Public Health Surveillance and Machine Learning for Predicting Opioid and Polysubstance Overdose in the United States: A Systematic Review

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Abstract
The United States is currently grappling with a severe and urgent overdose crisis, driven by synthetic fentanyl and the increasing involvement of multiple substances. This evolving pattern has made it increasingly challenging to detect, predict, and respond to overdose events in a timely manner. While public health surveillance systems play a crucial role in providing information about emerging trends, traditional data sources often struggle to keep pace with the rapid changes in the drug supply. However, the advent of machine learning presents a ray of hope, offering opportunities to identify individuals and communities at elevated risk and to forecast overdose patterns before they manifest in official statistics.
This review synthesizes studies that used public health surveillance, machine learning, or both to predict opioid or polysubstance overdose in the United States. A structured search of major academic databases identified research that employed modeling approaches, such as random forests, gradient boosting methods, neural networks, and spatiotemporal surveillance strategies, to estimate overdose risk. Studies were included if they were conducted in the United States, used a predictive or surveillance-based method, and reported fatal or nonfatal overdose outcomes.
The findings demonstrate growing interest in models that integrate multiple data sources, including electronic health records, Medicaid claims, emergency medical services data, criminal justice information, and statewide surveillance systems. Across studies, predictors that consistently contributed to overdose risk included prior overdose events, mental health conditions, patterns of substance use, and community-level factors. While model performance varied, many studies achieved intense discrimination.
This review highlights opportunities to strengthen prediction systems by combining advanced modelling strategies with more integrated and timely surveillance frameworks. Such approaches support earlier detection and more targeted public health responses to the ongoing overdose crisis in the United States.

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Introduction
The United States remains in the midst of an overdose crisis that continues to shift in scale, complexity, and speed. Earlier periods of the epidemic were primarily driven by prescription opioids, followed by a rise in heroin use. Today, the crisis has moved into a new phase shaped by illicitly manufactured fentanyl and a rapidly expanding pattern of polysubstance use. Many overdose deaths now involve fentanyl combined with stimulant substances such as methamphetamine or cocaine, as well as benzodiazepines, alcohol, or other drugs. This pattern has made overdose events more unpredictable and more challenging to monitor, and it has placed greater demands on the public health systems responsible for surveillance and response.
Public health surveillance systems are pivotal in understanding overdose trends in the United States. These systems, which rely on vital statistics, emergency medical services data, toxicology records, prescription monitoring programs, law enforcement information, and hospital encounters, are facing a new challenge-the speed of the modern drug supply. Delays in reporting, incomplete toxicology testing, and differences in data quality across states have hindered their ability to provide timely and

accurate information. In response, public health organizations have been advocating for more integrated and timely surveillance frameworks that can adapt to the rapidly changing landscape of the overdose crisis.

Alongside developments in surveillance, researchers have begun to apply machine learning to overdose prediction. A growing number of studies use advanced modelling techniques, including random forests, gradient boosting methods, neural networks, and other high-dimensional algorithms, to identify individuals and communities at elevated risk of overdose. These models have been applied to electronic health records, Medicaid claims, statewide integrated databases, and criminal justice information. Several model-based studies have shown strong accuracy in predicting overdose risk. For example, models developed for patients receiving long-term opioid therapy demonstrated intense discrimination when used to estimate future overdose events (Glanz *et al*., 2018) [9]. Statewide modelling work that links medical, social, and justice-related data has also improved the prediction of fatal overdose and helped communities with the greatest need for intervention (Naumann *et al*., 2021) [17].

Machine learning is now increasingly recognized as a valuable complement to traditional surveillance. Commentaries in public health and epidemiology describe how prediction models can strengthen early detection, support more targeted outreach, and guide resource allocation during periods of rapid change (Allen & Cerda, 2022). Additional research has explored the potential for modeling to detect patterns of drug interactions and to estimate individual vulnerability using biomedical and community-based data (Vunikili *et al*., 2021) [25]. Taken together, these studies suggest that the combination of modern surveillance and advanced modelling can offer a more responsive public health approach to an increasingly complex overdose environment.

Despite this progress, the evidence remains scattered across multiple disciplines. Some studies focus on clinical prediction within health systems, while others examine community or statewide trends using surveillance data. Few reviews have brought these bodies of work together in a single synthesis, and public health agencies lack a clear summary of the modelling strategies available, the predictors most consistently associated with overdose risk, and the limitations that must be considered when applying these models in practice.

The purpose of this systematic review is to integrate research that uses public health surveillance, machine learning, or both to predict opioid and polysubstance overdose in the United States. By examining a wide range of designs, data systems, and modelling techniques, this review aims to clarify current approaches, highlight major strengths and gaps, and outline future directions for building more effective and more timely prediction systems that support a stronger public health response to the national overdose crisis.

Methods

Study Framework

This review followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. All stages of the review, including the search strategy, eligibility criteria, and approach to synthesis, were specified in advance.

Search Strategy

A structured search was conducted across multiple academic databases to identify studies that used public health surveillance, machine learning, or other data-driven modelling approaches to predict opioid or polysubstance overdose in the United States. The databases included PubMed, Scopus, Web of Science, and Science Direct. Google Scholar was consulted only to confirm citation completeness.

The search strategy combined terms related to opioids, polysubstance use, overdose, prediction, modelling, surveillance, and data integration. Examples of search terms included opioid overdose, polysubstance overdose, fentanyl, predictive modelling, machine learning, overdose forecasting, surveillance strategies, and spatiotemporal modelling. Boolean operators were used to capture as many relevant studies as possible.

The search included all literature published up to and including the year 2022. Only studies written in English were reviewed. Reference lists of eligible studies and related reviews were examined to identify additional publications not captured in the database search.

Eligibility Criteria

Inclusion Criteria

Studies were eligible for inclusion if they met the following requirements:

1. Conducted in the United States.
2. Examined opioid overdose or polysubstance overdose involving opioids.
3. Applied machine learning, predictive modelling, surveillance-based methods, or other structured analytic strategies designed to estimate overdose risk or forecast overdose events.
4. Reported fatal or nonfatal overdose outcomes or provided a predictive estimate of these outcomes.
5. Used observational research, retrospective analyses, modelling studies, evaluations of surveillance systems, or integrated public health datasets.
6. Published in 2022 or earlier.
7. Written in English.

Exclusion Criteria

Studies were excluded if they:

1. Were conducted outside the United States.
2. Did not examine overdose outcomes.
3. Focused only on treatment or intervention effectiveness with no predictive component.
4. Examined substance use without opioid involvement.
5. Presented conceptual models without empirical data.
6. Were commentary or opinion articles without analytical methods.
7. Lacked adequate methodological detail to evaluate the predictive or surveillance approach.
8. Were published after 2022.

Study Selection

All retrieved citations were imported into a reference management program, and duplicates were removed. Screening occurred in two stages. First, titles and abstracts were reviewed to exclude studies that clearly did not meet the eligibility criteria. Second, a full-text review was performed for all remaining articles.

Any uncertainty in the screening process was resolved by evaluating the study objectives, data sources, and analytic approach. A PRISMA flow diagram will summarize the number of articles identified, screened, and retained.

Data Extraction

Data extraction was completed using a standardized form developed for this review. Extracted information included:

- Publication year
- Study objectives
- Data sources, such as electronic health records, Medicaid claims, emergency medical services data, criminal justice information, toxicology reports, or statewide integrated databases
- Characteristics of the study population
- Modelling approaches used
- Predictors included
- Overdose outcomes measured
- Measures of predictive performance
- Key findings
- Limitations noted by the authors
- Extraction focused on accuracy and consistency across studies.

Assessment of Methodological Quality

Risk of bias was assessed using the Prediction Model Risk of Bias Assessment Tool. This tool evaluates four domains: participant characteristics, predictor selection and measurement, outcome definition and assessment, and analytic procedures.

For surveillance-based studies, additional factors were evaluated, including the timeliness of reporting, completeness of toxicology data, clarity of analytic assumptions, and geographic coverage. These assessments were used to understand methodological strengths and limitations rather than to exclude studies.

Approach to Synthesis

Because the included studies differed widely in data sources, analytic methods, and outcome definitions, a quantitative meta-analysis was not appropriate. A narrative synthesis was used instead. The synthesis focused on identifying major modelling strategies, describing common predictors, summarizing model performance, and outlining opportunities to strengthen surveillance and prediction efforts in the United States.

Results

Overview of Included Studies

The search identified a diverse set of studies that examined the prediction of opioid and polysubstance overdose in the United States using surveillance systems, machine learning approaches, or combined modelling strategies. After screening and full-text review, the final group of included studies represented multiple methodological traditions, including clinical risk prediction, statewide integrated modeling, and population-level surveillance. These studies varied widely in terms of sample size, data source, modeling complexity, and target populations, reflecting the fragmented nature of overdose research in the United States (Glanz *et al*., 2018) [9]; (Naumann *et al*., 2021) [17].

Study Characteristics

Several studies relied on electronic health records, which provided detailed clinical histories, medication use patterns, chronic conditions, and prior overdose events. Glanz *et al*. (2018) [9] demonstrated that electronic health record data can produce strong individual-level risk predictions, particularly when combined with historical opioid use patterns.

Other studies used statewide integrated data systems that linked medical encounters with behavioral health information, social determinants of health, criminal justice involvement, and mortality records. Naumann *et al*. (2021) [17] found that integrating these domains created substantial improvements in identifying individuals and communities at increased risk of fatal overdose.

Population health surveillance data also played a significant role in several studies. For example, emergency medical services records, prescription monitoring program data, and toxicology findings were used to track real-time changes in overdose trends and geographic clustering of overdose events. Surveillance-focused studies have emphasized the importance of timely reporting and coordinated data systems in detecting rapid shifts in fentanyl prevalence (Association of Public Health Laboratories, 2020) [1].

Predictive Modelling Approaches

Machine learning approaches varied across studies and included random forests, gradient boosting algorithms, high-dimensional logistic regression, neural networks, ensemble models, and spatiotemporal forecasting techniques. Models developed for clinical populations often achieved strong predictive accuracy. For instance, Glanz *et al*. (2018) [9] reported notable discrimination when estimating future overdose risk among patients receiving long-term opioid therapy.

Statewide models, such as those developed by Naumann *et al*. (2021) [17], used large linked datasets and found that structural and social indicators, justice involvement, and prior emergency department encounters substantially increased the likelihood of fatal overdose.

Additional work explored prediction within specific subgroups. Studies that examined patients already prescribed opioids demonstrated that two-year overdose risk could be estimated with high accuracy using claims data, comorbidity patterns, and previous high-dose prescribing (Sohn *et al*., 2021) [23].

Models focused on polysubstance risk highlighted the elevated mortality associated with combinations of opioids, stimulant substances, benzodiazepines, and alcohol. Vunikili *et al*. (2021) [25] demonstrated that machine learning methods could capture complex interactions among substances that traditional models might miss.

Surveillance-Based Findings

Surveillance-oriented studies emphasized the need for more responsive systems capable of detecting rapid changes in overdose patterns. The Public Health Biosurveillance Strategy report (Association of Public Health Laboratories, 2020) [1] noted persistent delays in mortality data, inconsistent toxicology testing, and gaps in local capacity to integrate multiple data sources, all of which limit timely detection of emerging trends.

Several studies demonstrated how enhanced surveillance could identify geographic clusters of overdose activity more quickly than traditional reporting systems. For example, work using emergency medical services data showed that spatiotemporal modelling can detect sudden increases in overdose incidents, particularly during rapid shifts in fentanyl supply (Henderson *et al*., 2019) [11].

Common Predictors of Overdose Risk

Across studies, several predictors emerged consistently as strong indicators of increased overdose vulnerability. These included previous overdose events, co-occurring mental health conditions, chronic pain diagnoses, high-risk opioid prescribing, concurrent benzodiazepine use, prior substance use disorder treatment episodes, recent emergency department visits, and justice system involvement. Structural and social determinants such as housing instability, unemployment, and community-level deprivation were also significant in several population-level models (Naumann *et al*., 2021; Vunikili *et al*., 2021) [17] [25].

Model Performance and Limitations

Most modelling studies reported moderate to intense discrimination. Models based on linked statewide data often performed best due to the richness of the datasets and the inclusion of multiple domains of risk. Clinical models performed well when detailed prescribing and diagnostic information were available. Models predicting two-year overdose risk using claims and health system data generally produced accurate risk estimates (Sohn *et al*., 2021) [23].

However, limitations were consistently noted. Surveillance systems frequently suffer from incomplete toxicology testing, inconsistent data quality across states, and delayed reporting. Studies using electronic health records were constrained by missing behavioral health information and a lack of visibility into out-of-hospital overdose deaths. Researchers also noted challenges related to generalizability, as models trained in one state or population often performed less accurately when applied to other settings. Some authors emphasized the need for greater model transparency to improve clinical and public health adoption (Allen & Cerda, 2022).

Discussion

This systematic review examined how public health surveillance and machine learning have been used to predict opioid and polysubstance overdose in the United States. The findings demonstrate that predictive modeling has advanced significantly in recent years, supported by improvements in data integration, analytical capacity, and the increasing availability of statewide and clinical datasets. At the same time, the results highlight persistent gaps in surveillance systems and modelling practices that limit timely prediction and response.

A consistent theme across the included studies is that prediction improves substantially when multiple risk domains are integrated. Studies using linked datasets that combined medical records, behavioral health information, criminal justice involvement, and mortality data were able to identify individuals at elevated risk with greater accuracy than models using a single data source. For example, Naumann *et al*. (2021) [17] demonstrated that integrated statewide systems produced stronger predictions of fatal overdose than models based solely on clinical data. These results reinforce the importance of cross-sector collaboration in building robust prediction frameworks.

Clinical prediction models also showed strong performance when detailed electronic health record or claims information was available. Glanz *et al*. (2018) [9] found that historical prescribing patterns, previous substance use diagnoses, and prior overdose events were highly predictive of future overdose risk among patients receiving opioid therapy. Similarly, models estimating two-year overdose risk among individuals prescribed opioids demonstrated accurate discrimination when using claims data and comorbidity profiles (Sohn *et al*., 2021) [23]. These findings confirm that health system data represent an important resource for identifying patients who may benefit from proactive outreach or early intervention.

At the population level, surveillance-based studies provide important insights into how rapidly overdose patterns can shift. The Public Health Biosurveillance Strategy report identified significant gaps in toxicology completeness, timely reporting, and local analytic capacity, all of which weaken the ability of jurisdictions to detect emerging threats. These limitations were echoed in surveillance-centered studies, which noted delays in mortality reporting and uneven data quality across states (Association of Public Health Laboratories, 2020) [1]. The need for more responsive surveillance systems is particularly urgent as fentanyl and stimulant combinations continue to circulate unpredictably in the drug supply.

Machine learning approaches also add value in their ability to capture complex relationships that traditional statistical techniques may overlook. Studies using neural networks, ensemble models, and other advanced methods have demonstrated that polysubstance interactions can be modeled more precisely than through linear approaches. Vunikili *et al*. (2021) [25] showed that machine learning techniques could reveal subtle patterns in substance combinations that significantly elevated overdose risk. These findings highlight the potential of advanced modelling approaches to provide deeper insight into polysubstance use dynamics.

Despite these strengths, several limitations must be noted. Many models lacked external validation, raising concerns about their generalizability across states and populations. Some clinical models performed well within a single health system but demonstrated reduced accuracy when applied to different patient populations. Additionally, limited transparency in some machine learning approaches can hinder adoption by clinicians and public health leaders, who require interpretable models to guide their decision-making (Allen & Cerda, 2022).

Surveillance-based studies also faced persistent challenges in data quality. Incomplete toxicology reporting, delays in case identification, and variability in the classification of overdose deaths continue to impede timely detection. These issues create barriers to integrating surveillance and predictive modelling, since lagged or incomplete data reduce the effectiveness of early warning systems.

Overall, findings of this review suggest that predictive modeling can strengthen the national response to the overdose crisis when supported by integrated surveillance systems, high-quality data, and rigorous validation practices. Combining health system data, community-level indicators, behavioral health information, and justice involvement enhances the accuracy of prediction models and offers public health agencies a more comprehensive picture of risk. At the same time, improving the timeliness and consistency of surveillance is essential for prediction tools to function effectively in real-time.

Limitations

This review has several limitations that should be considered when interpreting the findings. First, the included studies varied widely in their design, population focus, data sources, and analytic approaches. This heterogeneity limited the ability to compare results directly across studies and prevented the use of meta-analytic techniques. Differences in model architecture, predictor sets, and outcome definitions also made it difficult to assess performance using a single standard metric.

Second, many of the studies relied on datasets that were limited by delayed reporting, incomplete toxicology information, and inconsistent documentation across jurisdictions. These constraints reflect broader challenges within public health surveillance systems in the United States, and they may have reduced the accuracy or timeliness of some prediction models. Studies using electronic health records and claims data were similarly affected by missing behavioral health information, lack of visibility into out-of-hospital overdose events, and differences in coding practices between health systems.

Third, several prediction models were evaluated only in the state or health system in which they were developed. Limited external validation reduces confidence in the generalizability of these models to other populations, particularly given the geographic variability of the illicit drug supply and differences in state-level reporting practices. Models that appear highly accurate in development settings may perform differently when applied to new regions or populations with different risk profiles.

Fourth, this review included only studies published in 2022 or earlier, and only those that provided empirical data on overdose prediction or surveillance-based modeling. As a result, newer modelling approaches and emerging surveillance tools published after this period were not captured. Restricting the search to English-language publications may have also excluded relevant work conducted in multilingual or bilingual jurisdictions within the United States.

Finally, although machine learning methods offer essential advantages, many studies provided limited information on model interpretability, variable importance, or decision rules. This lack of transparency makes it challenging to assess the practical applicability of specific models. It may hinder their adoption by clinicians and public health agencies that require clear explanations of risk estimation.

Despite these limitations, the studies included in this review provide valuable insight into the current landscape of overdose prediction and highlight meaningful opportunities to strengthen public health surveillance and analytic capacity in the United States.

Conclusion

This systematic review examined how public health surveillance and machine learning have been applied to predict opioid and polysubstance overdose in the United States. The findings indicate that predictive modelling has become an increasingly important tool for understanding overdose risk, particularly as the drug supply becomes more unpredictable and more heavily influenced by synthetic fentanyl and multiple substance combinations. Studies using electronic health records, statewide integrated systems, and surveillance datasets have consistently shown that prediction improves when multiple domains of risk are combined, including clinical history, substance use patterns, mental health indicators, and community-level factors (Glanz *et al*., 2018) [9]; (Naumann *et al*., 2021) [17].

The results also show that machine learning has the capacity to capture complex and nonlinear relationships that traditional analytic approaches may not fully identify, especially those involving polysubstance interactions and rapid shifts in local drug markets (Vunikili *et al*., 2021) [25]. However, prediction models are limited by the quality and timeliness of the data on which they are built. Surveillance systems in several jurisdictions continue to experience delays in toxicology reporting, inconsistent data standards, and limited capacity for real-time analysis. These limitations reduce the effectiveness of both forecasting strategies and early warning systems (Association of Public Health Laboratories, 2020) [1].

Despite these challenges, the evidence suggests substantial potential for integrating predictive modeling with enhanced public health surveillance. Improved data sharing across sectors, consistent toxicology practices, complete reporting, and comprehensive statewide data integration efforts can enhance model accuracy and better position health systems and public health agencies to respond quickly to emerging threats. As the overdose crisis continues to evolve, particularly with the increasing involvement of stimulant substances and counterfeit pills, the need for timely, data-driven prediction models will only grow.

The findings of this review suggest that future work should prioritize the validation of existing models across multiple settings, the development of interpretable prediction tools, and the deeper integration of surveillance systems capable of real-time analysis. By advancing these areas, public health agencies can benefit from more accurate forecasting, earlier detection of emerging overdose patterns, and improved allocation of prevention and response resources. Together, these efforts have the potential to strengthen the national response to overdose mortality and support more effective strategies for reducing harm across the United States.

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