Identifying counties at risk of high overdose mortality burden during the emerging fentanyl epidemic in the USA: a predictive statistical modelling study

Charles Marks, Daniela Abramovitz, Christl A Donnelly, Gabriel Carrasco-Escobar, Rocío Carrasco-Hernández, Daniel Ciccarone,
Arturo González-Izquierdo, Natasha K Martin, Steffanie A Strathdee, Davey M Smith, Annick Bórquez

Summary

Background The emergence of fentanyl around 2013 represented a new, deadly stage of the opioid epidemic in the USA. We aimed to develop a statistical regression approach to identify counties at the highest risk of high overdose mortality in the subsequent years by predicting annual county-level overdose death rates across the contiguous USA and to validate our approach against observed overdose mortality data collected between 2013 and 2018.

Methods We fit mixed-effects negative binomial regression models to predict overdose death rates in the subsequent year for 2013–18 for all contiguous state counties in the USA (ie, excluding Alaska and Hawaii). We used publicly available county-level data related to health-care access, drug markets, socio-demographics, and the geographical spread of opioid overdose as model predictors. The crude number of county-level overdose deaths was extracted from restricted US Centers for Disease Control and Prevention mortality records. To predict county-level overdose rates for the year 201X: (1) a model was trained on county-level predictor data for the years 2010–201(X–2) paired with county-level overdose deaths for the year 2011–201(X–1); (2) county-level predictor data for the year 201(X–1) was fed into the model to predict the 201X county-level crude number of overdose deaths; and (3) the latter were converted to a population-adjusted rate. For comparison, we generated a benchmark set of predictions by applying the observed slope of change in overdose death rates in the previous year to 201(X–1) rates. To assess the predictive performance of the model, we compared predicted values (of both the model and benchmark) to observed values by (1) calculating the mean average error, root mean squared error, and Spearman's correlation coefficient and (2) assessing the proportion of counties in the top decile (10%) of overdose death rates that were correctly predicted as such. Finally, in a post-hoc analysis, we sought to identify variables with greatest predictive utility.

Findings Between 2013 and 2018, among the 3106 US counties included, our modelling approach outperformed the benchmark strategy across all metrics. The observed average county-level overdose death rate rose from 11·8 per 100 000 people in 2013 to 15·4 in 2017 before falling to 14·6 in 2018. Our negative binomial modelling approach similarly identified an increasing trend, predicting an average 11·8 deaths per 100 000 in 2013, up to 15·1 in 2017, and increasing further to 16·4 in 2018. The benchmark model over-predicted average death rates each year, ranging from 13·0 per 100 000 in 2013 to 18·3 in 2018. Our modelling approach successfully ranked counties by overdose death rate identifying between 42% and 57% of counties in the top decile of overdose mortality (compared with 29% and 43% using the benchmark) each year and identified 194 of the 808 counties with emergent overdose outbreaks (ie, newly entered the top decile) across the study period, versus 31 using the benchmark. In the post-hoc analysis, we identified geospatial proximity of overdose in nearby counties, opioid prescription rate, presence of an urgent care facility, and several economic indicators as the variables with the greatest predictive utility.

Interpretation Our model shows that a regression approach can effectively predict county-level overdose death rates and serve as a risk assessment tool to identify future high mortality counties throughout an emerging drug use epidemic.

Funding National Institute on Drug Abuse.

Copyright © 2021 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

The opioid epidemic in the USA caused more than 400 000 documented opioid overdose deaths between 1999 and 2018, with 46 000 deaths in 2018 alone.[1,2] In particular, fentanyl, a synthetic opioid that is about 50 times more potent than heroin, emerged in the illicit drug market in eastern USA in 2013 as an adulterant of, or substitute for, heroin.[3–5] In 2012, synthetic opioid overdose resulted in fewer than 1 death per 100 000 individuals.[6] By 2018, synthetic opioids were responsible for nearly 10 deaths per 100 000—over 31 000 deaths—accounting for 65% of all opioid overdose deaths for that year.[6]

Rather than a uniform increase in opioid-related mortality, the opioid overdose crisis is the latest in a decades long series of escalating geographically concentrated, time-specific and drug-specific overdose outbreaks dating

Interdisciplinary Research on Substance Use Joint Doctoral Program, San Diego State University and University of California, San Diego, CA, USA (C Marks MPH); **Department of Medicine, University of California, San Diego, CA, USA** (D Abramovitz MS, G Carrasco-Escobar MS, R Carrasco-Hernández PhD, N K Martin DPhil, Prof S A Strathdee PhD, Prof D M Smith MD, A Bórquez PhD); **Department of Statistics, University of Oxford, Oxford, UK** (Prof C A Donnelly ScD); **MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College London, London, UK** (Prof C A Donnelly); **Health Innovation Lab, Institute of Tropical Medicine "Alexander von Humboldt", Universidad Peruana Cayetano Heredia, Lima, Peru** (G Carrasco-Escobar); **Department of Family and Community Medicine, University of California, San Francisco, CA, USA** (Prof D Ciccarone MD); **Institute of Health Informatics, University College London, London, UK** (A González-Izquierdo PhD); **Population Health Sciences, University of Bristol, Bristol, UK** (N K Martin)

Correspondence to:
Mx Charles Marks, Interdisciplinary Research on Substance Use Joint Doctoral Program, San Diego State University and University of California, San Diego, CA 92182, USA
cmarks@sdsu.edu

Research in context

Evidence before this study

The rapid diversification in synthetic opioids of increased potency, the expansion of drug markets via the dark web, and the increases in polydrug use associated with higher risk of health harms are all contributing to the emergence of increasingly rapid and harmful fatal overdose outbreaks in the USA. To mitigate future harms, it is crucial to predict where and when opioid use-related outbreaks will occur and plan for a pre-emptive response. We reviewed the literature to identify quantitative studies aimed at predicting public health outbreaks associated with opioid use epidemics in the USA by searching for the following terms in PubMed on Jan 20, 2021: ("Substance-related disorders"[MeSH] OR drug use[tiab] OR opioid[tiab]) AND (outbreak[tiab] OR "epidemics"[MeSH] OR overdose[tiab]) AND ("statistics as topic"[MeSH] OR "regression analysis"[MeSH] OR statistic*[tiab] OR predictive[tiab] OR model[tiab]) AND ("United States"). Although the search retrieved more than 1000 studies, 46 were directly relevant to our research question as most used an explanatory framework and few extended it for predictive purposes. An influential US Centers for Disease Control study by Van Handel and colleagues aimed to assess the risk of injection drug use for outbreaks associated with HIV and hepatitis C virus across US counties. However, their methods have not been validated and did not include fatal overdose as an outcome. A study by Sumetsky and colleagues addressed the urgent need for overdose outbreak prediction models and tested the performance of two statistical methods (standard log–linear *vs* log–logistic Bayesian hierarchical Poisson conditionally autoregressive spatial models) in predicting overdose deaths by county in two states in 2001–14. Although their findings are promising, they have not yet been evaluated across the entire country, which is important given the high geographical heterogeneity in overdose outcomes in the USA. Another study by Lyle Cooper and colleagues used three-degree polynomial models to investigate fatal overdose dynamics in 2012–16 by state, disaggregating rates by heroin, semi-synthetic, and synthetic opioids. They identified states with highest elasticity (ie, rate of change over time) for each of the opioid sub-epidemics. These findings are useful in terms of improving our understanding of different opioid sub-epidemics dynamics; however, there is no assessment of the model's predictive performance and how outputs might be operationalised to inform policy. Finally, a 2020 study by Campo and colleagues applied a variation of the random forest algorithm to predict state and county-level overdose death rates, by using concurrent Google search trends as model predictors. Predictive performance was high, but they

used publicly available overdose death data, hiding much of the heterogeneity across smaller counties. There remains a need to further develop the nascent field of overdose epidemic prediction through the design and validation of analytic methods that provide actionable information to guide the response at national and local levels in the context of emerging drug use epidemics.

Added value of this study

In this study, using publicly available predictor data, we implemented and validated a mixed-effects negative binomial regression method for predicting county-level overdose death rates in the subsequent year from the emergence of fentanyl in 2013–18, across the contiguous USA. We compared our yearly overdose mortality predictions to observed data and to a simple predictive benchmark to further characterise our model's predictive value. To produce meaningful results to guide policy, we identified counties in the top mortality decile and those newly entering that category (corresponding to counties with emerging outbreaks). We showed that, if our method had been implemented in real time, we would have had an improved capacity to identify counties at the highest risk of experiencing overdose outbreaks throughout the fentanyl wave of the opioid crisis.

Implications of all the available evidence

Taken together, to address the harms of the opioid crisis in the USA, it is crucial that available analytic approaches be used to identify localities at the highest risk of experiencing an overdose outbreak in the near future. Our study contributes to ongoing efforts to strengthen our epidemiological toolset to inform the opioid response, and the development of further quantitative methods, including geospatial, machine learning, and dynamic modelling approaches should be encouraged. Notably, timely and geographically representative data on drug use, associated outcomes, and drug markets are crucial to increasing predictive power of these tools. A stronger drug market surveillance infrastructure is needed. Further, it is important that strategies to disseminate findings to relevant stakeholders be implemented. Here, we display our findings through an interactive dashboard (ODPredict Explorer) to illustrate how such technology can aid in the transparent dissemination of predictions. By improving our ability to make such predictions and relay this information to appropriate stakeholders, we will improve our ability to swiftly and precisely allocate resources and implement responses to effectively mitigate potential overdose harms.

back to at least 1979.[7,8] The current crisis has been described as a quadruple wave of overdoses due to opioid pills, escalating heroin-related overdose, a crescendo in synthetic opioid deaths, and, most recently, by an increase in synthetic opioid deaths involving stimulants.[5,9] In the second and third waves, while the national opioid overdose

death rate rose steadily over the past decade, mortality has been concentrated within specific regions—primarily the Midwest, Appalachia, and New England.[5,6] However, increasingly greater synthetic opioid overdose death rates are being reported in the West, which is likely to have been exacerbated by socioeconomic, health-care, and drug

market disruptions associated with the COVID-19 pandemic.[10] This situation illustrates the need for the rapid development of tools to predict potential overdose outbreaks, particularly in localities that have not yet had fentanyl-related overdose outbreaks.

The primary aim of this study was to validate the application of a statistical modelling approach for identifying counties in the USA at highest risk of a drug overdose outbreak in the next year, throughout the fentanyl epidemic, by predicting county-level overdose death rates. Unfortunately, inconsistent and poor reporting of drug-specific overdose mortality[11] across counties inhibits us from modelling fentanyl-specific overdose outbreaks. We developed a series of regression models to predict county-level overdose death rates in the subsequent year in the USA for 2013–18. We validated our predictions against existing data on overdose death rates for each year to show how such a predictive tool could have been used throughout the course of the epidemic.

Methods

Data preparation

We aggregated annual, county-level data for both outcomes and predictors for all contiguous state counties in the USA (ie, excluding Alaska and Hawaii) for 2010–18.

The primary outcome was county-level crude overdose death rate for the next year (ie, predictors from year n are paired with overdose death rate from year n+1). This outcome was extracted from the US Centers for Disease Control and Prevention (CDC) WONDER restricted database (using underlying cause of death codes X40-44, X60-64, X85, and Y10-14). Due to statistical disclosure control, the CDC does not publicly report the number of overdose deaths for a given county in a given year if the absolute total was less than 10 to protect individual privacy. Following the request protocol from the CDC, we were given access to the full dataset with overdose death rates reported for all counties. To be consistent with CDC's protections, we will not report or reflect on an individual county's overdose death rate. Because this study relied on the use of secondary de-identified county-level data, the Institutional Review Board of the University of California San Diego determined that an ethics review was not required.

We obtained predictors included as fixed effects in our modelling approach (table 1) from publicly available databases reporting county-level estimates throughout the study period. They were chosen to be consistent with previous analyses modelling risk of overdose in the USA, including indicators of health-care access, drug markets, socioeconomic indicators, and the geographical spread of the epidemic over time.[12–15] To estimate the county-level availability of opioid use disorder treatment, we included the total number of physicians approved to prescribe buprenorphine by the Substance Abuse and Mental Health Administration for each given year. As well, to operationalise access to emergency health care, we included a

	Description	Source*
Health-care access		
Buprenorphine-waivered physicians	Crude number of physicians approved to prescribe buprenorphine for each given year	SAMHSA
Urgent care presence	Presence of an urgent care facility within county	HSIP Gold
Drug markets		
Opioid prescription rate	Opioid prescribing rate per 100 people each year	CDC (IQVIA Xponent)
Log fentanyl seizure data	State-level count of fentanyl tested in local, state, and federal forensic laboratories each year	NFLIS
Log jail population size	The log of the jail population size	VERA
Socioeconomic indicators		
High school graduation rate	Proportion of people living in the county estimated to have graduated from high school or received an equivalent certification	ACS
Poverty rate	Proportion of households in the county estimated to be living at or below the poverty line	ACS
Unemployment rate	Proportion of people able to work in the county estimated to be unemployed	ACS
Employee capacity difference	Difference in the employment capacity (measured as number of staff employed) of all companies across industries between current and past year in the county	CBP
Payroll difference	Difference in payroll (measured in US dollars) of all companies across industries between current and past year in the county	CBP
Log median household income	The log of the estimated median household income in the county	ACS
Proportion of homeowner households that spend at least 35% of income on mortgage	The proportion of homeowner households in the county that are estimated to spend at least 35% of their income on their mortgage	ACS
Proportion of renter households that spend at least 35% of income on rent	The proportion of renter households in the county that are estimated to spend at least 35% of their income on their rent	ACS
Geographical spread of epidemic		
Log overdose gravity	Continuous variable generated to operationalise overdose death rates in neighbouring counties. To derive the gravity variable for a given county x in year t, we first identified the set of all counties Y within 200 miles of county x. Distances were measured from central, internal points in each county and were extracted from a dataset created by the US National Bureau of Economic Research. Second, for each county y in Y, we divided the overdose death rate for county y in the year t by the distance between counties x and y, squared. Third, we summed the values calculated in the previous step for each county y in Y. Finally, we took the natural logarithm of this summed value to get the final value	NBER
Urbanicity	A six-category variable based on US Office of Management and Budget 2013 determination of metropolitan statistical areas, coded on a spectrum from most urban (1) to most rural (6)	NCHS

ACS=Census American Community Survey. CBP=County Business Patterns. CDC= Centers for Disease Control and Prevention. HSIP=Homeland Security Infrastructure Program. NBER=National Bureau of Economic Research. NCHS=National Center for Health Statistics. NFLIS=National Forensic Laboratory Information System. SAMHSA=Substance Use and Mental Health Services Administration. VERA=VERA Institute of Justice. *Detailed source information for each variable is provided in the appendix (pp 3–5).

Table 1: Predictors included as fixed effects in the final modeling approach

binary variable measuring the presence of an urgent care facility within the given county. We included the county-level opioid prescription rate per 100 people and the state-level count of substances identified as including fentanyl in local-level, state-level, and federal-level forensic laboratories. We included the log of the jail population and socioeconomic indicators, such as unemployment rate,
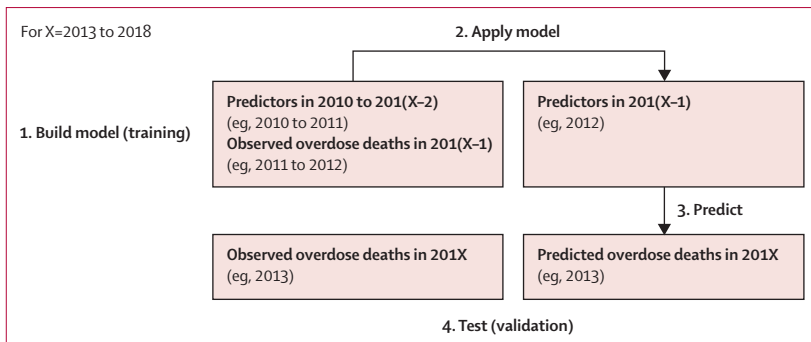
Figure 1: Workflow of our modelling approach
Predictors from the years 2010 to 201(X–2), paired with respective overdose outcomes from 2011 to 201(X–1) were used to train each model. Then, predictors from the year 201(X–1) were fed into the model to predict the overdose death rate in 201X. Finally, these predicted rates were compared with the observed rates for 201X to evaluate the model's predictive accuracy.

See **Online** for appendix

extracted from the Census American Community Survey. Consistent with health-related machine learning recommendations,[16] we do not hypothesise whether there is a relationship between race and overdose that is not mediated or confounded by latent structural racism (such as disparate opioid prescription patterns by race);[17] thus we do not include race as a predictor (appendix p 4). Finally, to account for the geographical spread of overdose death, we included a categorical measure of county urbanicity and a continuous gravity variable accounting for the overdose death rates of nearby counties. We provide full detail on the selection of variables in the appendix (pp 3–5), including our assessment of predictor collinearity.

Statistical modelling approach

We applied our modelling approach to predict overdose death rates for each year from 2013 to 2018. When predicting a given year (eg, 201X), the model is trained on paired predictor-death rate data from years 2010 to 2 years before the prediction year (201X–2). Predictor data for a given year is paired with the crude number of overdoses that occurred in the subsequent year as the model outcome. Then, predictors from the year before the prediction year (201X–1) are fed into the model (which specifies coefficients relating each predictor to the outcome) to predict county-level crude number of overdose deaths for 201X, which is then converted into a population rate (per 100 000).

For example, as shown in figure 1, to predict 2013 overdose death rates: 1) a model is trained using longitudinal predictor data from 2010–11 (paired with outcomes for 2011 and 2012, respectively); 2) predictor values from 2012 are then fed into the model to predict 2013 overdose death counts; 3) the predicted death counts are converted into overdose death rates (ie, deaths per 100 000); and 4) the predicted overdose death rates for 2013 are compared with the actual overdose death rates to evaluate predictive accuracy.

For predicting each year's overdose death rates, we applied mixed-effects negative binomial regression. A detailed discussion justifying our chosen modelling approach can be found in the appendix (p 1). A random intercept for each county was incorporated with a random slope for year. This model specification accounts for two hypothesised relationships within the data: 1) overdose death observations from the same county are correlated (justifying the random intercept for each county) and 2) the rate of change in overdose deaths will be dependent on the epidemic stage in a given county (justifying the application of random slopes for year). We also included an offset term for the log of the population carrying capacity, similar to Sumetsky and colleagues.[18] We hypothesised that as more overdose deaths occur in a location, the population of susceptible individuals would diminish. Thus, we defined carrying capacity as 5% of the 2010 county population minus the number of overdoses in the county in the previous 3 years (or the previous available years in the data for years 2011 and 2012), setting 50 as the minimum possible carrying capacity (appendix pp 2–3). The outcome of the model was the number of overdose deaths in the subsequent year in each county. We included each variable in table 1 as a fixed effect. Given that our goal was to simulate real-time prediction and that we cannot know the accuracy of model performance a priori, it would be unrealistic to choose a set of optimally performing fixed effects.

We used the lme4 package in R for all analyses.[19,20] Further details and code for running the analyses are available in the appendix (pp 13–19).

Prediction evaluation approach

We consider five primary metrics for assessing model performance. The first three, mean average error (MAE), root mean square error (RMSE), and Spearman's r, measure the accuracy of outcome predictions. The MAE is the average magnitude of the difference between the predicted and observed overdose death rate for each county. The RMSE is the square root of the average magnitude of the difference squared, therefore is similar to MAE but penalises prediction errors with greater magnitude. More accurate predictions will result in smaller MAE and RMSE. Spearman's r compares the predicted ranking of counties by overdose death rate compared with the actual observed rankings; results closer to 1 indicate that the model was more effective at rank-ordering counties based on overdose death rate.

The final two metrics seek to assess how well the model identified counties at highest risk of an overdose outbreak in the subsequent year (defined by an overdose death rate in the top decile relative to other counties). To do so, we first disaggregated the predicted and observed overdose death rates into deciles (10th, 20th, [...], 100th centile) and categorised all counties into their corresponding decile for both predicted and observed overdose rates. The first metric is the proportion of counties observed in the top decile (ie, top 10% of observed overdose death rates) that were rightly predicted to be in the top decile. To characterise model performance identifying counties

with emergent overdose outbreaks, we then defined such an emergent outbreak as a county being outside of the top decile in the year 201(X–1) and then entering the top decile in year 201X. The second metric is the proportion of all observed emergent outbreak counties that the modelling approach accurately predicted as newly being in the top decile in 201X.

To contextualise the results, we generated benchmark predictions for comparison. This benchmark strategy assumed the change in overdose death rate between years 201X–2 and 201X–1 would remain the same between the years 201X–1 and 201X. We calculated the slope for the change in overdose death rate from year 201X–2 to 201X–1 and added it to the 201X–1 overdose death rate to predict the 201X rate. If the value predicted for a county for a given year was below 0, we rounded it up to 0. This heuristic approach provides a simple, yet intuitive, way to predict future overdose death rates; the utility of our modelling approach can be understood in comparison to the performance of this benchmark approach.

Data exploration application

To address the challenges in presenting county-level data for all of the contiguous USA, we provide a web application, ODPredict Explorer, that can be used to explore the data in various ways. We provide this dashboard as an aid to this manuscript and to display how such findings can be readily disseminated to appropriate stakeholders. In accordance with CDC data protections, we have censored data that are not available in the unrestricted CDC mortality records.

Post-hoc analyses

It is of interest to understand the contribution of fixed effects to the predictive accuracy of the model. When making predictions, it is also uncertain what the best set of fixed effects will be, given that the model cannot be evaluated until after the predicted events occur. We used a bootstrapped forward variable selection strategy similar to that described by Beyene and colleagues to identify the fixed effects with the greatest predictive utility (appendix p 6).[21] We focus only on predicting overdose death rate for the year 2018 and the metric we are seeking to optimise is the proportion of counties correctly predicted in the top decile.

We ran 100 bootstrap iterations. We display, as the result, the proportion of times that each variable was included in the final model. Fixed effects that are chosen more frequently are considered to have greater predictive value than are fixed effects chosen less frequently.

We also used model diagnostics and a sensitivity analysis that involved applying the model in the eastern and western regions of the USA to confirm its results are robust to changes in the model training process (appendix pp 7–10). For the sensitivity analysis, we ran the analytic approach described separately for counties east and west of the Mississippi River, respectively. We evaluated the results to

	Observed mean overdose death rate	Benchmark prediction	Negative binomial prediction
2013	11·8	13·0	11·8
2014	12·6	14·1	11·5
2015	13·1	14·7	12·3
2016	14·6	15·8	13·3
2017	15·4	18·0	15·1
2018	14·6	18·3	16·4

Table 2: Mean observed, benchmark prediction, and model prediction of county-level overdose death rates per 100 000 for 2013–18

determine if the model still performed adequately when trained on smaller, distinct regions of the country.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Between 2013 and 2018, among the 3106 counties included in the study, observed mean county-level overdose death rates increased from 11·8 deaths per 100 000 in 2013 to 15·4 deaths in 2017, before falling to 14·6 deaths in 2018 (table 2). The benchmark prediction strategy over-predicted the mean county-level overdose death rate each year, increasing from 13·0 deaths per 100 000 in 2013 to 18·3 deaths in 2018. The negative binomial approach predicted a mean 11·8 deaths per 100 000 in 2013, followed by a steady increase from 11·5 deaths in 2014 to 15·1 deaths in 2017 and 16·4 deaths in 2018. The negative binomial approach outperformed the benchmark prediction strategy each year, according to MAE, RMSE, and Spearman's *r* (table 3). The benchmark MAE increased from 10·70 in 2013 to 12·37 in 2018, whereas the MAE of the negative binomial approach ranged from 6·58 to 7·73 for 2013–18. The RMSE of the benchmark approach ranged from 18·38 to 20·67 for 2013–18, whereas the negative binomial approach RMSE ranged from 10·04 in 2013 to 11·55 in 2016. The benchmark Spearman's *r* increased from 0·35 in 2013 to 0·45 in 2018, whereas the negative binomial model Spearman's *r* was generally 0·2 greater, increasing from 0·57 in 2013 to 0·65 in 2018.

We divided counties into deciles based on observed and predicted overdose death rates (ie, top decile were the 10% of counties with the highest overdose death rate, second decile the next 10%, and so on), to identify if the counties predicted to have the highest overdose death rates indeed experienced them. The benchmark prediction strategy correctly predicted between 89 (29%) and 132 (43%) of the 310 counties in the top decile for each year (table 4). The negative binomial approach generally improved over time, identifying 129 (42%) of the 310 counties in the top decile in 2013 and 171 (55%) in 2018, with a peak of 176 (57%) in 2017. This improvement

For **ODPredict Explorer** see http://overdosepredictiondashboard.emergens-project.com/

	Benchmark			Negative binomial		
	Mean average error	Root mean squared error	Spearman's r value	Mean average error	Root mean squared error	Spearman's r value
2013	10·70	18·38	0·35	6·58	10·04	0·57
2014	10·92	18·09	0·36	6·70	10·42	0·58
2015	11·18	19·32	0·40	6·74	10·34	0·62
2016	11·72	20·20	0·41	7·66	11·55	0·64
2017	12·34	20·67	0·45	7·52	11·22	0·67
2018	12·37	20·67	0·45	7·73	10·95	0·65

Table 3: Errors of benchmark and negative binomial predictions for 2013–18

	Benchmark	Negative binomial
Top decile*		
2013	102/310 (33%)	129/310 (42%)
2014	89/310 (29%)	145/310 (47%)
2015	104/310 (34%)	158/310 (51%)
2016	111/310 (36%)	154/310 (50%)
2017	132/310 (43%)	176/310 (57%)
2018	122/310 (40%)	171/310 (55%)
Newly in top decile†		
2014	8/175 (5%)	46/175 (26%)
2015	6/170 (4%)	40/170 (24%)
2016	6/165 (4%)	37/165 (22%)
2017	4/149 (3%)	38/149 (26%)
2018	7/149 (5%)	33/149 (22%)

Data are n/N (%). *The number of counties in the top decile (n=310) that were accurately predicted (ie, true positives) are shown for each year by approach. The number of false positives (ie, counties incorrectly predicted to be in the top decile) can be calculated by subtracting the number of true positives from 310. †The number of counties that newly entered the top decile (ie, were not in the top decile the year before) that were accurately predicted are shown for each year by approach.

Table 4: Number of total and new counties in the top decile of overdose death rates correctly predicted by the benchmark and model each year

may indicate that model performance increases in this regard given more training data.

The observed number of counties that newly entered the top decile fell from 175 counties in 2013–14 to 149 counties in 2017–18. The benchmark strategy, at its best in 2018, correctly predicted that seven of 149 counties would newly enter the top decile, whereas the negative binomial approach correctly predicted at least 33 (and up to 46) of the counties newly entering the top decile. Overall, our modelling approach identified 194 of the 808 counties that entered the top decile over the study period, compared with only 31 such counties identified by the benchmark approach. Although these results indicate further room for improvement, they show that the negative binomial approach used represents a meaningful predictive improvement over our benchmark heuristic of predicting based on annual overdose death rate trends.

Finally, we sought to characterise the predictive value of each fixed effect in the model via a forward selection

bootstrapping approach (table 5). The overdose gravity variable was included in 81% of simulations, indicating that the geospatial dimension of overdose is highly predictive of overdose death rate in each subsequent year. The opioid prescription rate was included in 66% of simulations and the presence of an urgent care facility in the county was included 53% of the time, indicating that such drug market and health-care indicators are of predictive value. The number of buprenorphine provider waivers in the county was only chosen 11% of the time. Several economic indicators, including changes in county payroll, median household income, and changes in employee capacity, were all chosen around 50% of the time. Diagnostic analyses showed that the model tended to underpredict the highest overdose death rates, but predictions improved over time. Separately implementing the model in the eastern and western regions, resulted in similar—although marginally better—performance (appendix pp 9–10).

Discussion

This study showed how a statistical modelling approach can be used to identify counties at risk of experiencing overdose death outbreaks. Our model predicted counties' overdose death rates from 2013 to 2018 with substantially greater accuracy than an intuitive benchmark heuristic. Most importantly, our model displayed far greater capacity than the benchmark for predicting counties experiencing emergent drug overdose outbreaks by identifying counties newly entering the top mortality bracket. As such, this model should be considered when attempting to identify which counties are in need of resources to respond to potential overdose outbreaks, including counties yet to experience them. Further research aimed at improving model performance and timely access to data are needed to ensure efficacious application. Our post-hoc analysis showed that our fixed effects capturing the geospatial spread of overdose, opioid prescribing patterns, and several economic indicators provided the most predictive utility.

Although similar models have been used to inform funding allocation, such as the CDC's drug-related HIV outbreak risk assessment model,[12,22] these models have not been validated against data and have not been designed to provide yearly predictions—studies by Sumetsky and colleagues[18] and Campo and colleagues[23] are two exceptions. Model validation is key to both ensuring that the tools used for policy guidance are providing accurate information and to improving our understanding of the epidemic processes. Given the changing nature of drug use epidemics, tools that capture risk over time are needed.

This study has limitations. First, the model performance is not optimal. However, predicting overdose outbreaks at national level is challenging and such improvements over a heuristic benchmark can prevent much harm by directing attention towards counties that might not

otherwise have been considered to be at risk. Although it was not possible to do so in this study, comparing the performance of our model with that of other models introduced in the literature (such as that by Sumetsky and colleagues,[18] Campo and colleagues,[23] and Lyle Cooper and colleagues[24]) might advance the broader effort to develop better performing models. Further, given that this is a nascent line of research, we highlight the importance of evaluating the performance of various modelling strategies. To our knowledge, this study is the first to apply a mixed-effects negative binomial regression strategy to predict overdose deaths. Previous works have applied Bayesian spatial-temporal models, polynomial functions, and a variation of the random forest algorithm.[18,23,24] Future research should aim to replicate and compare these methods to identify strengths of each approach, which can inform future model development.

Second, longitudinal predictive studies require the consistent and timely dissemination of data. Thus, the outcome and predictors need to be available for the same localities (ie, counties), same time periods, and same time steps (ie, years or months) to be used. Such requirements restrict the pool of available variables to include as predictors. For example, although we incorporated estimates of opioid prescription rates per county and fentanyl seizures by state to capture changes in drug markets, these indicators provide only partial information as they do not tell us about drug volume or potency. Having county-level seizure data would probably improve model performance. Similarly, we included active buprenorphine providers per year by county as a measure of drug treatment coverage. However, there is high variation in the number of patients seen by each provider and regulations on the limit of patients per provider have been relaxed over time.[25]

Third, we took a simple approach for identifying the susceptible population in each county. Most people in each county are not at risk of experiencing an overdose. Sumetsky and colleagues provide an example of a more computationally intensive calculation of county carrying capacity.[18] Future research should seek to design and validate approaches aimed at quantifying this county-level susceptible population.

Finally, the timeliness of data availability shapes the utility of the method. As of April, 2021, the restricted overdose death data from the CDC were available to 2019. Future applications of this or other predictive modelling approaches require more rapid dissemination of data to ensure the timely access of evidence-based guidance among relevant stakeholders. Increasingly, individual states and counties' public health departments are implementing web-portals, such as the Opioid Overdose Surveillance Dashboards for California, Rhode Island, and Michigan,[26–28] where preliminary data are made publicly available on a quarterly, biannual, and near-real time basis, respectively. States with more rapid data dissemination might apply this method for their specific locality. Analytic approaches can be modified to make predictions several

	Percentage of times chosen
Log overdose gravity	81%
Opioid prescriptions per 100 individuals	66%
Payroll difference	54%
Urgent care presence	53%
Median household income	48%
Employee difference	43%
Urbanicity	40%
Proportion of renter households that spend at least 35% of income on rent	39%
Log NFLIS	35%
Proportion of homeowner households that spend at least 35% of income on mortgage	32%
Poverty rate	25%
High school graduation rate	20%
Log jail population	17%
Buprenorphine provider waivers	11%
Unemployment rate	10%

Data are ordered from most frequently included to least. We did 100 simulations. NFLIS=National Forensic Laboratory Information System.

Table 5: Percentage of bootstrap simulations in which each fixed effect was selected

years into the future but given the rapidly changing nature of drug use epidemics, the timely availability of data promises to provide greater predictive benefit. This is particularly true in the context of the COVID-19 pandemic, which has affected and will continue to shape drug use-related behaviours and harms.[29,30]

Based on these findings, we provide directions for future research and endeavours that can improve the utility of this modelling approach. First, as highlighted in the limitations section, better and more timely data of both drug use patterns and drug markets are needed to enable rigorous analyses of drug use epidemics and prediction analyses. This need could be met through more timely and granular accessibility to National Forensic Laboratory Information System data and through establishing free and accessible drug testing programmes in collaboration with harm reduction organisations.[5] Publicly available data on prescription drugs is also key to evaluating risk in a population. Local data on the number and socio-demographic characteristics of people who use drugs could be systematically collected and linked through coordinated collaboration with primary and emergency medical services, law enforcement institutions, and harm reduction organisations. A 2020 study by Campo and colleagues showed that concurrent Google search trends might be an effective strategy for making real-time, dynamic predictions of county-level overdose death rates, given the immediate availability of this data.[23]

Second, to use prediction to mitigate the harms of the opioid crisis, it is crucial to swiftly communicate predictions to appropriate stakeholders; this communication is especially important considering how rapidly US drug

markets are understood to change.[31] The development of dashboards can facilitate the application of these peer-reviewed methods in a way that allows for the rapid dissemination of results. We provide a dashboard at ODPredict Explorer where the results of this study can be explored. This dashboard represents a model for how this method can be applied to inform relevant stakeholders in making decisions about overdose prevention measures. Through such platforms, stakeholders can access prediction results and use the findings to inform resource allocation and overdose response initiatives. Although this study focuses on the accuracy and validity of the approach employed, we expect to extend it to produce future predictions, depending on data availability.

In summary, our statistical model more effectively rank-orders counties based on the predicted overdose death rates for the subsequent year and is able to predict substantially more counties that will experience emergent increases in overdose mortality, compared with a heuristic model based on previous year trends in overdose mortality only. This study provides the first rigorously validated tool to inform policy planning in the context of overdose epidemics driven by emerging drugs and sets a new standard for the development of a data driven response to drug use epidemics.

Contributors
CM contributed to conceptualisation, data curation, data verification, formal analysis, methodology, software, validation, visualisation, and writing (original draft). DA contributed to conceptualisation, formal analysis, methodology, and writing (review and editing). CAD contributed to conceptualisation, methodology, and writing (review and editing). DC contributed to resources and writing (review and editing). GC-E contributed to methodology, data curation, data verification, formal analysis, methodology, and writing (review and editing). RC-H contributed to methodology, data curation, data validation, formal analysis, methodology, and writing (review and editing). AG-I contributed to methodology and writing (review and editing). NKM contributed to methodology and writing (review and editing). SAS and DMS contributed to writing (review and editing). AB contributed to conceptualisation, data curation, data validation, funding acquisition, methodology, resources, supervision, and writing (original draft and review and editing). CM, GC-E, RC-H, and AB had access to and verified data used in this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
CAD reports funding from the MRC Centre for Global Infectious Disease Analysis (reference MR/R015600/1), jointly funded by the UK Medical Research Council (MRC) and the UK Foreign, Commonwealth & Development Office (FCDO), under the MRC/FCDO Concordat agreement and is also part of the EDCTP2 programme supported by the EU. DC reports personal fees from Celero Systems, Motley Rice LLP, Mallinckrodt Pharmaceuticals, and Nektar Therapeutics, outside the submitted work. NKM reports unrestricted research grants from Gilead and Merck, outside the submitted work. CM, AB, DA, GC-E, RC-H, AG-I, SAS, and DMS declare no competing interests.

Data sharing
This study uses restricted secondary data and, therefore, we cannot provide the dataset required to recreate our study. However, since the predictor data was all publicly available, we have made a dataset available with variables generated from the restricted mortality records censored. This data is available at http://dx.doi.org/10.17632/t9wbtt3mt2.1. The R code we used to analyse data is included in the appendix (pp 13–19) and is available along with the censored dataset at the DOI listed.

References
1 Hedegaard H, Minino A, Warner M. Drug overdose deaths in the United States, 1999–2018. 2020. https://www.cdc.gov/nchs/data/databriefs/db356-h.pdf (accessed Feb 19, 2021).
2 Wilson N, Kariisa M, Seth P, Smith H 4th, Davis NL. Drug and opioid-involved overdose deaths—United States, 2017–2018. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 290–97.
3 Ciccarone D. Fentanyl in the US heroin supply: a rapidly changing risk environment. *Int J Drug Policy* 2017; **46:** 107–11.
4 Ciccarone D, Ondocsin J, Mars SG. Heroin uncertainties: exploring users' perceptions of fentanyl-adulterated and -substituted 'heroin'. *Int J Drug Policy* 2017; **46:** 146–55.
5 Ciccarone D. The triple wave epidemic: supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy* 2019; **71:** 183–88.
6 Centers for Disease Control and Prevention National Center for Health Statistics. Multiple cause of death 1999–2018 on CDC WONDER online database, released in 2020. 2020. http://wonder.cdc.gov/mcd-icd10.html (accessed Jan 10, 2021).
7 Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science* 2018; **361:** 1184.
8 Kiang MV, Basu S, Chen J, Alexander MJ. Assessment of changes in the geographical distribution of opioid-related mortality across the United States by opioid type, 1999–2016. *JAMA Netw Open* 2019; **2:** e190040.
9 Jones CM, Bekheet F, Park JN, Alexander GN. The evolving overdose epidemic: synthetic opioids and rising stimulant-related harms. *Epidemiol Rev* 2020; **42:** 154–66.
10 Shover CL, Falasinnu TO, Dwyer CL, et al. Steep increases in fentanyl-related mortality west of the Mississippi River: recent evidence from county and state surveillance. *Drug Alcohol Depend* 2020; **216:** 108314.
11 Slavova S, O'Brien DB, Creppage K, et al. Drug overdose deaths: let's get specific. *Public Health Rep* 2015; **130:** 339–42.
12 Van Handel MM, Rose CE, Hallisey EJ, et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. *J Acquir Immune Defic Syndr* 2016; **73:** 323–31.
13 Monnat SM, Peters DJ, Berg MT, Hochstetler A. Using Census data to understand county-level differences in overall drug mortality and opioid-related mortality by opioid type. *Am J Public Health* 2019; **109:** 1084–91.
14 Rossen LM, Khan D, Warner M. Trends and geographic patterns in drug-poisoning death rates in the U.S., 1999–2009. *Am J Prev Med* 2013; **45:** e19–25.
15 Haffajee RL, Lin LA, Bohnert ASB, Goldstick JE. Characteristics of US counties with high opioid overdose mortality and low capacity to deliver medications for opioid use disorder. *JAMA Netw Open* 2019; **2:** e196373.
16 Robinson WR, Renson A, Naimi AI. Teaching yourself about structural racism will improve your machine learning. *Biostatistics* 2020; **21:** 339–44.
17 Om A. The opioid crisis in black and white: the role of race in our nation's recent drug epidemic. *J Public Health (Bangkok)* 2018; **40:** e614–15.
18 Sumetsky N, Mair C, Wheeler-Martin K, et al. Predicting the future course of opioid overdose mortality: an example from two US states. *Epidemiology* 2021; **32:** 61–69.
19 R Core Team. R: a language and environment for statistical computing. 2019. https://www.r-project.org/ (accessed Feb 15, 2021).
20 Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; **67:** 1–48.
21 Beyene J, Atenafu EG, Hamid JS, To T, Sung L. Determining relative importance of variables in developing and validating predictive models. *BMC Med Res Methodol* 2009; **9:** 64.
22 Rickles M, Rebeiro PF, Sizemore L, et al. Tennessee's in-state vulnerability assessment for a "rapid dissemination of Human Immunodeficiency Virus or Hepatitis C Virus infection" event utilizing data about the opioid epidemic. *Clin Infect Dis* 2018; **66:** 1722–32.

23   Campo DS, Gussler JW, Sue A, Skums P, Khudyakov Y. Accurate spatiotemporal mapping of drug overdose deaths by machine learning of drug-related web-searches. *PLoS One* 2020; **15:** e0243622.

24   Lyle Cooper R, Thompson J, Edgerton R, et al. Modeling dynamics of fatal opioid overdose by state and across time. *Prev Med Rep* 2020; **20:** 101184.

25   Duncan A, Anderman J, Deseran T, Reynolds I, Stein BD. Monthly patient volumes of buprenorphine-waivered clinicians in the US. *JAMA Netw Open* 2020; **3:** e2014045.

26   California Department of Public Health. California Opioid Overdose Surveillance Dashboard. 2020. https://skylab.cdph.ca.gov/ODdash/ (accessed Jan 16, 2021).

27   Rhode Island Department of Health. Prevent Overdose Rhode Island. 2020. https://preventoverdoseri.org/overdose-deaths/ (accessed Jan 16, 2021).

28   University of Michigan. Michigan System for Opioid Overdose Surveillance. 2019. https://systemforoverdosesurveillance.com/ (accessed Jan 16, 2021).

29   Volkow ND. Collision of the COVID-19 and addiction epidemics. *Ann Intern Med* 2020; **173:** 61–62.

30   Becker WC, Fiellin DA. When epidemics collide: coronavirus disease 2019 (COVID-19) and the opioid crisis. *Ann Intern Med* 2020; **173:** 59–60.

31   Rosenblum D, Unick J, Ciccarone D. The rapidly changing US illicit drug market and the potential for an improved early warning system: evidence from Ohio drug crime labs. *Drug Alcohol Depend* 2020; **208:** 107779.