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Review Article

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Illicit drug supply, naloxone availability, and overdose mortality in the fentanyl era: a systematic review

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Abstract

Background **The overdose crisis is shaped by increasing synthetic opioids and expanding access to naloxone. We synthesized evidence on associations between illicit drug supply, naloxone availability/distribution, and overdose mortality.**

Methods **Following PRISMA, we searched 4 databases for studies between 2015 and 2025. Eligible studies examined associations of drug supply indicators or naloxone interventions, and overdose mortality. Data were extracted and synthesized narratively.**

Results **Forty-seven studies met inclusion criteria. Eighteen studies assessed drug supply changes and all but 2 found significant positive associations between increased fentanyl reports in drug seizures and overdose mortality. Drug seizure data were interpreted as indicators of supply trends or as enforcement disruptions. Thirty-one studies assessed naloxone availability. Thirteen studies reported naloxone access laws, take-home naloxone programs, and/or community interventions were associated with reductions in overdose deaths. Nine studies reported null effects, particularly during the COVID-19 pandemic.**

Conclusions **Fentanyl reports in drug seizures and drug potency are key drivers of overdose mortality. This review highlights variability in interpreting drug seizure data and the need for clearer conceptualization in future research. Naloxone interventions show promise but depend on consistent implementation and effective targeting of high-risk populations. Coordinated public health strategies are needed to monitor the drug market and strengthen overdose prevention.**

Keywords: overdose mortality, fentanyl, illicit drug supply, naloxone, opioid, drug policy

Introduction

The overdose crisis is characterized by the proliferation of synthetic opioids and polysubstance use.[1] In the United States, drug overdose deaths increased from 52 404 deaths in 2015 to 105 007 deaths in 2023, reflecting the rapid escalation of the overdose crisis over the past decade.[2] After years of increases, annual overdose deaths declined by 27% from their peak in mid-2023 through late 2024.[3] The drivers of the reversal are unclear and may reflect disruptions in the drug supply, including changes in the illicit drug market, demand patterns, shifts in drug use behavior, improved prevention, increased access to treatment, and a potential reduction in the population at risk due to cumulative overdose mortality in prior years.[3,4]

Drug supply changes, such as reductions in fentanyl purity, shifts toward less-potent analogs, or increased adulteration, can influence overdose risk.[1,5] Enforcement activities, and precursor-chemical controls, may also alter drug availability or reshape distribution networks.[5,6] These dynamics can be examined through drug composition identified through forensic analyses of law enforcement seizures, toxicological testing, and drug-checking programs.[5,7] Among these sources, law enforcement laboratory data represent the main source for characterizing street drug trends. Analyses of seized samples describe the types and relative prevalence of substances in local markets,[5,8,9] and reflect the reach and focus of enforcement, which can alter market dynamics and mortality trends.[5,6,10]

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In parallel, public health responses prioritized expanding access to naloxone, an opioid antagonist that reverses overdoses.[11,12] Naloxone distribution strategies, such as take-home naloxone programs, pharmacy standing orders, naloxone access laws, and Good Samaritan laws, have been implemented at varying scales across jurisdictions.[11,13-15] While these interventions aim to mitigate mortality, their impact may be constrained by barriers to access, stigma, implementation inconsistencies, and unpredictable changes in drug potency and composition.[16-18]

Despite interest in supply-side indicators and overdose prevention tools, evidence on how drug supply and naloxone availability influence overdose mortality remains limited.[5,19] Most studies focus on either drug supply toxicity or naloxone distribution in isolation, rarely examining both measures together. To address this gap, we conducted a systematic review from 2015 to 2025 examining associations between changes in the drug supply and/or naloxone availability/distribution and overdose mortality. This review aims to provide an integrated understanding of these relationships in the context of the fentanyl-driven overdose crisis, which followed years of rapid increases in mortality despite recent declines.

Methods

Search strategy and data sources

The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines[20] were followed. We registered the protocol on the Open Science Framework (10.17605/OSF.IO/95FPH). The search was performed across MEDLINE, Embase, APA PsycInfo, and Global Health up to April 28, 2025. The search included terms related to illicit drug supply, naloxone distribution, and overdose mortality. We excluded preclinical, in vitro, animal, and non-research articles and limited the search to peer-reviewed articles from 2015 onward (Table S1).

Eligibility criteria and study selection

Studies were eligible if published in English between January 2015 and April 2025 and reported analyses of association between changes in the illicit drug supply or naloxone and overdose mortality. We included studies of populations reporting mortality as an outcome. Exposures included seizure data, forensic testing, indicators of drug composition or potency, and naloxone policies/programs. Studies without a mortality outcome/analysis were excluded (Figure 1).

Data extraction

An EndNote library was created to manage records and remove duplicates. Titles/abstracts were screened by M.K. and J.H. using Covidence,[21] disagreements were resolved with T.F. Full texts of eligible studies were assessed, and a standardized data extraction form was used to capture study characteristics and findings. M.K., J.H., K.A., and F.L. extracted and verified data, with discrepancies resolved with T.F.

Data synthesis and categorization

Given the diversity of study designs, data sources, and analytical approaches, we conducted a narrative synthesis rather than a meta-analysis. We organized the findings thematically into 2 major domains: (1) associations between changes in the illicit drug supply and overdose mortality and (2) associations between naloxone availability/distribution and overdose mortality. Within each domain, studies were categorized by geographic scope (eg, city, state, national), methodological approach (eg, descriptive, time series, difference-in-differences), and direction and strength of findings.

Results

Study characteristics

Of 2514 studies, 1203 were unique records (Figure 1). Titles/abstracts screening identified 61 studies for full-text review, and 47 studies, published between 2015 and 2025, met the criteria (Table 1). The studies varied in scope, from local (eg, county/city-level, $n = 22$) to state ($n = 12$), and national ($n = 13$). Among these, 18 studies focused on associations between drug seizures and overdose mortality, while 31 studies evaluated the impact of naloxone access laws/programs. Two papers analyzed both drug seizures and a naloxone indicator and are counted in both sections.[23,57]

Most studies ($n = 45$) used observational designs; 2 randomized trials were conducted. Studies used multiple analysis methods: descriptive/cross-sectional ($n = 16$), longitudinal ($n = 20$), quasi-experimental approaches such as difference-in-differences ($n = 7$), interrupted and controlled interrupted time series ($n = 3$), and instrumental variables ($n = 1$). Studies integrated data from vital statistics and death records (eg, CDC WONDER, state medical examiner or coroner reports), law enforcement data systems (eg, DEA's National Forensic Laboratory Information System (NFLIS), local drug seizure records), prescription drug monitoring programs (PDMPs), emergency medical services (EMS) and emergency department records, and naloxone distribution programs (eg, community-based programs, pharmacy claims, or public health organizations).

Illicit drug supply changes and overdose mortality

Across the 18 studies assessing changes in drug supply and overdose mortality (Table S2), 9 examined seizure reports as a proxy of the drug supply, and 9 examined composition, potency, and lethality. Among studies focusing on reports, we identified 2 primary conceptual approaches to interpreting seizures reports (Figure 2). First, seizures as a proxy for drug supply levels and composition: most studies used forensic seizure data, especially from NFLIS, to infer trends in fentanyl and fentanyl-related compounds in the drug supply. These studies combined seizure and mortality data to estimate how variation in the prevalence of fentanyl reports in drug seizures correlates with overdose deaths. Second, seizures as a disruption of local markets: a smaller subset of studies focused on the spatial and temporal impacts of enforcement events, treating seizures as interventions that could alter local supply dynamics.

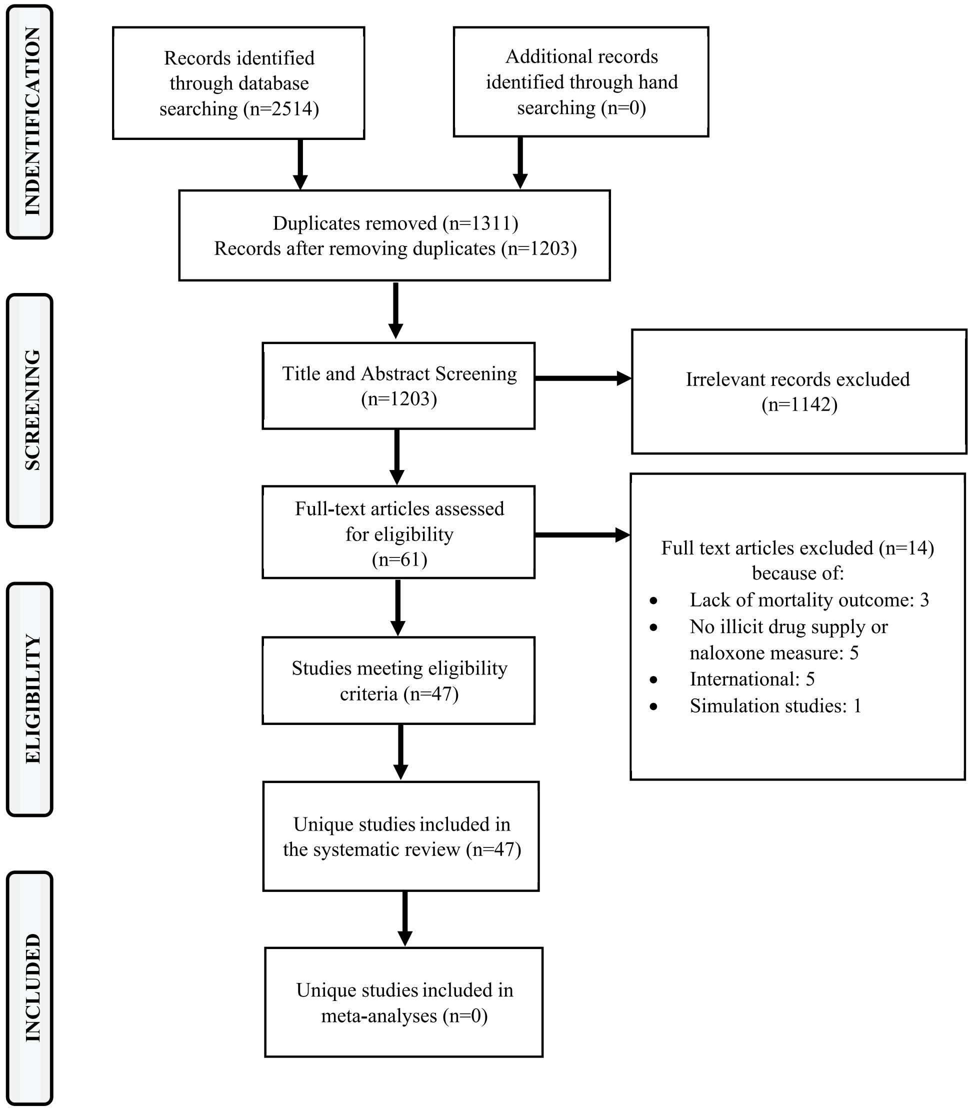

Figure 1. PRISMA flow diagram for selection of studies in the review.

Drug seizures as a proxy for fentanyl prevalence

Across 18 studies, seizure measures were consistently and positively associated with overdose mortality, supporting seizures as proxies for fentanyl prevalence. These associations were observed in cross-sectional analyses and in studies incorporating temporal dynamics.

Three studies demonstrated positive correlations between fentanyl seizures and overdose deaths involving synthetic opioids. For example, Gladden et al. reported a 426% increase in fentanyl submissions to NFLIS between 2013 and 2014, correlated with a 79% rise in synthetic opioid deaths across 8 US states ($r = 0.95$).[24] Slavova et al. found correlations between fentanyl seizures submitted to the Kentucky State Police crime lab and fentanyl-related deaths (state-level $r = 0.9$, county-level $r = 0.89$), and between county-level heroin seizures and heroin-related emergency department visits ($r = 0.97$).[26] Moreover, O'Donnell et al. observed increases in national rates of deaths involving synthetic opioids (0.98 rate change) and fentanyl drug reports (2.09 rate change) from 2013 to 2015.[27]

Beyond descriptive studies, several researchers conducted cross-sectional regression analyses ($n = 4$), all finding a positive association between drug seizures and mortality.[27,32,39,40] Eleven studies included a temporal component in their analyses,[6,8-10,33,47,56-58,62,63] nine of which found a positive association between drug seizures and mortality. For example, fentanyl exposure measured via fentanyl-positive seizure tests was associated with overdose mortality, with 1 study estimating fentanyl explained much of the national increase in overdose deaths between 2011 and 2017. Temporal analyses also linked seizures to polysubstance mortality: studies found methamphetamine and cocaine seizures containing IMF were associated with increases in stimulant-involved overdose deaths.[8,47,58] Studies examining seizure composition reported higher overdose mortality in counties with greater fentanyl seizure burden, including pill and powder, with elevated total and drug-specific mortality (eg, synthetic opioids and cocaine)[56]

Drug seizure as enforcement disruptions

Six studies examined whether enforcement or supply disruptions influenced overdose risk, with sharp spatial and temporal dimensions. For example, Ray et al. identified significant spatio-temporal clustering of fatal and nonfatal overdoses, and

Table 1. Key characteristics of the included studies.

Author, year	Setting	Data collection timeframe	Study design	Data source	Objective
Rando et al., 2015[22]	Lorain County, Ohio, United States	Jan 2011-Oct 2014	Prospective interventional ecological study	County coroner's office data, naloxone administration data from police officer NPP (Naloxone Prescription Program)	To evaluate whether intranasal naloxone administration by police officers is associated with a decrease in opioid overdose deaths
Peterson, 2016[23]	Florida and Ohio, United States	2013-2015 (with comparisons to 2010-2012)	Descriptive ecological	NFLIS, Medical examiner reports, Death certificates, E-FORCSE (FL), OARRS (OH)	To examine the association between increases in fentanyl-related law enforcement submissions and fentanyl overdose deaths
Gladden, 2016[24]	27 states, United States	2013-2014	Ecological, descriptive	NFLIS (Drug Enforcement Administration National Forensic Laboratory Information System) for fentanyl submissions, CDC NVSS mortality files for synthetic opioid deaths, IMS Health data for fentanyl prescribing, State medical examiner/coroner reports	To examine the relationship between law enforcement fentanyl submissions and increases in synthetic opioid-involved overdose deaths (primarily fentanyl deaths) in the United States, focusing on the rapid surge in IMF-driven deaths and highlighting demographic disparities and geographic concentration.
Rowe et al., 2016[25]	San Francisco, United States	2010-2012	Ecological study using spatial and neighborhood-level data	San Francisco Department of Public Health (DOPE Project), California Electronic Death Reporting System, Census, Police data	To identify neighborhood-level correlates and spatial relationships of lay naloxone distribution, overdose deaths, and reversal events.
Slavova et al., 2017[26]	Kentucky, United States	2000-2016	Descriptive ecological	Death certificates, postmortem toxicology, ED discharge records, prescription drug monitoring program (PDMP) data from the Kentucky All-Schedule Prescription Electronic Reporting (KASPER), prescription drug monitoring program (PDMP) data from the Kentucky All-Schedule Prescription Electronic Reporting (KASPER)	To describe changes in heroin and fentanyl overdose trends in Kentucky and demonstrate the utility of multi-source drug surveillance
O'Donnell, 2017[27]	United States (4 Census regions)	2006-2015	Descriptive ecological trend analysis	National Vital Statistics System mortality files (unintentional & undetermined overdose deaths) & DEA's NFLIS (heroin and fentanyl drug reports)	To examine trends in heroin and synthetic opioid (excluding methadone) overdose deaths and law enforcement drug reports, by Census region.

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Table 1. Continued

Author, year	Setting	Data collection timeframe	Study design	Data source	Objective
Lambdin et al., 2017[28]	United States	2014	Cross-sectional ecological	National Vital Statistics System (mortality data); Harm Reduction Coalition OEND database (program data)	To assess the geographic mismatch between drug overdose mortality rates and the implementation of naloxone programs (OEND) in the US.
Burrell et al., 2017[29]	Allegheny County, PA, United States	2015	Ecological GIS analysis; descriptive statistics	OverdoseFreePA database (medical examiner data on overdose deaths); pharmacy licensing data from the Pennsylvania Department of State; Naloxone Finder pharmacy locator data	To explore the relationship between overdose death rates and pharmacy presence (including pharmacies carrying naloxone) using GIS mapping to identify areas in need of pharmacy-based interventions.
McClellan et al., 2018[30]	United States (50 states + DC)	2000-2014 (mortality); 2002-2014 (non-medical opioid use)	Ecological, difference-in-differences analysis	National Vital Statistics System (NVSS) mortality data (2000-2014); National Survey on Drug Use and Health (NSDUH) data (2002-2014); Legal database of naloxone access and Good Samaritan laws (Westlaw and PDAPS)	To assess whether naloxone access laws and Good Samaritan laws are associated with changes in opioid overdose mortality and non-medical opioid use
Rowe et al., 2019[31]	San Francisco, United States	2014-2015	Descriptive	DOPE Project reports (naloxone distribution/refills, reversals), CA-EDRS, EMS data from SFFD	To document a community-based naloxone distribution program's response to a fentanyl overdose outbreak and its potential role in averting increases in overdose mortality through rapid outreach and naloxone dissemination.
Zibbell et al., 2019[9]	Ohio, United States	2014-2017	Cross-sectional ecological	Ohio Bureau of Criminal Investigation, Ohio Department of Health	Examining associations between law enforcement drug seizures and drug overdose deaths
Monnat, 2019[32]	United States	2000-2016	Cross-sectional ecological	Mortality data: the National Center for Health Statistics National Vital Statistics System, Exposure to fentanyl is a state-level variable based on state reports of law enforcement encounters (drugs submitted for analysis)	Examining relationships between county-level non-Hispanic white drug mortality rates for 2000-2002 and 2014-2016 and several socioeconomic and opioid supply measures across the urban-rural continuum and within different rural labor markets.
Zoorob, 2019[33]	United States (all states)	2011-2017	Ecological longitudinal	State-level NFLIS fentanyl drug seizure data (FOIA), National Center for Health Statistics (NCHS) mortality data, US Census data (state populations)	To examine how the differential influx of fentanyl reshaped the geography and demography of the US overdose crisis

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Table 1. Continued

Author, year	Setting	Data collection timeframe	Study design	Data source	Objective
Abouk et al., 2019[34]	United States (all 50 states and DC)	2005-2016	Longitudinal panel (quasi-experimental, difference-in-differences)	National Vital Statistics System (mortality), Medicaid data (naloxone prescribing), State Emergency Department Databases (nonfatal overdoses), legal/policy sources	To evaluate the impact of state naloxone access laws (NALs) on opioid-related mortality and nonfatal overdoses. Specifically, to identify which types of NALs (direct authority, indirect authority, other) are associated with reductions in fatal overdoses.
Naumann et al., 2019[35]	North Carolina, United States	August 2013-December 2016 (naloxone data); 2000-2016 (mortality data)	One-group pre-post (ecological, county-level) analysis	NC Harm Reduction Coalition (naloxone kit data) and NC Vital Statistics (mortality data)	To evaluate the impact of a community-based naloxone distribution program on county-level opioid overdose death rates and to conduct a cost-benefit analysis.
Jones et al., 2020[36]	North Carolina, United States	2010-2017	Descriptive ecological	North Carolina DHHS Opioid Data Dashboard, Vital Statistics, EMS, NC CSRS, Peer Support Program	To examine trends in opioid-related mortality and associations with intervention and treatment indicators in North Carolina counties
You et al., 2020[37]	United States	2013-2017	Cross-sectional observational study	National Vital Statistics System multiple cause-of-death mortality files; Prescription Drug Abuse Policy Surveillance System; US Census Bureau regional classifications	To assess how differences in state naloxone accessibility laws (NALs) regarding layperson distribution and possession are associated with changes in opioid overdose death rates by region.
Forati et al., 2021[38]	Milwaukee County, Wisconsin, United States	2019	Ecological, cross-sectional, multiscale spatial regression	Milwaukee County Medical Examiner Office (OOD data); DEA ARCOS (opioid availability); Milwaukee Fire Department (EMS); US Census ACS 2018; Wisconsin DHS; crime data; digital divide index	To examine how structural, demographic, and health-related community-level factors, especially naloxone availability, affect opioid overdose deaths across racially segregated neighborhoods
Jalal & Burke, 2021[39]	United States	1979-2019 (focus on 2016-2018)	Descriptive ecological	CDC Wonder (mortality data), DEA NFLIS (carfentanil, fentanyl, heroin seizures)	To investigate the association between overdose deaths and carfentanil availability
Hall et al., 2021[40]	Ohio, United States	2009-2018 (focus on 2017)	Descriptive	Ohio Bureau of Criminal Investigation (drug seizure data); Ohio Department of Health (overdose death records)	To develop and evaluate a novel Street-Drug Lethality Index (SDLI) to predict unintentional overdose mortality using seizure data
Zang et al., 2021[41]	Massachusetts and Rhode Island, United States	2016-2019	Descriptive spatial analysis	Public health department data on opioid deaths and naloxone distribution	To compare naloxone distribution through community-based OEND programs and opioid overdose death rates to identify priority areas for targeted naloxone expansion.

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Table 1. Continued

Author, year	Setting	Data collection timeframe	Study design	Data source	Objective
Cataife et al., 2021[42]	United States	1999-2014	Ecological, difference-in-differences (DID) with matching	CDC WONDER (mortality); Prescription Drug Abuse Policy System (NALs); GSL and PDMP data; Medicaid expansion data	To estimate the regional and temporal effects of Naloxone Access Laws (NALs) on opioid-related mortality across 4 US regions using a semi-dynamic staggered DID model.
Hamilton et al., 2021[43]	United States (3109 counties)	2013-2018	Hierarchical Bayesian spatiotemporal ecological analysis	CDC's multiple cause-of-death mortality data, PDAPS repository, Geolytics demographic data, state policy data	To examine whether Good Samaritan laws (GSLs) with arrest protections (vs limited protections) and naloxone access laws (NALs), individually or jointly, were associated with changes in overdose mortality.
Lee et al., 2021[44]	United States (50 states)	2007-2018	Cross-sectional difference-in-differences using panel matching	Optum Clinformatics Data Mart database (23 million patients), National Vital Statistics System mortality data, state policy databases	To assess the associations of 6 state-level opioid policies with prescription opioid misuse, opioid use disorder and overdose, MAT prescription, and drug overdose mortality rates.
Chatterjee et al., 2022[45]	Massachusetts, United States	2014-2018	Descriptive ecological	Retail pharmacy standing order data (70% coverage of retail pharmacies), ACS 5-year estimates, MDPH overdose data, treatment admission data (buprenorphine, methadone), OEND data	To examine community-level predictors (demographics, rurality, opioid treatment indicators, overdose deaths) of pharmacy-based standing order naloxone distribution
Doleac & Mukherjee, 2022[46]	United States (urban areas, 33 states)	2010-2015	Quasi-experimental, difference-in-differences (DD) panel fixed-effects model	Google Trends data (naloxone and drug rehab searches), National Incident-Based Reporting System (crime data), CDC restricted mortality data, Healthcare Cost and Utilization Project (ER data)	To examine the effects of naloxone access laws on opioid-related ER visits, opioid-related mortality, and opioid-related crime
Lowder et al., 2022[10]	Washington/ Baltimore HIDTA region (45 local jurisdictions: DC, Maryland, Virginia, West Virginia), United States	2015-2019 (exposure); 2016-2020 (outcome)	Descriptive ecological	W/B HIDTA PMP database (drug seizures, DTO/MLO disruption), medical examiner & vital stats data (fatal overdoses), US Census ACS data (covariates), opioid dispensing rates	To examine whether drug seizures and disruption of drug trafficking and money laundering organizations predict next-year fatal overdose rates (overall, opioid-involved, fentanyl-involved) in the W/B HIDTA region.

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Table 1. Continued

Author, year	Setting	Data collection timeframe	Study design	Data source	Objective
Zibbell et al., 2022[47]	Ohio, United States	2014-2019	Descriptive ecological, multivariate time-series analysis	Ohio Department of Health (mortality data), Ohio Bureau of Criminal Investigation (drug seizure data)	To examine associations between law enforcement seizures of illicit drugs (cocaine, methamphetamine, IMF) and illicit stimulant-involved overdose deaths (ISODs).
Taylor et al., 2022[48]	Maryland, United States	2015-2019	Descriptive ecological	Maryland Department of Health Overdose reports, American Community Survey data (demographics, employment, insurance, education), Maryland Office of the Chief Medical Examiner	To assess the change in trends of fatal opioid overdose rates following the expansion of the Naloxone Standing Order (eNSO) in 2017 and its association with social determinants of health
Morgan et al., 2022[49]	Massachusetts, Rhode Island, and New York City, United States	2016-2018	Ecological study	Retail pharmacy claims data, community naloxone distribution data, CDC opioid overdose mortality data, American Community Survey data	To assess the association of retail pharmacy and community naloxone distribution with opioid-related overdose mortality
Dun et al., 2022[50]	Baltimore City, United States	2012-2017	Retrospective observational cohort	Baltimore City Fire Department EMS data on naloxone administrations (BQUEST project); US Census data for population estimates	To describe the demographic, geographic, and temporal patterns of opioid-related overdoses (proxied by EMS naloxone administration) and their changes over time in Baltimore City.
Tabatabai et al., 2023[51]	United States (37 states)	2006-2019	Ecological, longitudinal mixed-effects model	National Vital Statistics System mortality data; Prescription Drug Abuse Policy System (NALs, Good Samaritan Laws); amfAR's End the HIV Epidemic Plan (MOUD capacity); opioid prescription rates	To assess the impact of Naloxone Access Laws (NALs), Good Samaritan Laws, opioid prescription rate, and Medication for Opioid Use Disorder (MOUD) availability on synthetic opioid overdose death rates
Zibbell et al., 2023[8]	United States, National (all 50 US states and DC)	2014-2019	Ecological longitudinal	Seizure data: National Forensic Laboratory Information System (NFLIS-Drug); Overdose death data: CDC's National Vital Statistics System (NVSS)	Demonstrating how fluctuations in the illicit drug supply correlate with opioid overdose mortality rates.
Ray et al., 2023[6]	Indianapolis, IN, United States	2020-2021	Retrospective, population-based, cohort study	Property room drug seizure data (IMPD), fatal overdose data (Marion County Coroner), EMS nonfatal overdose calls and naloxone administration	To test the hypothesis that law enforcement efforts to disrupt local drug markets by seizing opioids or stimulants are associated with increased spatiotemporal clustering of overdose events in the surrounding geographic area.

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Table 1. Continued

Author, year	Setting	Data collection timeframe	Study design	Data source	Objective
Dowd, 2023[52]	Pennsylvania, United States (6 urban counties)	2017-2020	Difference-in-differences, event study	Pennsylvania Bureau of Health Statistics & Registries (fatal overdoses), Office of Drug Surveillance and Misuse Prevention (ED visits), US Census data, PA Opioid Dashboard	To estimate the causal impact of 2 naloxone giveaways (2018 and 2019) on fatal opioid overdoses and opioid-related emergency department visits in Pennsylvania.
Zang et al., 2023[53]	Massachusetts, United States	January 2016-June 2021	Interrupted time-series analysis	Massachusetts Department of Public Health (OOD data and naloxone kit distribution data), US Census Bureau (population estimates)	To assess the impact of the COVID-19 pandemic on opioid overdose deaths (OOD) and naloxone distribution from community-based programs across racial and ethnic groups in Massachusetts.
Sohn et al., 2023[54]	United States (10 states with naloxone co-prescribing/ offering mandates vs other states)	2006-2020	Difference-in-difference	CDC WONDER mortality data	To assess the impact of naloxone co-prescribing/ offering mandates on opioid-involved overdose deaths, stratified by prescription/ treatment opioids and illicit/synthetic opioids
Freiermuth et al., 2023[55]	Hamilton County, Ohio, United States	October 2017-December 2019	Retrospective program evaluation	Hamilton County Public Health data (naloxone distribution), overdose death data from vital records, census data	To report per-capita naloxone distribution to lay bystanders and evaluate changes in opioid overdose mortality in the county
Bruzelius et al., 2024[56]	606 counties, United States	2013-2020	Ecological longitudinal	Seizure data: the High Intensity Drug Trafficking Area (HIDTA); Overdose death data: the National Center for Health Statistics (NCHS); Population estimates: US Census Bureau (County-level bridged-race estimates); Covariates: American Community Survey, SAIPE, EdFacts, LEOKA, UCR	Examining overall and drug-specific associations between county-level fentanyl burden, based on seizures of fentanyl in pills and powder, pills only, or powder only, and county-level fatal drug overdoses in the United States.
Brown et al., 2024[57]	Pinellas County, FL, United States	January 2019-December 2021	Descriptive ecological, time series, and quasi-Poisson regression	Medical Examiner toxicology data, interdiction (drug seizures, arrests), treatment services (methadone, buprenorphine), social services (homelessness, Medicaid), rescue (EMS transports, naloxone distribution), county population data, CDC WONDER mortality data.	To examine immediate and long-term impacts of the COVID-19 pandemic on overdose deaths, changes in drug seizures, treatment, social services, and to assess the contribution of these factors to overdose mortality at the local (county) level.

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Table 1. Continued

Author, year	Setting	Data collection timeframe	Study design	Data source	Objective
Rosenblum et al., 2024[58]	Ohio, United States	January 2015-September 2021	Cross-sectional ecological	Ohio Bureau of Criminal Investigation (BCI) crime lab data, Ohio Department of Health mortality data, other county-level data (COVID-19 cases, unemployment, prescription opioids)	To estimate the relationship between the relative presence of methamphetamine in law enforcement seizures and overdose death rates; to assess whether past overdose deaths predict future methamphetamine supply.
Toce et al., 2024[59]	United States (all states, youth population)	1999-2021	Retrospective ecological analysis (interrupted time-series)	CDC WONDER database (opioid-related overdose deaths in youths aged 15-24 years)	To examine the association between state-level naloxone access laws (NALs) and opioid-related overdose deaths in youths aged 15-24 years
HEALing Communities Study[60]	67 communities in Kentucky, Massachusetts, New York, Ohio, United States	2020-2022	Cluster-randomized controlled trial, community-level	Death certificates (opioid overdose deaths), EMS data, community-level implementation data	To evaluate the effectiveness of a community-engaged, data-driven intervention (Communities That HEAL, CTH) in reducing opioid-related overdose deaths.
Freisthler et al., 2024[61]	4 states (KY, MA, NY, OH), United States	2020-2023 (comparison period: July 2021-June 2022)	Cluster-randomized, community-level clinical trial (parallel arm, waitlist control)	Death certificate data (ICD-10 coding for drug poisoning deaths); community-level data; surveys on community stigma; EBP implementation tracking data	To assess the impact of the Communities That HEAL (CTH) intervention on overdose death rates (total and polysubstance), and to identify effect modifications by community and demographic factors.
Tran et al., 2024[62]	Ohio, United States	2014-2018	Ecological, time-series, cross-sectional	Ohio Bureau of Criminal Investigation (BCI) drug seizure data and Ohio Department of Health overdose mortality data	To examine the association between drug seizures (composition and weight) and drug overdose deaths in Ohio
Kral et al., 2025[63]	San Francisco, United States	January 2020-September 2023	Cross-sectional ecological, spatial temporal	Overdose mortality data (OCME), SFPD crime data, American Community Survey data (NDI)	To determine whether there is a geospatial association between law enforcement drug seizures and opioid-involved overdose mortality in San Francisco.
Newman et al., 2025[64]	Five counties in Eastern Missouri: St. Louis City, St. Louis County, and "Collar Counties" (Franklin, Jefferson, St. Charles), United States	2011-2022	Controlled Interrupted Time Series (CITS) analysis	County-level medical examiner data (opioid overdose deaths), university-based naloxone distribution data (2017-2022)	To assess the impact of fentanyl emergence and subsequent community-based naloxone distribution on opioid overdose deaths in Missouri's St. Louis region

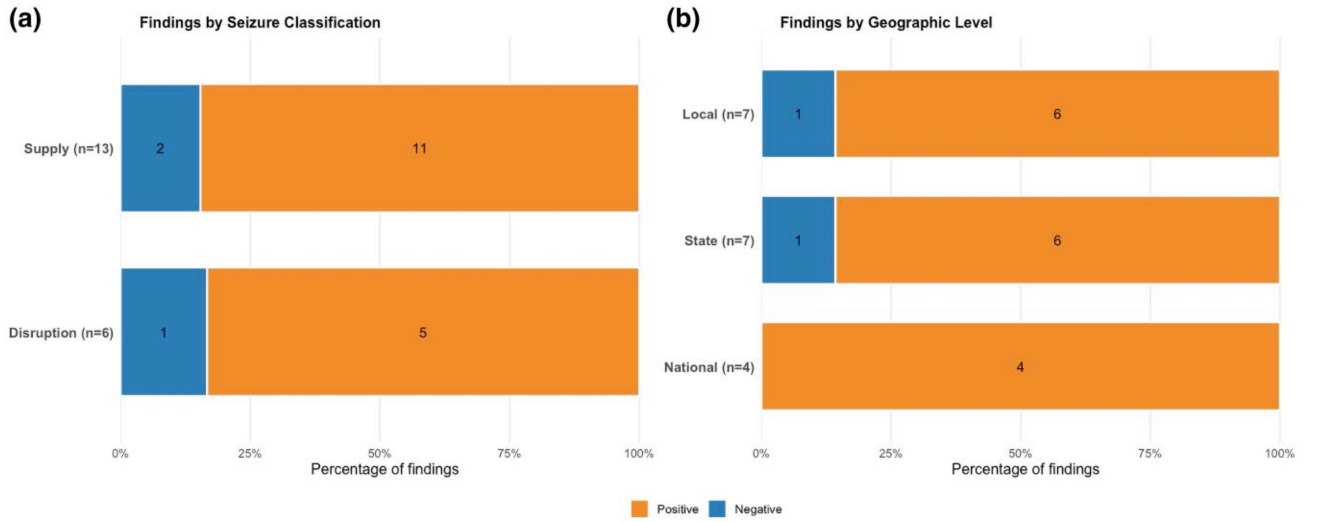

Figure 2. Results of illicit drug supply studies by seizure classification and geographic level. (a) Seizure classifications by authors include supply (seizures as a proxy for prevalence of fentanyl in the area) and disruption (seizures as a direct disruption of local drug markets). (b) Seizure studies varied by geographic level, local areas included county, city and metropolitan service area (MSA). Negative (positive) result indicates a significant negative (positive) relationship between the intervention and overdose mortality.

naloxone administration, within 100 meters and 7 days of seizure events in Indianapolis.[6] Kral et al. found that opioid-involved deaths were more likely within 1 day and 100 meters of a seizure, with a relative risk of 1.74 compared with before the seizure. These effects persisted over a 7-day period.[63]

Other studies expanded this focus beyond immediate proximity. Lowder et al. examined trends in the Washington/Baltimore area and found more seizure cases predicted increased overdose mortality in the following year, particularly for fentanyl-related deaths.[10] However, Brown et al. found reduced seizures during the COVID-19 pandemic were associated with increases in overdose deaths in Florida while service disruptions (methadone and counseling) were not associated with deaths ($\beta = -0.691$).[57]

Drug composition, potency, and lethality

Three studies moved beyond seizure counts to assess drug potency and composition. Kennedy et al. found higher median fentanyl concentrations in drug-checking samples were associated with monthly overdose death rates.[65] Hall et al. developed a Street Drug Lethality Index that combines law enforcement drug seizure data and overdose mortality data to estimate the relative lethality of drugs in the illicit market. Drug-specific lethality ratios were calculated by dividing single-drug overdose deaths by single-drug seizures, and these ratios were applied to annual seizure counts and summed to create a composite index predicting overdose mortality, explaining 93% of annual variance in unintentional overdose deaths ($R^2 = 0.93$).[40] Moreover, Tran et al. showed that seizure composition and weight predicted overdose mortality ($R^2 = 0.78$).[62]

Naloxone availability/distribution and overdose mortality

Overall, 31 studies examined the impact of naloxone-related interventions, including take-home naloxone (THN) programs, naloxone access laws (NALs), Good Samaritan laws (GSLs), standing orders, and overdose education and naloxone distribution (OEND) programs, on opioid overdose mortality (Table S3). While findings varied, a proportion ($n = 13$) of studies suggested that greater naloxone availability/access was associated with reductions in deaths. However, the magnitude and consistency of these effects differ depending on geographic region, implementation strategy, and structural context (Figure 3).

Local and community-level interventions

Six of 17 studies conducted at the local/community level found significant associations between naloxone distribution and reduced overdose deaths. For example, Rando et al. documented a reversal in overdose death trends in Lorain County, Ohio, following the introduction of police-administered naloxone. Using quarterly data, the study compared an 11-quarter pre-intervention baseline period (January 2011 to September 2013) with a 4-quarter post-intervention period after program implementation (October 2013 to October 2014). During the pre-intervention period, overdose deaths increased by 1.5 deaths per quarter; after implementation, the trend shifted to a decrease of 4.1 deaths per quarter, and 77.6% of naloxone recipients survived.[22] In North Carolina, Naumann et al. found counties with more than 100 kits distributed per 100 000 population had a 14% lower overdose death rate than counties with no distribution (RR = 0.88), with an estimated 352 deaths averted.[35] Newman et al. reported that community-based naloxone distribution in St. Louis was associated with an immediate drop in overdose deaths after implementation. The monthly opioid overdose death rate decreased by 2.17 per 100 000 population at the time naloxone distribution began, followed by a slower increase in overdose deaths over time thereafter.[64]

Policy-level interventions

At the policy level, 7 of 12 studies demonstrated that NALs and GSLs were associated with decreased overdose mortality.

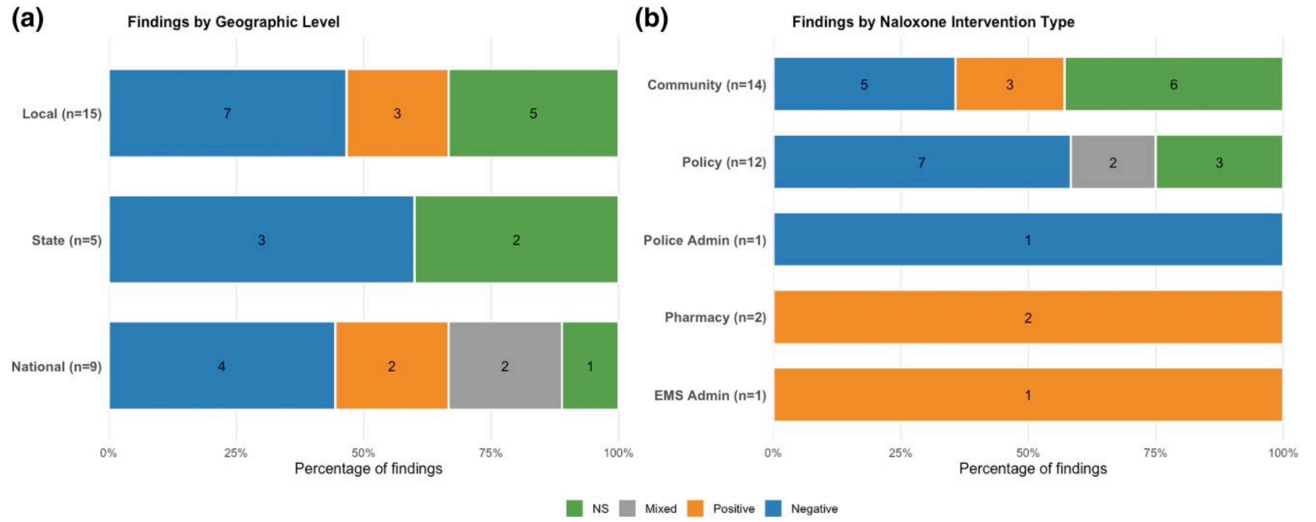

Figure 3. Results of naloxone studies by geographic level and intervention domain. (a) Naloxone study findings by geographic area. Local includes county, city, and metropolitan service area (MSA). (b) Naloxone study findings by intervention type. Negative (positive) result indicates a significant negative (positive) relationship between the intervention and overdose mortality, NS: not significant.

McClellan et al. found that, compared with states without such laws, those with NALs had a 14% lower incidence of overdose mortality ($P = 0.033$), and those with GSLs had a 15% lower incidence ($P = 0.050$).[30] Hamilton et al. found GSLs with arrest protections and NALs led to 10% to 11% reductions in heroin/synthetic opioid-involved deaths 2 years post-enactment.[43] Abouk et al. found that direct-authority NALs (allowing pharmacists to dispense naloxone without a prescription) significantly reduced overdoses by 0.387 per 100,000, or a 34% decrease in opioid deaths.[34] Tabatabai et al. found the presence of NALs was associated with a 27% reduction in synthetic opioid deaths.[51] Sohn et al. reported co-prescribing mandates for naloxone were associated with a 16% reduction in deaths involving prescription or treatment opioids but had no significant effect on deaths involving illicit/synthetic opioids.[54]

Mixed/null findings

Twelve studies reported null/mixed associations. Toce et al. found no significant associations between naloxone laws and overdose deaths,[59] while You et al. found mixed results, with Western regions exhibiting a decrease in overdose death rates in states with NALs, and Northeastern NAL states exhibiting an increase in overdose deaths.[37] Rowe et al. found proximity to naloxone sites in San Francisco was not associated with overdose deaths.[25] Freiermuth et al. evaluated a THN program in Ohio distributing over 10 000 naloxone cartons but found no change in overdose mortality.[55] Rowe et al. observed increased naloxone reversals following the emergence of fentanyl in San Francisco's Civic Center, but overdose deaths remained stable.[31] A HEALing Communities Study analysis reported the intervention was associated with a non-significant 8% reduction in overall overdose deaths (aRR = 0.92), but a statistically significant 37% reduction in deaths involving opioids and non-cocaine psychostimulants (aRR = 0.63).[61] In a separate analysis of the same intervention that focused specifically on opioid-involved overdose mortality, the HEALing Communities Study found a non-significant 9% reduction in opioid-involved overdose mortality (aRR = 0.91) across 67 communities receiving support to implement evidence-based practices to prevent adolescent substance use.[60]

Pandemic-era findings

Two studies examined naloxone's role during the COVID-19 pandemic. Brown et al. found a 377% increase in naloxone distribution in Pinellas County, Florida, during the pandemic but found no corresponding decline in overdose deaths.[57] Zang et al. reported a 63% increase in overdose deaths among Black residents after COVID-19 began, with naloxone distribution increases failing to mitigate this mortality surge.[53]

Discussion

This review synthesized how changes in the drug supply and naloxone availability are associated with overdose mortality. Four themes emerged: (1) consistent association between rising fentanyl presence, whether measured through seizures, potency, or contamination, and increased overdose deaths; (2) variation in how seizure data were interpreted, either as proxies for supply trends or as indicators of enforcement disruptions; (3) studies finding greater naloxone availability/access was associated with reductions in overdose deaths; and (4) the mixed effectiveness of naloxone interventions shaped by intervention domains and population reach. These findings highlight complexity in overdose risk during the fentanyl crisis and offer insights into improving drug data systems to monitor changes in drug supply, naloxone distribution, policy responses, and effects on overdose outcomes.

A central finding was the strong association between increased fentanyl presence and overdose mortality, particularly from synthetic opioids.[8,9,33,47,56] Across several data sources, including forensic seizure records, drug-checking indicators, and toxicology reports, fentanyl and its analogs consistently emerged as key drivers of overdose trends. Several studies demonstrated rising drug toxicity and potency, reflected in fentanyl concentrations and the circulation of potent analogs, were associated with mortality.[62,65] Some studies found declines in the availability of potent synthetic opioids, including carfentanil, were followed by reductions in overdose deaths,[39] suggesting shifts in drug toxicity can effect mortality. Differences in drug composition also shaped overdose risk: studies using drug-checking data or distinguishing powder and pill formulations showed that seizures varied in lethality.[56,62] These findings highlight how not only the presence, but the lethality, of substances contributes to overdose risk, underscoring the importance of toxicological surveillance.[40] Polysubstance involvement also emerged as a theme. Seizures of methamphetamine and cocaine contaminated with fentanyl were associated with stimulant-involved overdose deaths, supporting a trend in polysubstance-related mortality and risk profiles driven by fentanyl contamination of non-opioid drugs.[8,58]

A conceptual distinction emerged in how studies interpreted seizure data. Most studies treated seizures or forensic submissions as proxies for changes in the unregulated supply, using them to estimate variation in fentanyl prevalence or contamination across time and space.[8,24,27,33,47,56] However, a smaller group conceptualized seizures as enforcement disruptions that may destabilize local markets and affect overdose risk in the short term, through abrupt shifts in availability/potency.[6,63] These studies reported elevated overdose risk clustered by time and space near seizure events, with effects within days and within a few hundred meters of seizure locations, consistent with supply shock dynamics. While both perspectives are informative, treating seizure data as indicators of drug supply trends may be more useful for surveillance and long-term epidemiologic analyses, whereas interpreting seizures as enforcement disruptions may be more appropriate for studying short-term, localized impacts on overdose risk.

Evidence on naloxone and overdose mortality was supportive but nuanced, depending on multiple factors, including geographic coverage, scale of implementation, population reach, and integration with other services.[35,66,67] Community naloxone distribution, pharmacy standing orders, and legal protections (eg, NALs, GSLs) were associated with reductions in overdose deaths.[22,30,43,66] Localized interventions, especially those involving law enforcement or public health organizations, demonstrated significant reductions in deaths following community or large-scale naloxone distribution efforts.[52,67] Programs targeting high-risk populations or distributed high volumes of kits showed promising results.[35,52,66] However, studies reported null/inconsistent findings in large-scale or low-coverage settings, or during the COVID-19 pandemic when service delivery was disrupted.[31,37,55,68] Even in jurisdictions with expanded naloxone access, deaths continued to rise in some populations, suggesting naloxone distribution may not have been effectively reaching those populations most in need.[53,55] Policy-level evaluations supported the role of NALs and GSLs in reducing deaths, especially when accompanied by pharmacist authority or legal protections from arrest.[30,43,51]

The effectiveness of naloxone interventions depended on factors including geographic coverage, scale of implementation, population reach, and integration with other services.[35,66,67] Effective implementation of distribution programs depends on the successful identification of the most relevant and appropriate distribution channels (ie, pharmacies, healthcare clinics). Structural barriers, such as housing instability and stigma, likely moderated access and outcomes, particularly during periods of heightened drug toxicity and reduced health system functioning.[53,57,60] These highlight the importance of embedding naloxone distribution within broader public health ecosystems and addressing upstream determinants of health.[53,55,57]

This study has limitations. First, exposure and outcome variables were often subject to misclassification: seizure data lacked information on drug potency, purity, quantity, and mixtures; mortality records could not consistently distinguish between pharmaceutical and illicit fentanyl; and naloxone distribution data lacked recipient-level tracking. Second, findings from COVID-19-era studies may not generalize to other periods due to service disruptions and changes in healthcare access. Third, focusing on overdose mortality rather than non-fatal overdose events or overdose reversals may underestimate the impact of naloxone distribution, because many overdose events are successfully reversed and therefore do not appear in mortality statistics. Fourth, we did not systematically extract the interval between intervention or policy implementation and outcome assessment across studies. Because mortality effects may require longer follow-up to emerge, variation in evaluation windows may have contributed to heterogeneity in findings, particularly for naloxone interventions. Future studies should examine implementation-to-outcome timing to determine whether null findings reflect insufficient follow-up rather than a lack of effect. Finally, the observational nature of most studies limits causal inference, despite advanced statistical methods and adjustments.

Despite this, the review has methodological strength and diversity. Among the 47 studies, 44 employed robust statistical methods and conducted sensitivity analyses to assess the stability of findings (Table S4). Many studies leveraged large samples spanning neighborhood, county, state, or national levels, often covering multiple or all US states. Studies frequently integrated multiple linked data sources, including crime laboratory data, supply-side indicators, and legislative/policy measures. Several analyses exploited natural experiments, and 1 study used a randomized controlled trial design. Collectively, this methodological breadth across geographic and temporal contexts strengthens confidence in the overall evidence base. Findings also did not appear to vary systematically by study design. While more rigorous designs, including difference-in-differences analyses, interrupted time-series studies, and 1 cluster-randomized trial, strengthened causal interpretation, these studies still reported mixed findings, particularly for naloxone interventions. This pattern suggests that variation in results likely reflected differences in implementation scale, timing, coverage, and local context, rather than study design alone.

Conclusion

Findings can inform research, policy, and practice. Future studies should explicitly define how drug seizure data are conceptualized, whether as supply indicators or enforcement events, to improve comparability and interpretation. Integrated study designs linking drug supply indicators, naloxone distribution, and overdose outcomes could provide clearer insights into overdose dynamics. Linking seizure data, toxicology results, naloxone distribution records, and overdose mortality at the community level could help assess how changes in drug supply and naloxone coverage jointly influence outcomes. Surveillance systems should integrate toxicology, seizure, and mortality data in near real-time to detect emerging threats in the drug market.[9,40,62,65]

While naloxone remains a cornerstone of overdose prevention, naloxone distribution requires improved measurement of reach through standardized, linked data across pharmacies, community THN programs, EMS, corrections, and mail-based channels, including recipient demographics and coverage in high-burden communities, as part of comprehensive overdose prevention strategies incorporating drug checking and low-barrier MOUD.[53,55,57] Overdose prevention efforts should target underserved and high-burden communities, particularly those disproportionately affected by fentanyl.[53,57,60] Finally, public health strategies must remain flexible and responsive to the rapid changes in drug supply, composition, and drug use behaviors.[8,56,58]

Supplementary material

Supplementary material is available at *Health Affairs Scholar* online.

Author disclaimer

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Conflicts of interest

Please see ICMJE form(s) for author conflicts of interest. These have been provided as supplementary materials.

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