Modelling the combined impact of interventions in averting deaths during a synthetic-opioid overdose epidemic - Supplementary material

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1 Model Overview

We sought to estimate the overdose risk and probability of death following an overdose, on a monthly and regional level (Fig. S1). This was achieved by first stratifying the population into different risk groups and then using these to estimate the monthly regional overdose rate. Overdoses, lead to overdose-related deaths, with a certain time-dependent probability. Surveillance data can be incorporated into this model structure by defining how these data are derived from the underlying model rates in an evidence synthesis fashion[6].

The model is built up in three stages: 1) a baseline hierarchical model incorporating overdose and death risk, 2) the inclusion of provincial level observables and, 3) the inclusion of the impact of interventions. The process driving change in overdose rates is modelled as the underlying proportion of contact with fentanyl in the illicit-drug supply, which is taken as a latent (unobserved) time-series. The death rate following an overdose is assumed to be dependent on weather effects (temperature, precipitation and wind), as well as the effect of fentanyl analogues in the illicit-drug supply.

The model also incorporates certain provincial level variables including carfentanil adulterant (which requires a latent time-series), and the ambulance call out rate (which requires another latent time-series). This accurately determines the overdose and death risk for the population stratified at the regional level in the absence of intervention.

The model further incorporates the impact of treatment. With the monthly overdose and death risk properly estimated, the impact of intervention can be estimated by altering the overdose risk and probability of death. This stage incorporates intervention data on overdose prevention service sites and supervised consumption sites (OPS/SCS), take-home naloxone (THN) and opioid agonist therapy (OAT).

1.1 Time-series modelling

A number of latent variables (proportion of fentanyl contact, effectiveness of naloxone, and proportion of carfentanil contaminant) were modelled as a time-series. First a random walk is constructed on the real line, and this is then transformed into a proportion. An initial value at time zero is drawn from a normal distribution, with precision τ^2 and mean 0, $z_0 \sim N(0, 1/\tau^2)$. The value for a following month z_t is dependent on the previous month z_{t-1}, through a normal distribution with mean μ and precision τ^2,

$$z_t \sim N(\mu + z_{t-1}, 1/\tau^2). \tag{1}$$

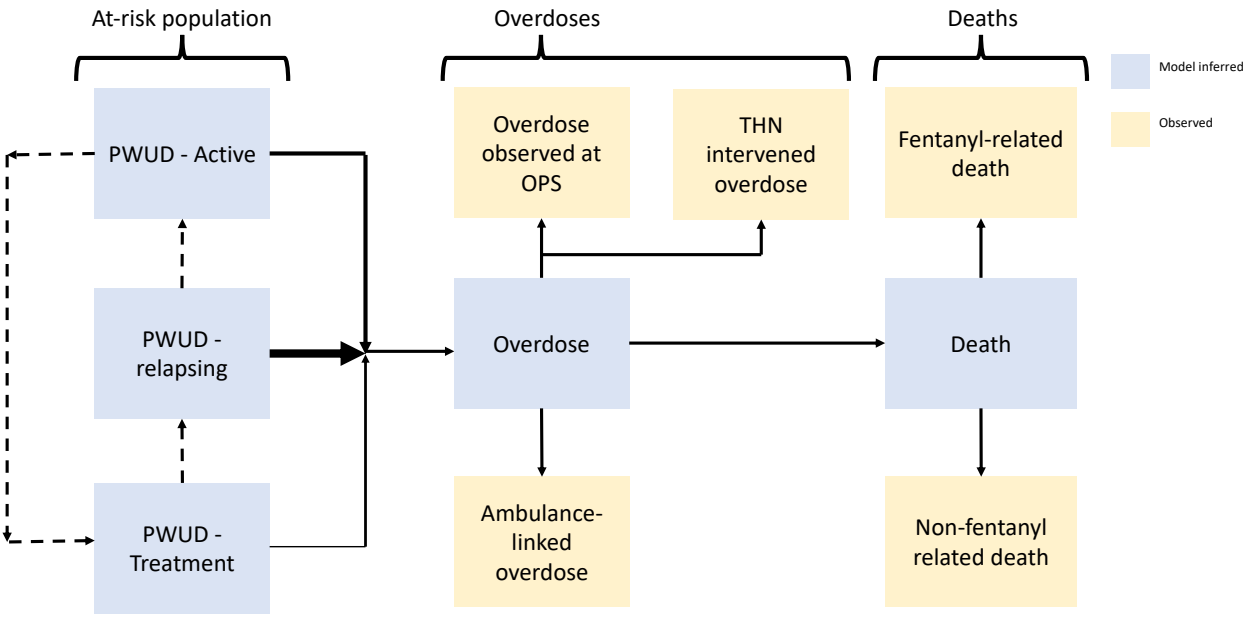


Figure S1: Simplified overview of model. The dashed lines represent the flow of the population into different risk groups, with the solid lines representing the interaction between population/events and various other events. Blue nodes are inferred or partially observed and yellow are directly observed in the data for each month and region. Note this is a simplified diagram aide to give an overview of the overall structure.

The precision τ^2 describes the size of variation between months and the drift term μ describes the trend from month to month. A link-function f is then used to transform the z-variables into a proportion (between 0 and 1) as was performed in the previous study[1],

$$f(z) = \frac{1}{2} + \frac{1}{2}\tanh(z). \tag{2}$$

The proportion of the latent variable at time t, p_t is defined as $p_t = f(z_t)$. Note that when $z = 0$, $f(z) = 1/2$ which is the mean of the initial variable p_0. Certain latent variables are assumed to have some geographic variation. If a regional estimate of a latent proportion is required, this is drawn from a Beta distribution parameterized by the provincial mean p_t and a standard deviation σ,

$$p_{t,i} \sim B(p_t, \sigma). \tag{3}$$

Note here Beta is parameterised by its mean and standard deviation. $p_{t,i}$ then describes the proportion of a variable at time t and in region i. Each latent variable with geographic variation, has its own drift μ, monthly precision τ^2, and regional variance σ set as hyper-parameters prior to model fitting (See Table S1 for a list of hyper-parameters used). These are described in detail for each latent variable below.

1.2 Overdose model

The per-capita overdose rate is modelled as the combined rate of overdose due to fentanyl adulterant and the overdose rate due to other illicit opioids. The proportion of fentanyl contact in the illicit-drug supply is modelled as a time-series described above, with drift $\mu_f = 0$, and monthly precision $\tau_f = 10$, to produce the provincial monthly proportion of fentanyl contact f_t. Hyper-parameter values were chosen such that no prior assumptions were made over whether the proportion was increasing or decreasing and to produce reasonable monthly proportional variance prior to model fitting. The regional proportion of fentanyl contact for region i and month t, $f_{t,i}$ is then drawn from a Beta distribution with standard deviation $\sigma_f = 0.1$.

The monthly per-capita rate of overdose when exposed to fentanyl κ_F is combined with the proportion of fentanyl exposure $f_{t,i}$ to produce the per-capita monthly regional rate of a fentanyl-related overdose $\kappa_F f_{t,i}$. The rate of an overdose for non-fentanyl-related opioids κ_N, given no contact with fentanyl, $(1 - f_{t,i})$, produces the monthly regional rate of a non-fentanyl overdose, $\kappa_N(1 - f_{t,i})$. The total per-capita monthly regional overdose rate is then,

$$\kappa_N(1 - f_{t,i}) + \kappa_F f_{t,i}. \tag{4}$$

The per-capita overdose rate is then combined with the monthly regional weighted population size, $\tilde{N}_{t,i}$ (which includes the impact of treatment, deaths, and relapsing) to calculate the monthly regional overdose rate $(o_{t,i})$,

$$o_{t,i} = (\kappa_N(1 - f_{t,i}) + \kappa_F f_{t,i})\tilde{N}_{t,i}. \tag{5}$$

Similarly the total monthly regional overdose rate related to fentanyl alone $(o^f_{t,i})$ is given by

$$o^f_{t,i} = \kappa_F f_{t,i}\tilde{N}_{t,i}. \tag{6}$$

1.3 Probability of overdose death

The probability of death following an overdose is modelled as a composite of various factors. The baseline log-probability of death following an overdose, c_0 was incorporated with both weather and fentanyl-analogue effects. Average monthly weather, including ambient temperature has been suggested as a risk

factor in overdose death[2,3]. Regional and monthly wind $w^w_{t,i}$ with strength c_W, precipitation $w^p_{t,i}$, with strength c_P, and feels-like temperature $w^t_{t,i}$, with strength c_T were incorporated into the probability of death following an overdose. We also included the presence of carfentanil as a factor that can increase the probability of a death following an overdose. Carfentanil was first observed in the provincial illicit-drug supply in October 2016 and since then has shown high monthly variability. In order to account for this we denote δ^c_t as the probability that carfentanil is in the illicit-drug supply during month t, and f^c_t as the scaled proportion of carfentanil within a sample containing fentanyl. f^c_t was modelled as a random walk with drift $\mu_c = 0$ and precision $\tau_c = 10$, with the resulting proportion p^c_t. The probability of a death following an overdose (in the absence of OPS/SCS or THN) in region i and at month t was modelled as an exponentiated linear composition of the effects of each weather variable and the effects of carfentanil,

$$\mu_{t,i} = \exp\left(c_0 + c_w w^w_{t,i} + c_p w^p_{t,i} + c_t w^t_{t,i} + f^c_t \delta^c_t\right). \tag{7}$$

The presence of carfentanil in the illicit-drug supply δ^c_t was set to be zero prior to October 2016, and one there after.

1.4 Ambulance-linked overdoses and callouts

Ambulance-linked overdoses were recorded within each region and for each month from January 2012 to December 2017. The proportion of overdoses linked to ambulance-callouts were used to calibrate the total number of total overdoses predicted by the model. Taking $f_{t,i}$ as the proportion of fentanyl-contact in region i at month t, the overall overdose rate is

$$\kappa_N(1 - f_{t,i}) + \kappa_F f_{t,i}. \tag{8}$$

Given $p^A_{t,i}$ for the probability that an ambulance was called for any given overdose at month t in region i, the per-capita rate of ambulance attended overdoses is

$$p^A_{t,i}(\kappa_N(1 - f_{t,i}) + \kappa_F f_{t,i}). \tag{9}$$

Data on whether an ambulance was called exists from January 2015 through the THN kit program, with no data existing for 2012, 2013 and 2014 (Table S2). In order to account for the missing data and that data only exists at a provincial level, the regional monthly probability was drawn from an underlying fixed provincial distribution with probability p_A. This value was set with a prior distribution based on initial assumptions around the ambulance call-out rate. The regional monthly ambulance call-out variables are assumed to be beta-distributed around the provincial call-out rate according to $p^A_{t,i} \sim B(p^A, \sigma_A)$ (note that the beta distribution is parameterised according to the mean and standard deviation, see Table S1 for summary of hyper-parameter values). The regional monthly variance σ^2_A was chosen such that the call-out rate prior varied smoothly from month to month and between region.

1.5 Effective population size model

The population was partitioned into three categories: individuals actively using drugs, who are at risk of an illicit-drug overdose $P_{t,i}$, individuals on treatment $T_{t,i}$, and individuals at an elevated risk of overdose due to relapse of treatment $R_{t,i}$. As a simplifying assumption, the population was assumed to remain at a dynamic equilibrium where those individuals leaving and entering the population remained balanced with the exception of individuals who had died of an illicit-drug overdose. The at-risk illicit-drug overdose population was modelled with a point estimate for each region N_i. This was derived from the persons who inject drugs (PWID) population estimate (See Table S2 for a description of data sources). In order to

account for the potential bias in this estimate, this parameter was modelled as normally-distributed with standard deviation $N_i/100$. Mis-specification and prior uncertainty has been explored within the previous study and also within this study's sensitivity analysis[3].

The total number of individuals on treatment was derived from data for each month and region, $T_{t,i}$. A risk reduction parameter, τ_{OAT} was applied to the population as the extent to which treatment reduces the overdose risk, with the assumption that individuals on treatment are at risk of coming into contact with the illicit drug-supply, but remain on OAT[4].

The population of individuals actively using drugs and not relapsing from treatment, who are at risk of an illicit-drug overdose, $P_{t,i}$ is then the total at-risk population N_i with the effective number of individuals on treatment $\tau_{OAT}T_{t,i}$, the number of individuals at elevated risk of overdose $R_{t,i}$, and the total number of deaths to date removed,

$$P_{t,i} = N_i - \tau_{OAT}T_{t,i} - R_{t,i} - \sum_{k=0}^{t-1} D_{k,i}. \tag{10}$$

The number of individuals at elevated risk of an overdose, $R_{t,i}$ are those individuals who have moved off OAT in a given month and region. This is estimated using a relapse rate γ, and assuming all individuals who have relapsed have rejoined the at-risk population within one month. This was modelled with a Poisson distribution, $R_{t,i} \sim Poi(\gamma T_{t,i})$. The elevated risk ratio for an individual who is relapsing is given as a factor κ_H. The weighted population size for a given month and region $\tilde{N}_{t,i}$, taking into account the relapsing population and the at-risk population is therefore,

$$\tilde{N}_{t,i} = P_{t,i} + \kappa_H R_{t,i}. \tag{11}$$

This weighted population takes into account both the active person who use drugs population ($P_{t,i}$) and a weighted proportion of individuals who are relapsing from treatment, weighted by their increased risk of an overdose ($\kappa_H R_{t,i}$). Although this is not strictly a population size, it does provide a total population risk of an overdose when combined with the per-capita overdose rate and has been defined for mathematical convenience.

1.6 Overdose intervention modelling

The two interventions that impact the probability of death following an overdose considered are the OPS/SCS and THN kits. If an individual overdoses then there is a probability that THN is effectively administered. There is also a probability that the overdose is observed at an OPS/SCS. If either is true then the individual survives. Otherwise, with a certain probability the individual dies from the overdose. Each intervention was therefore incorporated into a modified probability of death following an overdose as described below.

1.6.1 Take-home naloxone (THN) program

The probability that a THN kit is used during an overdose event is a composition of the probability that a kit is present during an overdose multiplied by the probability the kit is used by a bystander to effectively reverse the overdose. As many details on how kits have been distributed amongst the at-risk population are unknown, we defined an effectiveness parameter τ^N to include all the uncertainty in the impact of the program, as we assume no prior knowledge of this parameter it was given a uniform prior between 0 and 1 as was done in the previous study[3]. To account for the regional and monthly variability in the program effectiveness, this was modelled on a regional and monthly level, $\tau^N_{t,i}$. The number of THN kits that had

been distributed to people at time t and HA i ($K^D_{t,i}$) was used to estimate the probability that THN was used at any overdose event in region i and time t,

$$p^N_{t,i} = \tau^N_{t,i} \frac{K^D_{t,i}}{P_{t,i}}. \tag{12}$$

The modified death rate given the THN program, is therefore for region i at time t is the probability that THN was not used at an overdose event multiplied by the probability of a death following an overdose,

$$(1 - p^N_{t,i})\mu_{t,i}. \tag{13}$$

The provincial effectiveness of the THN program, τ^{THN}_t is modelled as a random-walk with drift $\mu_{thn} = 0$ and precision $\tau_{thn} = 10$, and then sampled for each region i at each month t from a beta distribution with variance σ_{thn}, $\tau^N_{t,i} \sim B(\tau^N_t, \sigma_N)$.

The rate of kits used for a given month and region, $k^r_{t,i}$, can then be calculated as the probability that a THN kit is used during an overdose event $p^N_{t,i}$, multiplied by the total number of overdoses $o_{t,i}$,

$$k^r_{t,i} = p^N_{t,i} o_{t,i}. \tag{14}$$

1.6.2 Overdose prevention sites & supervised consumption sites

The probability that an overdose occurs inside an OPS/SCS given that an overdose has occurred is derived from the OPS/SCS overdose witnessed data. This was modelled as the number of reported overdoses observed in an OPS divided by the estimated number of overdoses,

$$p^{OPS}_{t,i} = \frac{\#\{\text{reported overdoses observed in OPS in month } t \text{ and region } i\}}{o_{t,i}}. \tag{15}$$

Independence is assumed between the probability of an overdose being observed at an OPS and being intervened through the use of THN. This was justified as there is little to no overlap between THN kits used and overdoses observed at an OPS/SCS (see Table S2 for limitations). The probability of death following an overdose is therefore modified to be

$$(1 - p^N_{t,i})(1 - p^{OPS}_{t,i})\mu_{t,i}. \tag{16}$$

1.6.3 Intervention-impacted death rate

The intervention-modified probability of death following an overdose can then be combined with the total illicit-drug overdose rate and the fentanyl-related overdose rate to produce the rate of death for a given month and region. The illicit-drug overdose death rate $d_{t,i}$ is the rate of illicit-drug overdoses $o_{t,i}$, multiplied by the modified probability of death following an overdose,

$$d_{t,i} = (1 - p^N_{t,i})(1 - p^{OPS}_{t,i})\mu_{t,i} o_{t,i}. \tag{17}$$

Similarly, the fentanyl-related overdose death rate $d^f_{t,i}$ is the rate of fentanyl-related overdoses $o^f_{t,i}$, multiplied by the modified probability of death following an overdose,

$$d^F_{t,i} = (1 - p^N_{t,i})(1 - p^{OPS}_{t,i})\mu_{t,i} o^f_{t,i}. \tag{18}$$

1.7 Urinalysis sample modelling

Fentanyl-analogue contact was also modelled due to the availability of urinalysis data. We should not consider urinalysis data to be the definitive source of data regarding fentanyl adulterant in the general supply as these data are based on samples ordered by healthcare providers as part of treatment monitoring programs (See limitations in Table S2). As this was a biased source of data, it does not directly inform the proportion of fentanyl contact p_t^f. Instead, in order to incorporate these data, the proportion of carfentanil contact within those samples that tested positive for fentanyl was modelled. This then provides a trend for carfentanil and other fentanyl analogues in the illicit-drug supply. The proportion of fentanyl contacts that also come into contact with carfentanil p_t^c was modelled as a random walk with drift $\mu_c = 0$ and monthly precision $\tau_c = 10$. The proportion of urine samples testing positive for carfentanil of those that were positive for fentanyl ($p_t^{c,S}$) is assumed to be Beta distributed around the underlying carfentanil proportion $p_t^{c,S} \sim B(p_t^c, \sigma_c)$ (See Table S1 for summary of hyper-parameter values). The data-derived number of fentanyl positive samples at time t, F_t^S and the data-derived number of carfentanil positive samples (which are a subset of fentanyl samples) C_t^S are modelled through a binomial distribution $C_t^S \sim Bin(F_t^S, p_t^{c,S})$.

1.8 Rates summary

We summarise the rates and parameters for the model. For each region i and month t, the population at-risk is

$$P_{t,i} = N_i - \tau_{OAT} T_{t,i} - R_{t,i} - \sum_{k<=t} D_{k,i}. \tag{19}$$

Where $T_{t,i}$ is the number of individuals on treatment, $D_{t,i}$ is the number of deaths and the number of relapsing individuals, $R_{t,i}$ as

$$R_{t,i} \sim Poi(\gamma T_{t,i}). \tag{20}$$

The weighted population size, taking into account the relapsing population and the at-risk population is,

$$\tilde{N}_{t,i} = P_{t,i} + \kappa_H R_{t,i}. \tag{21}$$

The probability of a THN kit that has been distributed by time t in HA i $K_{t,i}^D$, $p_{t,i}^N$ is

$$p_{t,i}^N = \tau_{t,i}^N \frac{K_{t,i}^D}{P_{t,i}}. \tag{22}$$

The events, rate of overdose $o_{t,i}$, rate of fentanyl-detected death $d_{t,i}^F$, rate of overdose-related death $d_{t,i}$, rate of use of naloxone kit $k_{t,i}^r$, rate of ambulance-attended overdose $o_{t,i}^A$, and probability of death following an overdose $\mu_{t,i}$ are defined as,

$$o_{t,i} = (\kappa_N(1 - f_{t,i}) + \kappa_F f_{t,i})\tilde{N}_{t,i}, \tag{23a}$$
$$d_{t,i}^F = (1 - p_{t,i}^N)(1 - p_{t,i}^{OPS})\mu_{t,i} o_{t,i}^f, \tag{23b}$$
$$d_{t,i} = (1 - p_{t,i}^N)(1 - p_{t,i}^{OPS})\mu_{t,i} o_{t,i}, \tag{23c}$$
$$k_{t,i}^r = p_{t,i}^N o_{t,i}, \tag{23d}$$
$$o_{t,i}^A = p_{t,i}^A o_{t,i}, \tag{23e}$$
$$\mu_{t,i} = \exp(c_0 + c_p p_{t,i} + c_t t_{t,i} + c_w w_{t,i} + f_t^c \delta_t^c). \tag{23f}$$

1.9 Likelihood construction

The model likelihood is then composed of: the number of kits used, the ambulance-attended overdoses, the fentanyl-related deaths, the illicit-drug overdose deaths, the carfentanil positivity for fentanyl-detected urinalysis, and the surveyed number of ambulance call-outs. Each of these modelled data are described below.

Surveyed responses to calling an ambulance in a given month t, A_t, out of the total responses for that month N_t^A are modelled as a binomial,

$$A_t \sim \text{Bin}(N_t^A, p^A). \tag{24}$$

The number of kits used in HA i at time t, $K_{t,i}^R$ is modelled as a Poisson,

$$K_{t,i}^R \sim \text{Poi}(k_{t,i}^r). \tag{25}$$

The number of ambulance-linked overdoses, $O_{t,i}^A$ is modelled as a Poisson,

$$O_{t,i}^A \sim \text{Poi}(o_{t,i}^A). \tag{26}$$

The number of fentanyl-related overdose deaths at time t and HA i, $D_{t,i}^F$ is modelled as a Poisson,

$$D_{t,i}^F \sim \text{Poi}(d_{t,i}^F). \tag{27}$$

The number of illicit-drug related deaths at time t and HA i, $D_{t,i}$ is modelled as a Poisson,

$$D_{t,i} \sim \text{Poi}(d_{t,i}). \tag{28}$$

For a urine sample that was positive for fentanyl F_t^s, those that were additionally positive for carfentanil C_t^s are modelled as,

$$C_t^S \sim \text{Bin}(F_t^s, p_t^{c,S}). \tag{29}$$

2 Model fitting & posterior predictive distribution

The model fitting included regional monthly fits to ambulance-attend overdoses (Fig. S3), coroner-confirmed illicit-drug related deaths (Fig. S4), coroner-confirmed fentanyl-detected deaths (Fig. S5), number of take-home naloxone kits returned (Fig. S6), carfentanil positive urinalysis samples, and sampled ambulance call-outs. These data were incorporated into the likelihood as described in the previous section. The model was fit in a Bayesian framework using the variational Bayes scheme ADVI[5]. The approximate posterior was fitted for 200 000 steps. Replicate data y^{rep} were sampled from the posterior and used in model fit evaluation, cross-validation, and counterfactual analysis. The derived posterior $p(\theta|D)$ was sampled to produce a set of parameter samples $\{\theta_1, \ldots, \theta_m\}$. These samples were then applied to the sampling distribution $p(y|\theta)$, to produce m replicates of the data, $\{y_1^{rep}, \ldots, y_m^{rep}\}$. For the model evaluation, cross-validation and counterfactual analysis 10000 replicates were sampled separately for each analysis.

Goodness of fit was measured through four measures: the coverage of the 95% posterior predictive distribution, relative absolute error, root mean squared error (RMSE), and mean absolute error (MAE). The first statistic uses the posterior predictive distribution to determine how accurate the predictive distribution aligns with the observed data. For a given observable and time-point, the model can replicate the

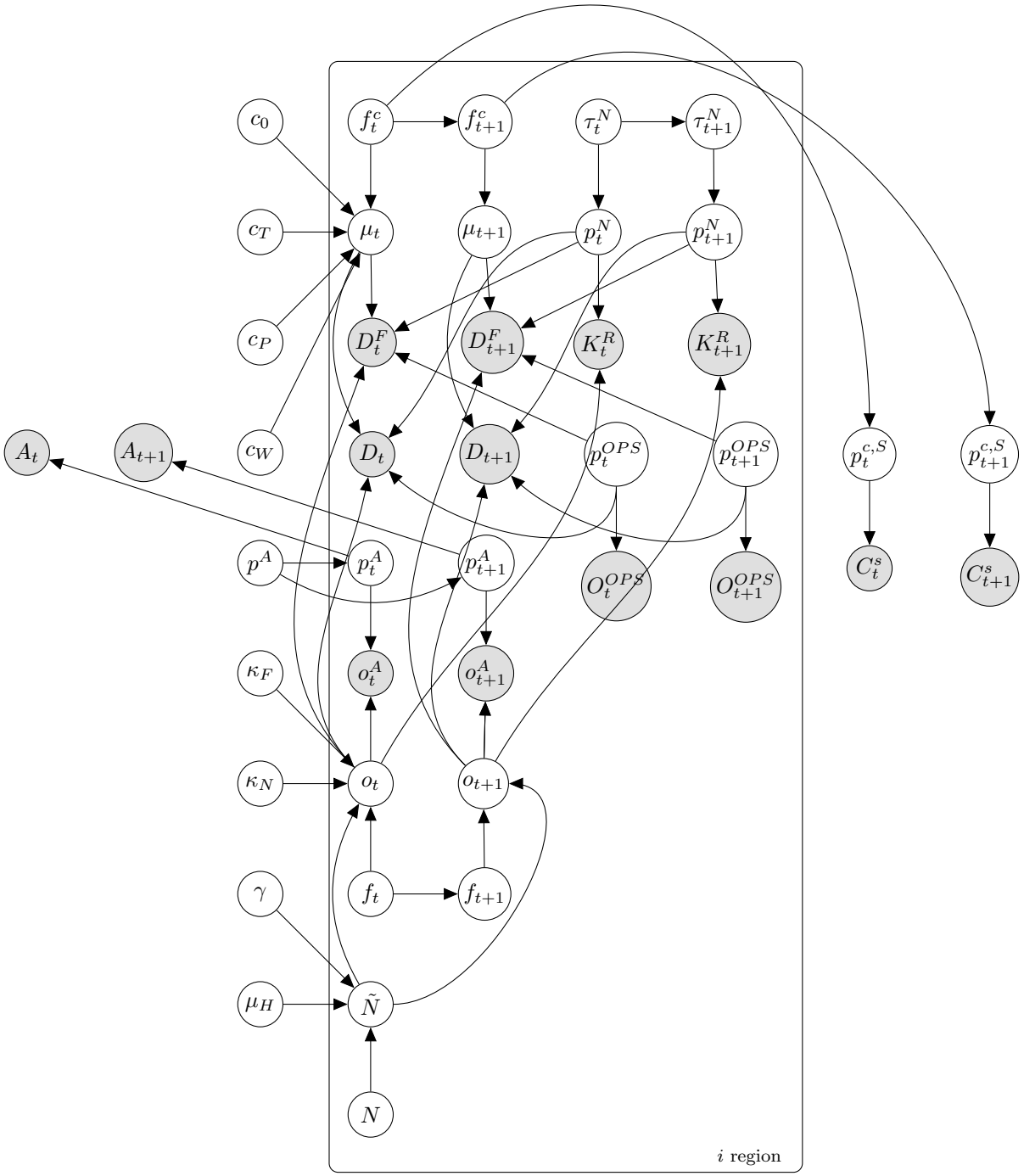


Figure S2: Overview of diagram in dynamics Bayes net plate notation with partially rolled-out form in time (showing only time-dependent variables at t and $t+1$). Latent parameters are white, with observations in grey. Provincial-based parameters and variables are on the left. Overdose and death-related variables are in the two columns one from the left, intervention-related variables are the two columns two from the right, with urinalysis variables are in the two columns on the far-right. Note hyper-parameters associated with random walks e.g. f_t, or p_t^A to $p_{i,t}^A$, have been suppressed here for clarity. Also note that some arrows in the time-dependent variables have also been suppressed for clarity e.g. c_0,c_T,c_P,c_W on μ_{t+1}.

observed data if it falls within the 95% posterior predictive distribution. The percentage of points that fall within the range was then calculated to produce the 95% posterior predictive distribution coverage.

The relative error is calculated by taking the absolute difference between the maximum a posteriori (MAP) at point t, m_t with the observed number plus one $o_t + 1$ and dividing by $o_t + 1$,

$$\frac{|m_t - o_t - 1|}{o_t + 1}. \tag{30}$$

The average percentage relative error is then calculated as the following mean,

$$100 \times \frac{1}{n} \sum_{t=1}^{n} \frac{|m_t - o_t - 1|}{o_t + 1}. \tag{31}$$

The RMSE was calculated by averaging over each month t, between the posterior-derived observable y_t^{rep} and the data y_t,

$$\sqrt{\frac{1}{n} \sum_{t=1}^{n} (y_t^{rep} - y_t)^2}. \tag{32}$$

The MAE was calculated similarly by taking the absolute difference between the posterior-derived observable and the data,

$$\frac{1}{n} \sum_{t=1}^{n} |y_t^{rep} - y_t|. \tag{33}$$

3 Validation

The main goal of the cross-validation methodology was to assess the out-of-sample error of each overdose-related observable at the regional level. This was achieved by fitting the model to all data excluding a single region and then predicting on the observables of that region. This cross-validation method gives a sense of how generalizable the model estimates are to other regions not directly observed.

Four forms of validation accuracy/error were considered: RMSE, MAE, the coverage of the 95% posterior predictive distribution, and relative absolute error. These statistics were calculated in turn for each region, and as an average for the province by combining the resulting accuracy and relative error for each region.

The cross-validation scheme was performed on the full model, with a modified likelihood where the data for coroner-confirmed deaths, ambulance-attended overdoses, and THN kits returned were removed for a region. All data from which rates were derived (e.g. kits distributed, overdoses witnessed at an OPS/SCS, population size) were still included for the region.

4 Model fitting results

The RMSE at the provincial level for ambulance-attended overdoses were 12.3 (MAE 9.0), for the illicit-drug overdose deaths were 3.8 (MAE 2.8), and fentanyl-related overdose deaths were 3.0 (MAE 1.8) (Table S4). There was some variability between the regions in terms of error of the model fit. For ambulance-attended overdoses regional fits, the lowest RMSE was 6.5 (MAE 5.1) and the highest was 14.7 (MAE 10.2). Illicit-drug overdose deaths had a regional RMSE range of 2.1–5.4 and a MAE range of 1.5–4.4. The fentanyl-detected overdose deaths had a regional RMSE range of 1.9 – 4.5 and a MAE range of 1.2–3.1 .

The model estimated a diverging number of monthly regional overdoses compared to ambulance-attended overdoses, due to shifts in the rate of ambulance call-outs (Fig. S3). These diverging trends were estimated to begin initially towards the end of 2015. By 2017 the total estimated overdoses were nearly double the ambulance-attended overdoses in some regions with high monthly variation in regions where the number of monthly overdoses was greatest. The number of take-home naloxone kits returned also show high variability in 2017 (Fig. S6). This is reflected in a model fit that is tightly constrained to the data, although there are two notable exceptions within two regions in August 2017. The tight fitting relationship is in part because the naloxone effectiveness (i.e. availability of distributed kits, use during an overdose and successful reversal) is allowed to vary as a latent time-series for each region in a hierarchical fashion.

4.1 Estimated covariate and latent states

The model also estimates the various probabilities following a randomly selected overdose event within a region for a given month in the study period (Fig. S10). These include whether a take-home naloxone kit was used (Fig. S10a), whether the overdose was witnessed at an overdose prevention site (Fig. S10b), whether an ambulance was called following an overdose (Fig. S10c), and whether a death occurred following an overdose (Fig. S10d).

The initial relatively small scale-up of the THN program is reflected in the low probability of less than 10% of THN use within the first three years since the program's inception (Fig. S10a). In 2015 some regions saw increases to of up to 20% within some regions, although this growth was not observed everywhere. In 2016 and 2017, this increased further reaching a maximum of 80% within one region for one month. There is a large degree of heterogeneity both in time and between regions, which reflects the variability in the number of kits returned as well as the variability in the estimated overdoses.

Overdose prevention sites also showed a wide-range of variability between months and regions. This was due to the the variability in when regions established sites and how many were established from late 2016 through 2017. By the end of 2017 the probability of an overdose occurring at a site was over 40% in one region, but negligible in others.

The probability of an ambulance call-out showed a general pattern of decline from the start of 2015 (approximately 65%), where estimates were first collected, to the end of 2017. The model estimated similar trends within each region up until mid-2017, where rates began to diverge in part due to the wider variability in overdoses and overdose-related deaths occurring in those months. The estimated ambulance call-out rate within certain regions could have dropped below 40%, although there is high month-to-month variation.

The trend in the probability of death following an overdose was informed by weather effects as well as the introduction of the potent fentanyl analogue carfentanil within the illicit drug supply (Fig. S10d). Weather was incorporated with the hypothesis that harsher conditions could lead to individuals using in isolation increase their risk of death following an overdose. There was found to be no strong association with this however, which is reflected in a static probability of death until late 2016. With the introduction of carfentanil into the supply in late 2016, there is an increase in the probability of death, where it remains higher with some variability throughout 2017.

The model fitting incorporates an estimated latent time-series of synthetic opioid adulterant within the general illicit-drug supply (Fig. S11). This was estimated at a regional level for fentanyl adulterant, due to the observed fentanyl-detected deaths within each region (Fig. S11a), and provincially for carfentanil adulterant due to lack of regional data (Fig. S11b). The general trend observed for fentanyl is a slow increase up until late 2015, with little variation between regions(Fig. S11a). In 2016 this rises and in 2017 there is a dramatic increase with a large amount of variability between months and regions reaching a

maximum of 55%. The provincial carfentanil contaminant within fentanyl was a-priori fixed at zero before cases were observed in late 2016. The model predicts the value increased and then remained at a constant level with some variability through 2017.

4.2 Prior & posterior comparison

The marginal distributions of the prior and posterior were compared for the fitted parameters (Table S5). The covariates associated with probability of death following an overdose all displayed significant updating from prior to posterior. The weather-dependent covariates (temperature, wind and precipitation), were all updated where the priors had high uncertainty (0.0–2×10^{10} 95 percentile range) to a tightly constrained region around one. This indicates that the model fitting did not find any of the weather covariates to significantly impact the change in the probability of death. The provincial-level probability of an ambulance call-out p^A, was significantly updated from 0.8 (0.78–0.82) to 1.00 (1.00–1.00). As a fixed hyper-parameter was used to describe the monthly and regional variance σ_A (see the Ambulance-linked overdoses and callouts subsection in the model overview), this meant that the monthly regional probability of an ambulance call-out did vary from 2015 – 2017 (see Fig. S10c). The model update is then reflective of the conditions before 2015 where data was not available. The estimates of at-risk population size for each region were not significantly updated during the model fitting. The increased rate of an overdose during relapse was strongly informed by the model likelihood from 180 (154–211) in the prior to 91 (90–92) in the posterior. This was also true of the rate of fentanyl related overdose (from 0.6227 (0.3657–1.0576) to 0.0781 (0.0774–0.0789)), as well as for non-fentanyl related overdose (from 0.0085 (0.0072–0.0099) to 0.0039 (0.0039–0.0040)). The rate of relapse from treatment was similarly updated from 0.0589 month^{-1} (0.0585–0.0594) or approximately 1.4 years to 0.0272 month^{-1} (0.0269–0.0275) or approximately 3 years. Finally the reduction in an overdose due to being on opioid agonist therapy did not change significantly from prior to posterior.

5 Validation Results

The regional average RMSE is 7.44 (MAE 4.9) for illicit-drug overdose deaths, 6.4 (MAE 3.7) for fentanyl-related overdose deaths, and 33.6 (MAE 83.1) for the overdoses.

The RMSE and MAE are not uniform across each region (Table S3). For overdoses, the lowest RMSE was observed for region 4 with 15.4 (MAE 11.5), and the highest was region 1 with RMSE 67.0 (MAE 40.8) (Fig. S7).

For illicit drug overdose deaths, the lowest RMSE was found for region 3 with 4.6 (MAE 2.9) and the highest was region 1 with 12.0 (MAE 7.3) (Fig. S8).

For the fentanyl-related overdose deaths, the lowest RMSE was region 2 with 3.8 (MAE 2.1) and the highest was region 1 with 13.5 (MAE 7.9) (Fig. S9). Overall, the error in prediction on each region and each observable is reasonable for the model given the highly variable nature of the overdose epidemic.

6 Sensitivity analysis

6.1 Impact of removing a dataset from fitting

We adopt an established method for assessing how data contributes to the main measured outcome by removing each dataset in turn and re-fitting the model in a cross-validation scheme[6]. The sensitivity of the main intervention outcome statistic (numbers of deaths averted) were compared for the model with full data to the models where a dataset was removed. This provides insight into how each dataset influences the overall fit and outcome on the important metrics used in the analysis. The datasets used in model fitting were the surveyed number of ambulances called, the number of illicit-drug related overdose deaths, the number of fentanyl related overdose deaths, the number of take home naloxone kits used, and the number of ambulance-attended overdoses. The main outcomes considered were the total provincial number of deaths averted, the provincial deaths averted due to take-home naloxone, the deaths averted due to overdose prevention sites and supervised consumption sites, and the deaths averted due to opioid agonist therapy. All outcomes were considered from January 2012 to December 2017.

The results are highlighted in Table S6. When surveyed ambulance call-out data are removed from the model fitting the total deaths averted estimate increases by 37% over the model where no data had been removed. This is mainly due to an increased estimate of the number of deaths averted due to take home naloxone (2335 (2125–2552) compared to 1650 (1540–1850), an increase of 42%). Without these data the prior estimate dominates leading to a probability of ambulance call-out closer to 100%. This in turn causes the deaths observed per estimated number of overdoses to be higher, meaning that an overdose overall is more risky and hence naloxone has a greater impact. Removing the death data, both the total illicit-drug related deaths and the fentanyl-detected deaths, leads to comparable deaths averted statistics to where no data are removed. The total deaths averted were reduced by 13%, the naloxone deaths averted were reduced by 17%, the OPS/SCS deaths averted were reduced by 21% , and the OAT deaths averted were reduced by 8%. The removal of fentanyl-detected deaths lead to slightly elevated statistics. The total deaths averted were increased by 17%, the naloxone deaths averted were increased by 13%, the OPS deaths averted were increased by 14%, and the OAT deaths averted were increased by 21%.

With removal of the number of take home naloxone use data, the total deaths averted estimate are greatly reduced by 43% (2547 compared to 3650). This was unsurprisingly due to the lowering of the estimated deaths averted due to naloxone (740 compared to 1650, reduction of 123%). The OPS/SCS deaths averted (difference of 9%) and OAT deaths averted (difference of 9%) remained relatively unaffected, however. The ambulance-attended overdose data (note this is different to the surveyed ambulance call-out data) had the biggest impact when removed from the model fitting. The total deaths averted were reduced by 76%. With deaths averted reductions of 78% for THN, 74% for OPS/SCS, and 61% for OAT.

6.2 Impact of changing priors

We explored the impact of changes to the prior on the main model outcomes. We investigated two scenarios: if the prior for population size had been mis-specified, and if the prior indicated no impact of the weather on mortality. The population prior for the baseline model was composed of a series of normal distributions for each region with mean of a single point-estimate for population at risk N_i, and a standard deviation of $N_i/100$. Due to the nature of this point estimate, it is likely that it is an under-estimate of the true size of the population at-risk. We explored how an increase in the population of 20% would impact the estimated deaths averted. We constructed a series of normally-distributed priors with mean $1.2N_i$, and standard deviation $N_i/100$.

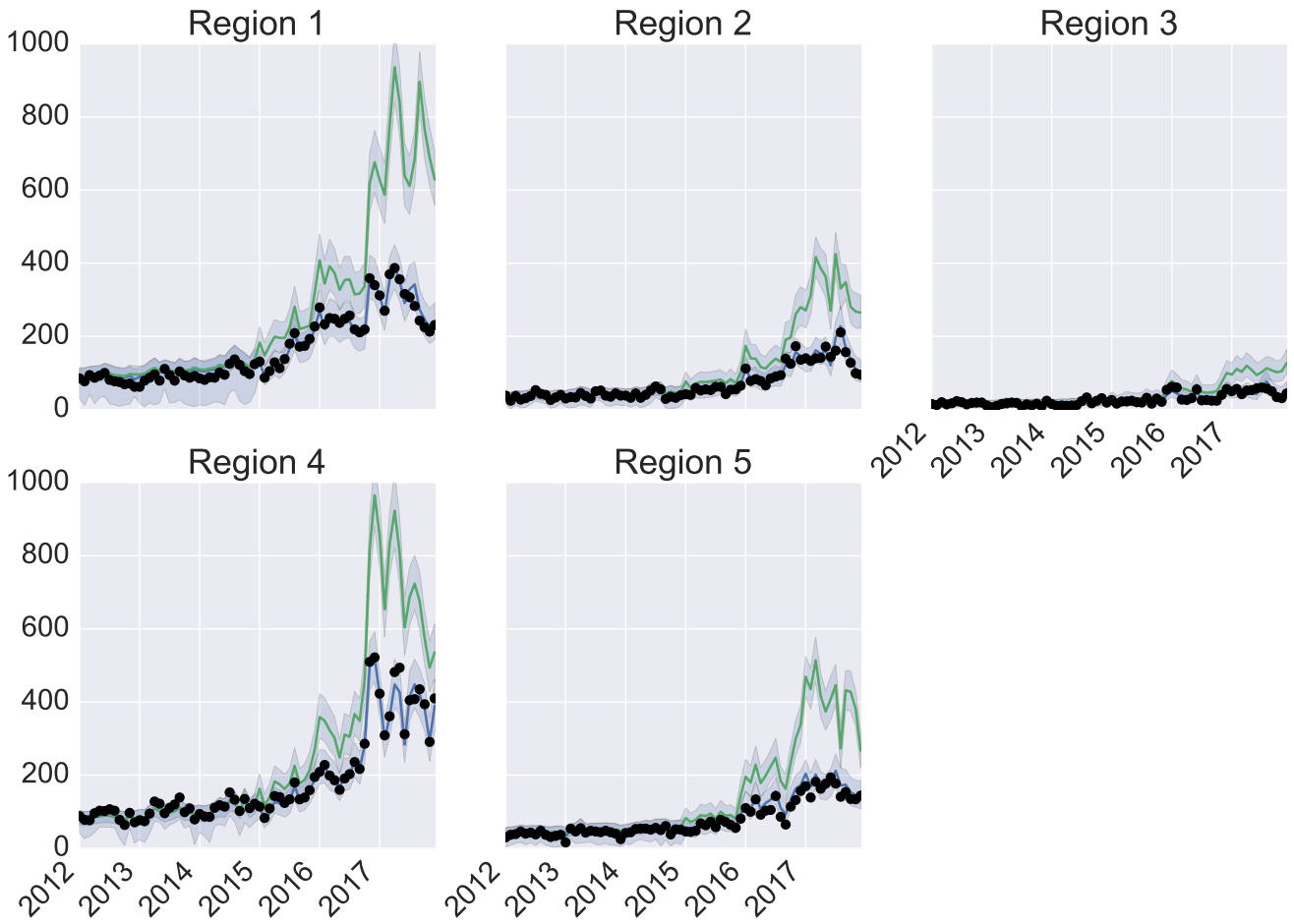


Figure S3: Model fit to regional observed ambulance-attended overdoses. Estimated ambulance-attended overdoses are shown in blue, with 95% credible interval as a shaded region, with observed data shown as black points. The total estimated overdoses are shown in green with a shaded region representing the 95% credible interval.

In the second scenario we investigated there being no impact of weather on mortality. This was constructed by implementing priors for the weather-dependent variables that indicate a very strong prior belief that there are no weather effects (c_W,c_T,c_P). The priors chosen were normally-distributed with with mean 0 and standard deviation 10^{-10} for each covariate.

For both scenarios there is negligible impact on the estimated deaths averted under all counterfactual analysis (Table S7). For the change in population size, the difference in total deaths averted to the baseline model was 0.3% (3640 deaths averted (95% crI 3500 – 3910)). For the absence of weather effects, the difference in total deaths was 4.4% (3800 deaths averted (95% crI 3670 – 4030)), which is well within the 95% posterior distribution of the deaths averted statistic in the baseline model, which had a range of 11%.

7 Figures

Figure S4: Model fit to regional observed coroner-confirmed illicit-drug overdose deaths. Estimated illicit-drug overdose deaths are shown in blue, with 95% posterior predictive distribution shown as a shaded region, with observed data shown as black points.

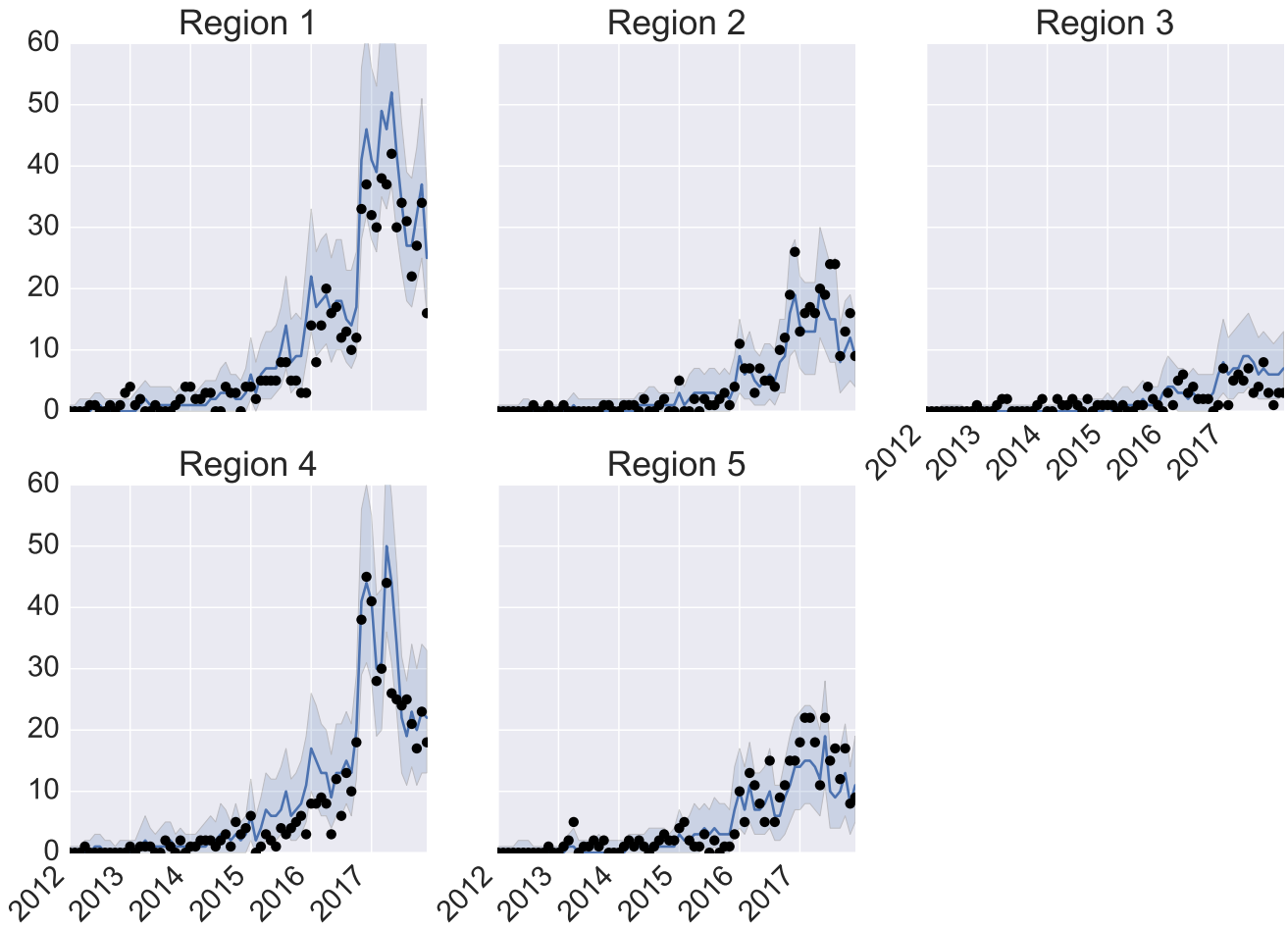


Figure S5: Model fit to regional observed coroner-confirmed fentanyl-detected overdose deaths. Estimated fentanyl-detected overdose deaths are shown in blue, with 95% posterior predictive distribution shown as a shaded region, with observed data shown as black points.

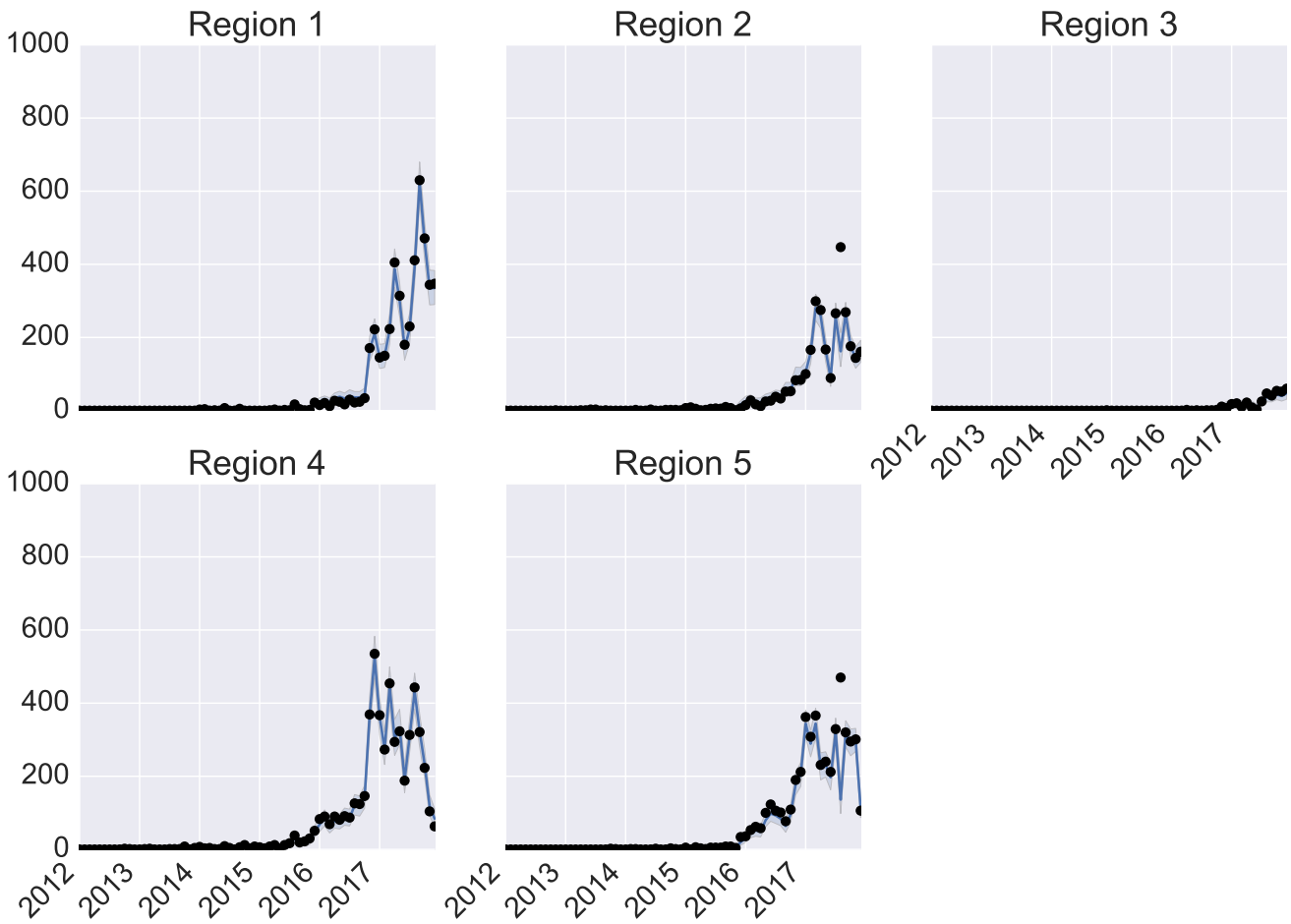


Figure S6: Model fit to regional monthly number of take-home naloxone kits returned due to use. Estimated kits returned are shown in blue, with 95% posterior predictive distribution shown as a shaded region, with observed data shown as black points.

Figure S7: Regional cross-validation comparison to monthly number of ambulance-attended overdoses. Estimated overdoses are shown in blue, with 95% posterior predictive distribution shown as a shaded region, with observed data shown as black points.

Figure S8: Regional cross-validation comparison to monthly number of illicit-drug related overdose deaths. Estimated deaths are shown in blue, with 95% posterior predictive distribution shown as a shaded region, with observed data shown as black points.

Figure S9: Regional cross-validation comparison to monthly number of fentanyl-related overdose deaths. Estimated deaths are shown in blue, with 95% posterior predictive distribution shown as a shaded region, with observed data shown as black points.

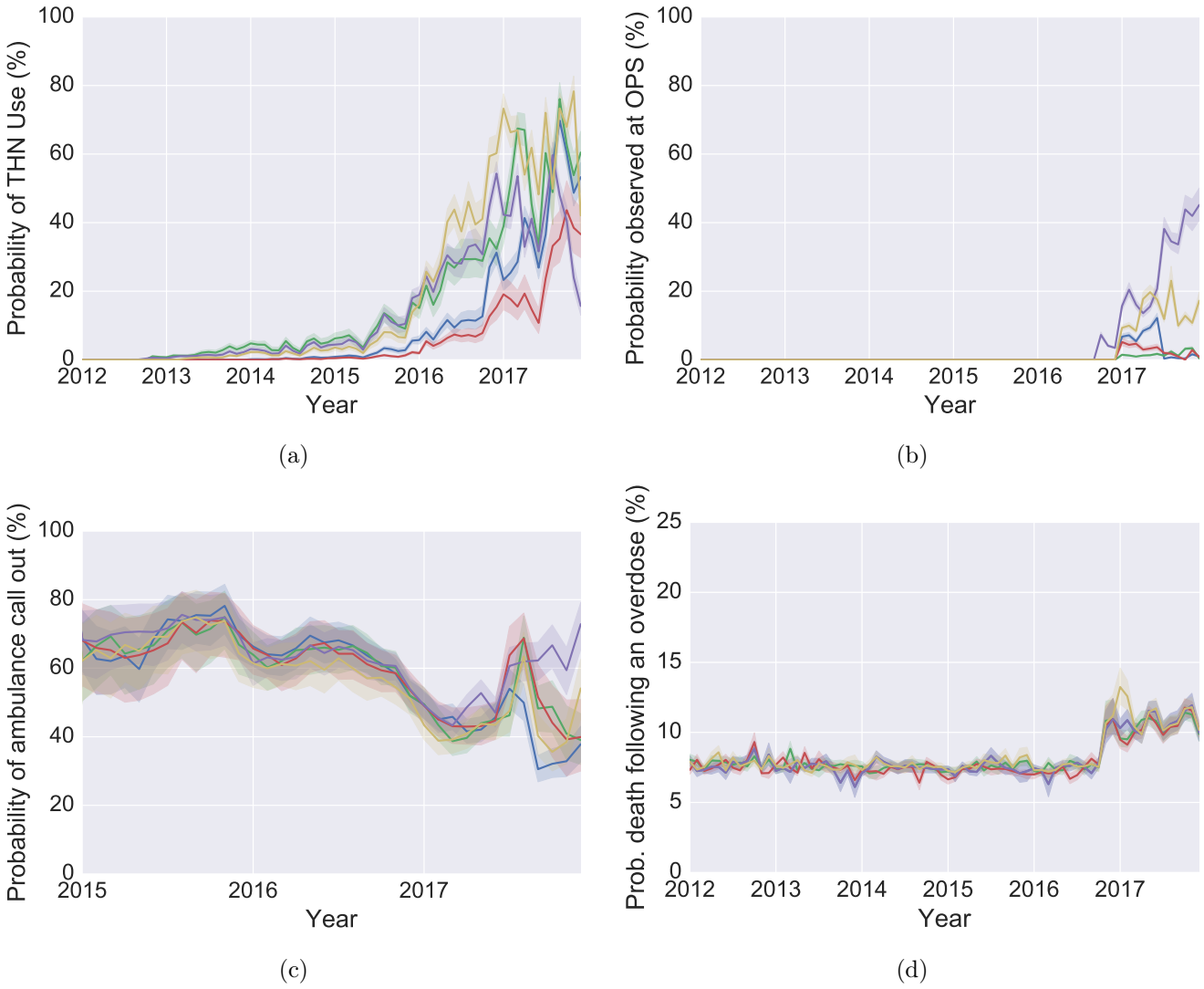
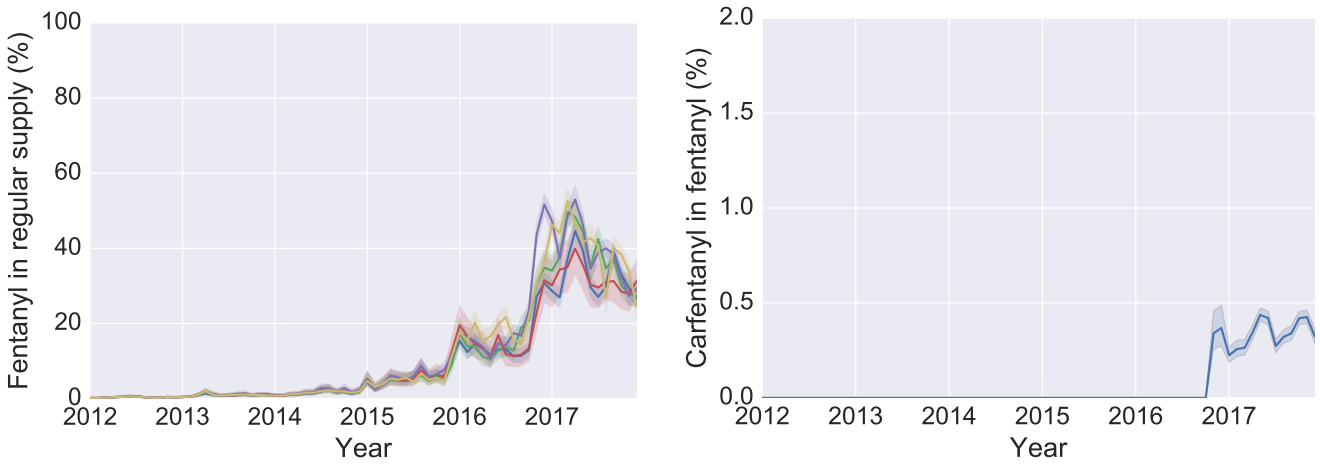


Figure S10: Probability of events following an overdose within each region **(a)** The probability of take-home naloxone kit use following an overdose. **(b)** Probability an overdose is observed at an overdose prevention site **(c)** The probability of an ambulance call-out following an overdose (from where ambulance call-out data exists beginning in 2015). **(d)** The probability of a death following an overdose.



(a) (b)

Figure S11: Synthetic opioid adulterant within the illicit-drug supply. **(a)** Regional proportion of contact with fentanyl within the illicit-drug supply. **(b)** Provincial carfentanil proportion within the fentanyl contaminated illicit drug supply.

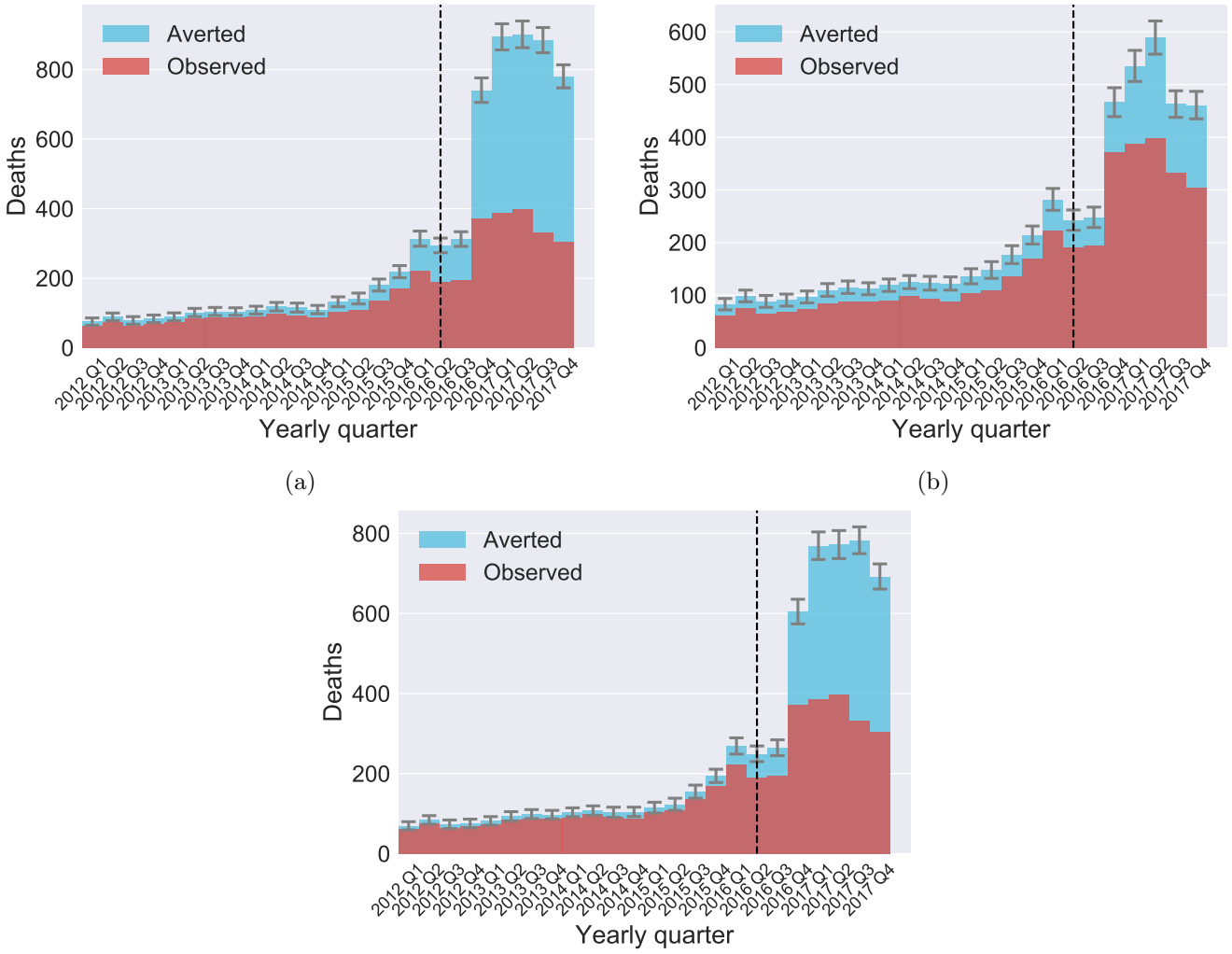


Figure S12: Pair-wise counterfactual scenarios **(a)** Impact of THN and OAT on the total number of illicit-drug overdose deaths **(b)** Impact of OPS and OAT on the total number of illicit-drug overdose deaths. **(c)** Impact of OPS and OAT on the total number of illicit-drug overdose deaths.

8 Tables

Parameter	Symbol	Value	SE	CI	Prior	Reference
Total size of at-risk population	N_i	varies by HA	$N_i/100$	varies by HA	Normal	[7]
Rate of overdosing (non-fentanyl) (month^{-1})	κ_N	0.008	6×10^{-4}	0.007–0.01	Gamma	[3,8]
Rate of overdosing (fentanyl) (month^{-1})	κ_F	0.6	0.2	0.4–1.0	Gamma	[3,9]
Increased risk of overdosing due to relapse	μ_H	181	13	156–208	Gamma	[3,10]
Rate of relapsing while on treatment (month^{-1})	γ	0.08	0.5	0–0.9	Gamma	[3,11]
Effectiveness of THN kit program	τ_N	0.5	-	0.025–0.975	Uniform	Assumption
Effectiveness of OAT	τ_{OAT}	0.89	0.01	0.87–0.90	Beta	[11]
Baseline log-death rate	c_0	0	10	-20–20	Normal	Assumption
Temperature log-death rate	c_T	0	10	-20–20	Normal	Assumption
Precipitation log-death rate	c_P	0	10	-20–20	Normal	Assumption
Wind-speed log-death rate	c_W	0	10	-20–20	Normal	Assumption
Provincial probability of an ambulance call-out	p_A	0.8	0.01	0.78 – 0.82	Beta	Assumption
Hyper-parameters						
Fentanyl random-walk trend	μ_f	0	NA	NA	NA	Hyper-parameter. Assumption.
Fentanyl monthly precision	τ_f	10	NA	NA	NA	Hyper-parameter. Assumption.
Carfentanil random-walk trend	μ_c	0	NA	NA	NA	Hyper-parameter. Assumption.
Carfentanil monthly precision	τ_c	10	NA	NA	NA	Hyper-parameter. Assumption.
THN effectiveness random-walk monthly trend	μ_{thn}	0	NA	NA	NA	Hyper-parameter. Assumption.
Carfentanil monthly precision	τ_{thn}	10	NA	NA	NA	Hyper-parameter. Assumption.
Baseline ambulance call-out probability	τ_A	0.8	0.1	0.7–0.9	Beta	Hyper-parameter. Assumption.
Ambulance call-out hierarchical parameter	σ_A	0.01	NA	NA	NA	Hyper-parameter. Assumption.
THN effectiveness regional variance	σ_{thn}	0.1	NA	NA	NA	Hyper-parameter. Assumption.
Carfentanil urinalysis variation	σ_c	0.1	NA	NA	NA	Hyper-parameter. Assumption.

Table S1: Table of prior parameters used in opioid overdose model. All parameters, with the exception of hyper-parameters were updated in the model fitting, these values reflect the prior uncertainty before observed data. Hyper-parameters were fixed at moderate values, such that data could strongly inform the time-dependent parameters on which they depended.

Model input	Source	Data collection	Case definition	Known limitations
Illicit-drug overdose deaths	BC Coroners Service	Autopsy reports	Street drugs (Controlled and illicit drugs: heroin, cocaine, MDMA, methamphetamine, illicit fentanyl etc.). Medications not prescribed to the decedent but obtained/purchased on the street, from unknown means or where origin of drug not known. Combinations of the above with prescribed medications.	
Fentanyl-detected overdose deaths	BC Coroners Service	Autopsy reports	Fentanyl or its analogues were detected, whether alone or in combination with other drugs, and the death resulted from illicit drug use. In the majority of deaths, fentanyl or its analogues were detected in combination with other drugs. Deaths were excluded if the fentanyl was known to be prescribed or the death was suspected to be due to intentional self-harm.	
Ambulance-linked overdoses	BC Ambulance Service	Administrative records	Codes associated with accidental opioid-overdose or probable overdose were selected	Overdoses where an ambulance was not called would not be accounted for
THN kits used	Provincial THN program	Kit replacement forms	The number of client re-fills due to client stating that a kit had be used	Only able to capture those clients who are returning a kit due to their use. Likely missing kits used where client does not return
THN kits distributed	Provincial THN program	THN request form	Registered THN sites are able to order THN kits for distribution to clients. Sites are expected to return distribution records on a regular basis. Distribution numbers represent the number of kits distributed according to records returned by THN sites	Numbers are reliant on reporting by THN sites and are likely an underestimate of the total number of kits given out to clients
OPS overdose	Provincial OPS	OPS staff	An overdose that is witnessed to have occurred within an OPS facility	
OPS site	Provincial OPS	Regional health authority	An OPS facility that is active in a given month	
Ambulance call-outs	Provincial THN program	kit forms	All returned forms where a kit was used and the question on whether an ambulance was called was answered	Only for kit forms returned, which may introduce a systematic bias

Table S2: **Data sources** Surveillance and intervention data collected for study including model input, source of data, data collection method, case definition, and any known limitations. Note table is incorporated into main manuscript and provided here for reference.

Model input	Source	Data collection	Case definition	Known limitations
Patients registered on OAT	Provincial Health Officer report & Pharmanet	Composition of hospital discharges, community pharmacies, and the provincial medical services plan claims	Patient registered to receive methadone or suboxone/buprenorphine	Data prior to 2015 was retrieved from an opioid substitution treatment performance measure report commissioned by the Provincial Health Officer[11]. Data post 2017 was taken from the BCCDC reported statistics. Where data overlapped, an average of the two was taken. Typically data differed by 1–5%
Weather	World Weather Online[12]	API	Monthly aggregated wind speed, precipitation and temperature located at most populous location in region	Weather statistics were taken from most densely populated urban area within each region
Fentanyl contaminant	LifeLabs	Urinalysis	Collected urine sample testing positive for fentanyl	Samples are requisition by OAT provider and hence represent a biased sample of the at-risk population. Testing only began in 2017.
Carfentanil contaminant	LifeLabs	Urinalysis	Collected urine sample testing positive for carfentanil	See above.
PWUD	Literature[7]	Estimated	Methodology based on known indications of injection drug use	Only captures injection drug use

Table S2: **Data sources** Surveillance and intervention data collected for study including model input, source of data, data collection method, case definition, and any known limitations. Note table is incorporated into main manuscript and provided here for reference.

region	observable	95% posterior coverage (%)	relative error (%)	MAE	RMSE
1	overdoses	94.4	27.8	40.9	54.3
1	deaths	81.9	32.0	7.3	12.0
1	fentanyl deaths	72.2	76.1	7.9	13.5
2	overdoses	98.6	18.4	11.5	15.4
2	deaths	93.1	35.4	3.0	5.0
2	fentanyl deaths	98.6	53.0	2.1	3.8
3	overdoses	73.6	52.1	14.2	20.0
3	deaths	84.7	74.4	2.9	4.6
3	fentanyl deaths	81.9	112.4	2.6	4.5
4	overdoses	70.8	19.0	40.8	67.0
4	deaths	66.7	49.0	7.0	9.6
4	fentanyl deaths	94.4	70.1	3.3	5.6
5	overdoses	94.4	22.4	16.4	25.3
5	deaths	90.3	43.1	3.8	6.0
5	fentanyl deaths	88.9	70.1	2.8	4.8

Table S3: **Cross-validation accuracy.** Cross-validation results with comparison to illicit drug related overdose deaths, ambulance-attended overdoses and fentanyl related deaths for the model excluding the provincial covariates. Each region was removed from the data, and the resulting posterior was used to predict on the out-of-sample region. The validation was compared using the percent overlap with the posterior predictive check, the relative absolute error, the mean absolute error (MAE), and the mean squared error (MSE).

region	observable	95% posterior coverage (%)	relative error (%)	MAE	RMSE
Provincial	overdoses	98.9	12.7	9.0	12.3
1	overdoses	98.6	10.2	12.4	15.5
2	overdoses	100.0	11.0	6.8	9.1
3	overdoses	100.0	21.9	5.1	6.5
4	overdoses	97.2	6.9	10.3	14.7
5	overdoses	98.6	13.4	10.2	13.5
Provincial	deaths	93.1	35.6	2.8	3.8
1	deaths	95.8	19.1	2.8	3.8
2	deaths	95.8	33.0	2.6	3.6
3	deaths	97.2	49.4	1.5	2.1
4	deaths	79.2	39.0	4.4	5.4
5	deaths	97.2	37.5	2.6	3.5
Provincial	fentanyl deaths	96.7	61.7	1.8	3.0
1	fentanyl deaths	94.4	51.2	3.1	4.5
2	fentanyl deaths	100.0	55.1	1.3	2.2
3	fentanyl deaths	93.1	81.1	1.2	1.9
4	fentanyl deaths	97.2	57.4	1.8	3.3
5	fentanyl deaths	98.6	63.5	1.7	2.5

Table S4: **Model fitting accuracy.** Model fitting accuracy and relative error for full model with all considered data and covariates. Model fit was assessed on the illicit drug related overdose deaths, ambulance-attended overdoses and fentanyl related deaths. The model fitting was compared using the percent overlap with the posterior predictive check, the relative absolute error, the mean absolute error (MAE), and the mean squared error (MSE).

Parameter	Prior	Posterior
Baseline death rate ($\exp(cT0)$)	1.0 (0.0–2×10^{10})	0.0682 (0.0663–0.0701)
Temperature covariate ($\exp(c_T)$)	1.0 (0.0–2×10^{10})	1.0011 (0.9988–1.0033)
Precipitation covariate ($\exp(c_P)$)	1.0 (0.0–2×10^{10})	0.9858 (0.9810–0.9906)
Wind covariate ($\exp(c_W)$)	1.0 (0.0–2×10^{10})	1.0092 (1.0075–1.0110)
Probability of ambulance call-out after an overdose (p^A)	0.8 (0.78–0.82)	1.000 (1.000–1.000)
Regional population estimate, region 1	13 300 (13 000–13 600)	13 300 (13 000–13 500)
Regional population estimate, region 2	5 600 (5 500–5 700)	5 600 (5 500–5 700)
Regional population estimate, region 3	3 300 (3 200–3 400)	3 300 (3 200–3 300)
Regional population estimate, region 4	12 900 (12 600–13 200)	12 900 (12 700–13 100)
Regional population estimate, region 5	6 800 (6 700–6 900)	6 800 (6 700–6 900)
Increased rate of overdosing due to relapse (μ_H)	180 (154–211)	91 (90–92)
Rate of fentanyl related overdose (κ_F) (month^{-1})	0.6227 (0.3657–1.0576)	0.0781 (0.0774–0.0789)
Rate of non-fentanyl related overdose (κ_N) (month^{-1})	0.0085 (0.0072–0.0099)	0.0039 (0.0039–0.0040)
Rate of relapse from treatment (γ) (month^{-1})	0.0589 (0.0585–0.0594)	0.0272 (0.0269–0.0275)
Reduction in overdose risk of OAT	0.1110 (0.0917–0.1336)	0.1102 (0.0942–0.1280)

Table S5: **Prior posterior comparison.** Parameter mean and 95% credible intervals for the marginal prior before fitting and the marginal posterior after fitting.

Data removed	Total deaths averted	THN deaths averted	OPS deaths averted	OAT deaths averted
none	3650 (3490–3910)	1650 (1540–1850)	390 (290 – 550)	960 (860–1150)
provincial ambulance call-out survey data	5013 (4709–5328)	2335 (2125–2552)	527 (359–699)	1088 (909–1267)
regional illicit-drug overdose deaths	3225 (2920–3550)	1410 (1214–1614)	323 (170–476)	886 (716–1063)
regional fentanyl-detected overdose deaths	4281 (3971–4610)	1866 (1653–2086)	444 (271–622)	1166 (977–1360)
regional take-home naloxone kits used	2547 (2326–2775)	740 (568–915)	427 (261–589)	1048 (868–1230)
regional ambulance-attended overdoses	883 (702–1068)	364 (192–537)	100 (-71–271)	371 (199–545)

Table S6: **Deaths averted sensitivity analysis to data source.** Robustness of deaths averted due to intervention statistics when different observations are removed from the model fitting and analysis. Median values from the posterior sample are shown with 95% credible interval shown in parentheses. The complete model fit, where no data are removed is highlighted on the top row.

Scenario	Total deaths averted	THN deaths averted	OPS deaths averted	OAT deaths averted
Base model	3650 (3490–3910)	1650 (1540–1850)	390 (290 – 550)	960 (860–1150)
Population estimates increased by 20%	3640 (3500 – 3910)	1700 (1590 – 1900)	410 (310 – 570)	900 (790 – 1 070)
No weather-dependent mortality	3800 (3670 – 4030)	1640 (1530 – 1820)	410 (310 – 570)	1060 (950 – 1200)

Table S7: **Deaths averted sensitivity analysis to priors.** Robustness of deaths averted due to intervention statistics when different priors are implemented into model fitting. The two scenarios explored were if the population priors had a 20% increase in the mean of their original values, and if the prior for weather-dependent effects was set strongly to there being no effect. Median values from the posterior sample are shown with 95% credible interval shown in parentheses. The complete model fit, with the baseline priors is indicated in the first row.

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