaths in the context of a dramatic increase in the use of fentanyl. Our model analysis suggests that, based on our findings specific to British Columbia, distribution of naloxone and other resources should be mobilised as early as possible when there has been an increase in fentanyl-linked deaths. Combination of THN with treatment and other harm-reduction strategies could have an additive impact on the number of deaths averted and might further reduce the number of overdoses and associated demands on the health-care system.

Contributors

MAI, DC, MG, and JAB conceived the study. MO and RB collected data. MAI, DC, MG, and JAB developed the model. MAI, MG, and DC developed the analysis plan. MAI did the analysis. All authors interpreted results. MAI, DC, and MG drafted the initial manuscript. MAI, DC, MG, JAB, MO, RB, and RG revised the manuscript. All authors reviewed and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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